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(54) **MATRIX METALLOPROTEINASE
SUBSTRATES AND OTHER CLEAVABLE
MOIETIES AND METHODS OF USE
THEREOF**

(71) Applicant: **CytomX Therapeutics, Inc.**, South San Francisco, CA (US)

(72) Inventors: **Stephen James Moore**, Danville, CA (US); **Margaret Thy Luu Nguyen**, San Jose, CA (US); **Daniel R. Hostetter**, Palo Alto, CA (US); **Olga Vasiljeva**, Cupertino, CA (US); **Jeanne Grace Flandez**, Oakland, CA (US)

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USPC **530/387.3**; 530/300

(57)

ABSTRACT

The invention relates generally to polypeptides that include a cleavable moiety that is a substrate for at least one matrix metalloprotease (MMP), to activatable antibodies and other larger molecules that include the cleavable moiety that is a substrate for at least one MMP protease, and to methods of making and using these polypeptides that include a cleavable moiety that is a substrate for at least one MMP protease in a variety of therapeutic, diagnostic and prophylactic indications.

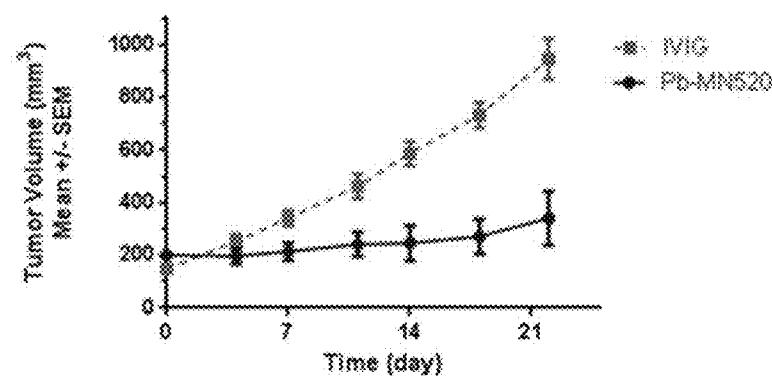
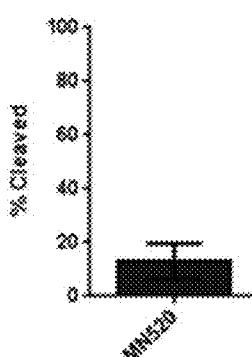
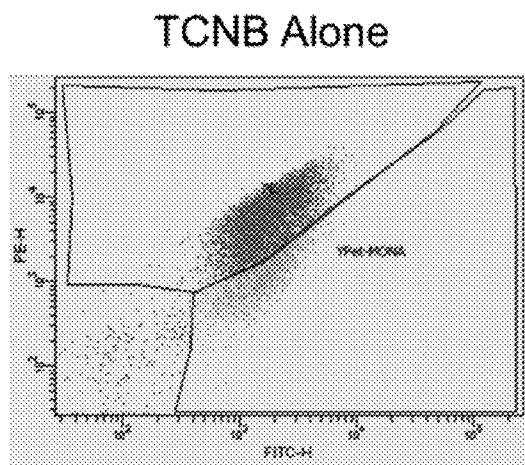
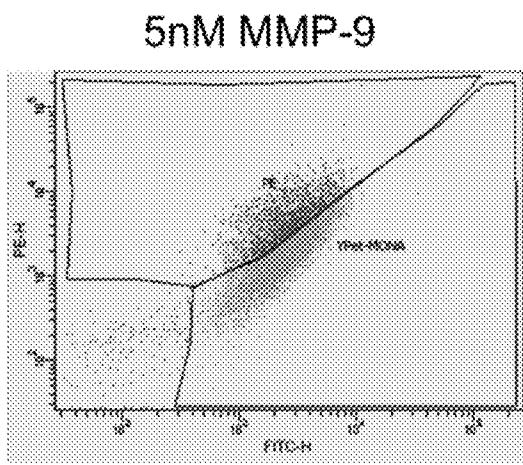
FIGURE 1A**FIGURE 1B****FIGURE 2A****FIGURE 2B****TCNB Alone****5nM MMP-9**

FIGURE 3A

TCNB Alone

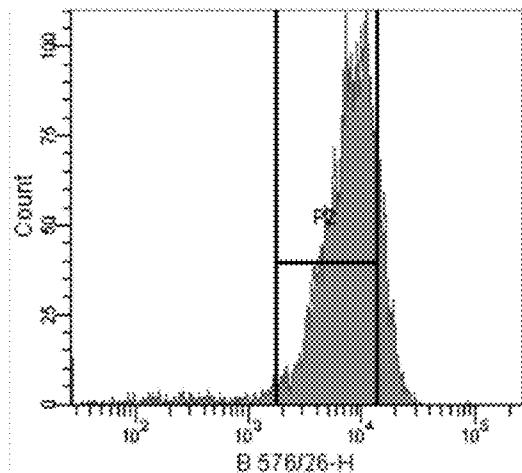


FIGURE 3B

5nM MMP-9

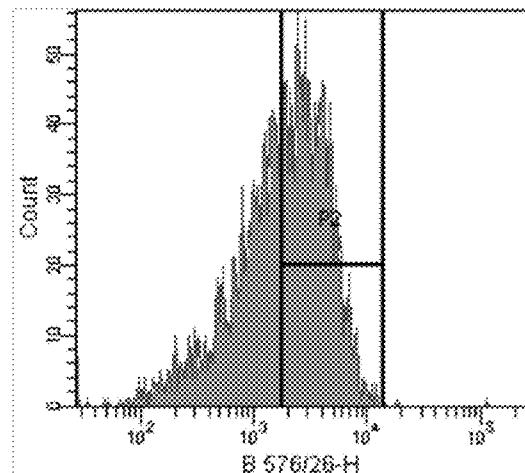


FIGURE 4

Frequency versus Function

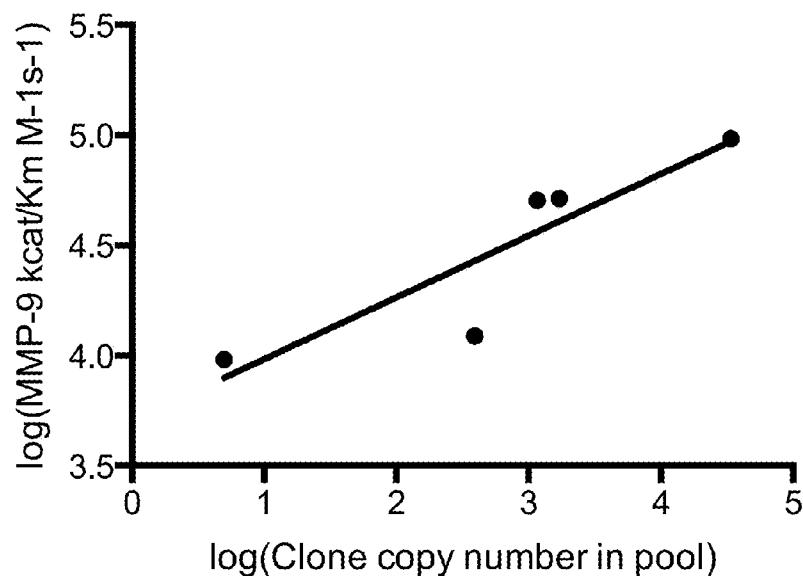


FIGURE 5A

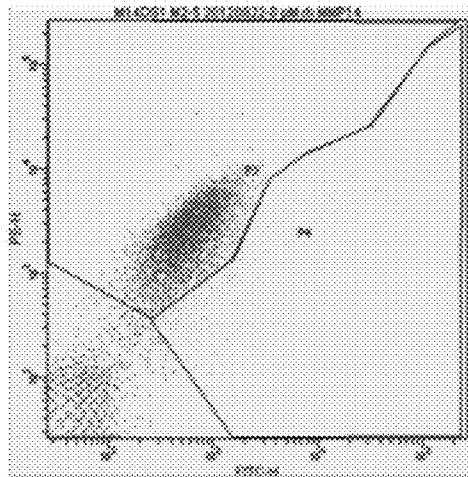
HCM Alone

FIGURE 5B

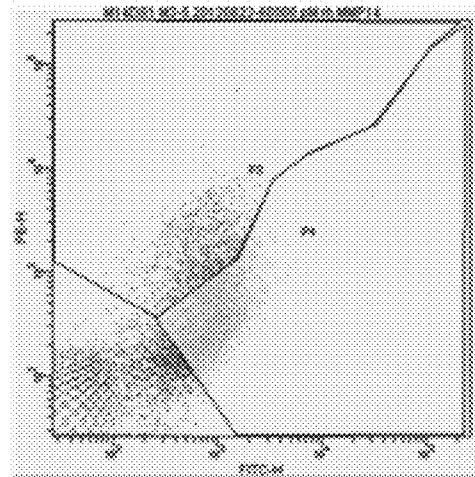
60 nM MMP14

FIGURE 6A

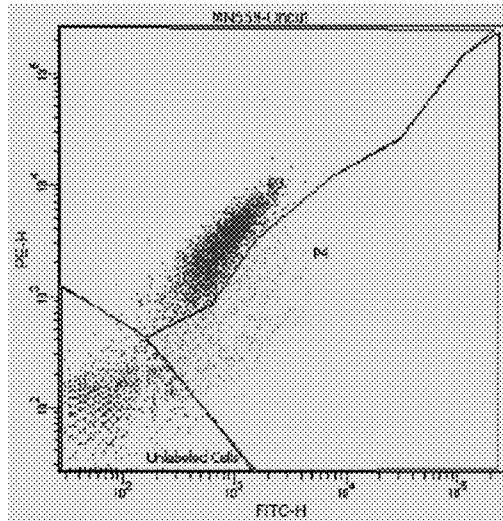
HCM Alone

FIGURE 6B

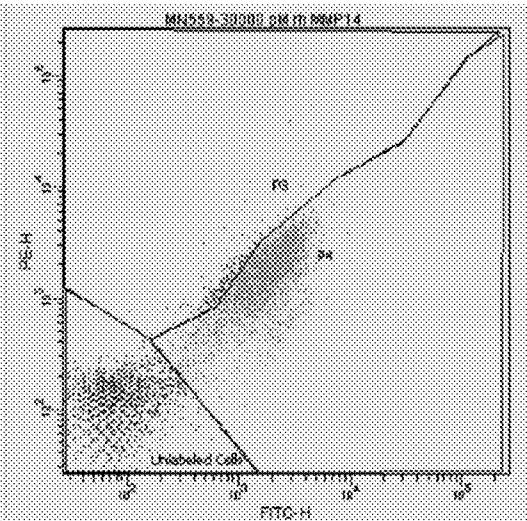
30 nM MMP14

FIGURE 7A

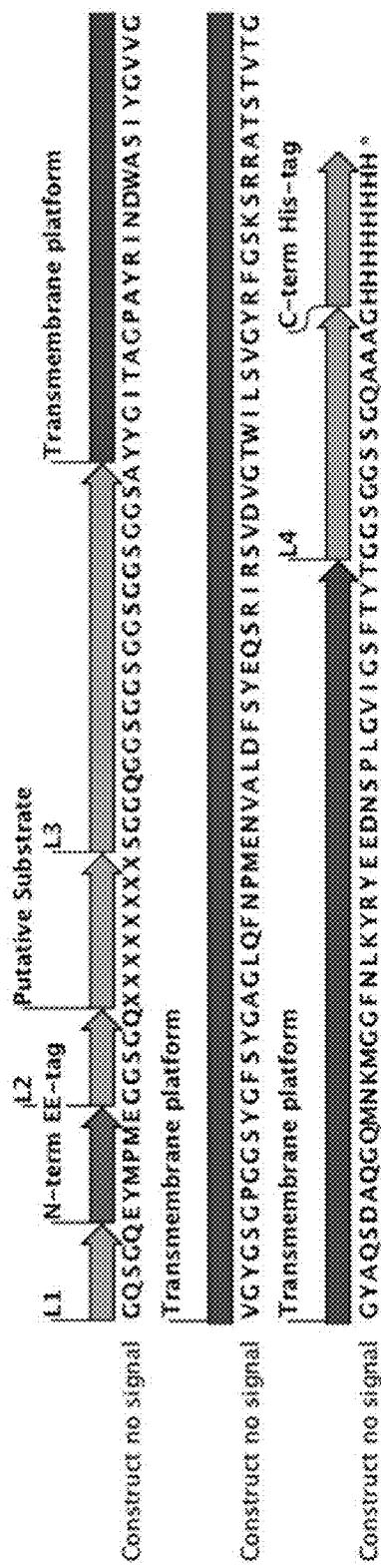
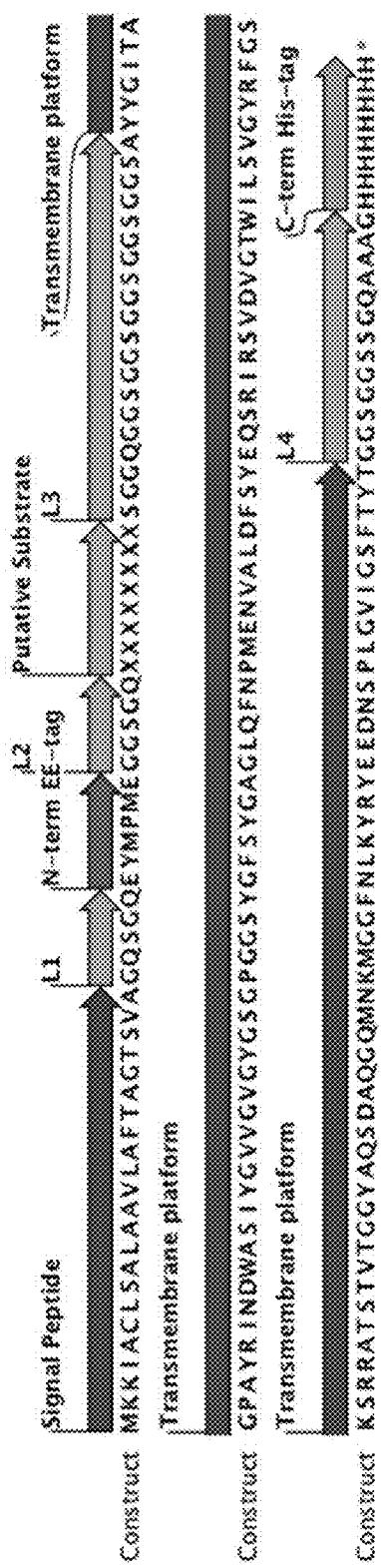


FIGURE 7B



**MATRIX METALLOPROTEINASE
SUBSTRATES AND OTHER CLEAVABLE
MOIETIES AND METHODS OF USE
THEREOF**

RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 61/882,377, filed Sep. 25, 2013 and U.S. Provisional Application No. 61/971,332, filed Mar. 27, 2014, the contents of each of which are incorporated herein by reference in their entireties.

FIELD OF THE INVENTION

[0002] The invention relates generally to polypeptides that include a cleavable moiety that is a substrate for at least one matrix metalloprotease (MMP), to activatable antibodies and other larger molecules that include the cleavable moiety that is a substrate for at least one MMP protease, and to methods of making and using these polypeptides that include a cleavable moiety that is a substrate for at least one MMP protease in a variety of therapeutic, diagnostic and prophylactic indications.

BACKGROUND OF THE INVENTION

[0003] Proteases are enzymes that degrade proteins by cleaving the peptide bonds between amino acid residues. Proteases occur naturally in all organisms and are involved in a variety of physiological reactions from simple degradation to highly regulated pathways. Some proteases are known to break specific peptide bonds based on the presence of a particular amino acid sequence within a protein.

[0004] Accordingly, there exists a need to identify new substrates for proteases and to use these substrates in a variety of therapeutic, diagnostic and prophylactic indications.

SUMMARY OF THE INVENTION

[0005] The disclosure provides amino acid sequences that include a cleavable moiety (CM) that is a substrate for at least one matrix metalloprotease (MMP). These CMs are useful in a variety of therapeutic, diagnostic and prophylactic indications.

[0006] In some embodiments, the CM is a substrate for at least one matrix metalloprotease (MMP). Examples of MMPs include MMP1; MMP2; MMP3; MMP7; MMP8; MMP9; MMP10; MMP11; MMP12; MMP13; MMP14; MMP15; MMP16; MMP17; MMP19; MMP20; MMP23; MMP24; MMP26; and MMP27. In some embodiments, the CM is a substrate for MMP9, MMP14, MMP1, MMP3, MMP13, MMP17, MMP11, and MMP19. In some embodiments, the CM is a substrate for MMP9. In some embodiments, the CM is a substrate for MMP14. In some embodiments, the CM is a substrate for two or more MMPs. In some embodiments, the CM is a substrate for at least MMP9 and MMP14. In some embodiments, the CM comprises two or more substrates for the same MMP. In some embodiments, the CM comprises at least two or more MMP9 substrates. In some embodiments, the CM comprises at least two or more MMP14 substrates.

[0007] In some embodiments, the CM is a substrate for an MMP and includes the sequence ISSGLLSS (SEQ ID NO: 14); QNQALRMA (SEQ ID NO: 15); AQNLLGMV (SEQ ID NO: 16); STFPFGMF (SEQ ID NO: 17); PVGYTSSL (SEQ ID NO: 18); DWLYWPGI (SEQ ID NO: 19);

MIAPVAYR (SEQ ID NO: 20); RPSPMWAY (SEQ ID NO: 21); WATPRPMR (SEQ ID NO: 22); FRLLDWQW (SEQ ID NO: 23); LKAAPRWA (SEQ ID NO: 24); GPSHLVLT (SEQ ID NO: 25); LPGGLSPW (SEQ ID NO: 26); MGLFSEAG (SEQ ID NO: 27); SPLPLRVP (SEQ ID NO: 28); RMHL-RSLG (SEQ ID NO: 29); LAAPLGLL (SEQ ID NO: 30); AVGLLAPP (SEQ ID NO: 31); LLAPSHRA (SEQ ID NO: 32); PAGLWLDP (SEQ ID NO: 33); and/or ISSGLSS (SEQ ID NO: 159).

[0008] In some embodiments, the CM comprises the amino acid sequence ISSGLLSS (SEQ ID NO: 14). In some embodiments, the CM comprises the amino acid sequence QNQALRMA (SEQ ID NO: 15). In some embodiments, the CM comprises the amino acid sequence AQNLLGMV (SEQ ID NO: 16). In some embodiments, the CM comprises the amino acid sequence STFPFGMF (SEQ ID NO: 17). In some embodiments, the CM comprises the amino acid sequence PVGYTSSL (SEQ ID NO: 18). In some embodiments, the CM comprises the amino acid sequence DWLYWPGI (SEQ ID NO: 19). In some embodiments, the CM comprises the amino acid sequence MIAPVAYR (SEQ ID NO: 20). In some embodiments, the CM comprises the amino acid sequence RPSPMWAY (SEQ ID NO: 21). In some embodiments, the CM comprises the amino acid sequence WATPRPMR (SEQ ID NO: 22). In some embodiments, the CM comprises the amino acid sequence FRLLDWQW (SEQ ID NO: 23). In some embodiments, the CM comprises the amino acid sequence LKAAPRWA (SEQ ID NO: 24). In some embodiments, the CM comprises the amino acid sequence GPSHLVLT (SEQ ID NO: 25). In some embodiments, the CM comprises the amino acid sequence LPGGLSPW (SEQ ID NO: 26). In some embodiments, the CM comprises the amino acid sequence MGLFSEAG (SEQ ID NO: 27). In some embodiments, the CM comprises the amino acid sequence SPLPLRVP (SEQ ID NO: 28). In some embodiments, the CM comprises the amino acid sequence RMHL-RSLG (SEQ ID NO: 29). In some embodiments, the CM comprises the amino acid sequence LAAPLGLL (SEQ ID NO: 30). In some embodiments, the CM comprises the amino acid sequence AVGLLAPP (SEQ ID NO: 31). In some embodiments, the CM comprises the amino acid sequence LLAPSHRA (SEQ ID NO: 32). In some embodiments, the CM comprises the amino acid sequence PAGLWLDP (SEQ ID NO: 33). In some embodiments, the CM comprises the amino acid sequence ISSGLSS (SEQ ID NO: 159).

[0009] In some embodiments, the CM is linked or otherwise attached to an antibody. For example, the CM is used to link one or more agents to the antibody or antigen binding fragment thereof (AB) that binds a given target, such that the CM is cleaved when exposed to the MMP and the agent is released from the AB. Exemplary targets include, but are not limited to the targets shown in Table 1. Exemplary ABs include, but are not limited to, the targets shown in Table 2. In some embodiments, the antibody in the uncleaved state has the structural arrangement from N-terminus to C-terminus as follows: Agent-CM-AB or AB-CM-Agent. In some embodiments, the antibody comprises a linking peptide between the AB and the CM. In some embodiments, the antibody comprises a linking peptide between the CM and the conjugated agent.

[0010] In some embodiments, the antibody comprises a first linking peptide (LP1) and a second linking peptide (LP2), and the antibody in the uncleaved state has the structural arrangement from N-terminus to C-terminus as follows:

Agent-LP1-CM-LP2-AB or AB-LP2-CM-LP1-Agent. In some embodiments, each of LP1 and LP2 is a peptide of about 1 to 20 amino acids in length. In some embodiments, the two linking peptides need not be identical to each other.

[0011] In some embodiments, at least one of LP1 or LP2 comprises an amino acid sequence selected from the group consisting of (GS)_n, (GGS)_n, (GSGGS)_n (SEQ ID NO: 1) and (GGGS)_n (SEQ ID NO: 2), where n is an integer of at least one.

[0012] In some embodiments, at least one of LP1 or LP2 comprises an amino acid sequence selected from the group consisting of GGSG (SEQ ID NO: 3), GGSGG (SEQ ID NO: 4), GSGSG (SEQ ID NO: 5), GSGGG (SEQ ID NO: 6), GGGSG (SEQ ID NO: 7), and GSSSG (SEQ ID NO: 8).

[0013] In some embodiments, LP1 comprises the amino acid sequence GSSGGSGGSGGSG (SEQ ID NO: 9), GSSGGSGGSGG (SEQ ID NO: 10), GSSGGSGGSGGSG (SEQ ID NO: 11), GSSGGSGGSGGSGGS (SEQ ID NO: 155), GSSGGSGGS (SEQ ID NO: 156), or GSSGGSGGS (SEQ ID NO: 157).

[0014] In some embodiments, LP2 comprises the amino acid sequence GSS, GGS, GGGS (SEQ ID NO: 158), GSSGT (SEQ ID NO: 12) or GSSG (SEQ ID NO: 13).

[0015] In some embodiments, the AB has an equilibrium dissociation constant of about 100 nM or less for binding to the target.

[0016] In some embodiments, the antibody includes an antibody or antigen-binding fragment thereof that specifically binds a target. In some embodiments, the antibody or immunologically active fragment thereof that binds the target is a monoclonal antibody, domain antibody, single chain, Fab fragment, a F(ab')₂ fragment, a scFv, a scab, a dAb, a single domain heavy chain antibody, or a single domain light chain antibody. In some embodiments, such an antibody or immunologically active fragment thereof that binds the target is a mouse, other rodent, chimeric, humanized or fully human monoclonal antibody.

[0017] In some embodiments, the MMP protease is co-localized with the target in a tissue, and the MMP protease cleaves the CM in the antibody when the antibody is exposed to the protease.

[0018] In some embodiments, the CM is a polypeptide of up to 15 amino acids in length.

[0019] In some embodiments, the CM is a substrate for at least one matrix metalloprotease (MMP). Examples of MMPs include MMP1; MMP2; MMP3; MMP7; MMP8; MMP9; MMP10; MMP11; MMP12; MMP13; MMP14; MMP15; MMP16; MMP17; MMP19; MMP20; MMP23; MMP24; MMP26; and MMP27. In some embodiments, the CM is a substrate for MMP9, MMP14, MMP1, MMP3, MMP13, MMP17, MMP11, and MMP19. In some embodiments, the CM is a substrate for MMP9. In some embodiments, the CM is a substrate for MMP14. In some embodiments, the CM is a substrate for two or more MMPs. In some embodiments, the CM is a substrate for at least MMP9 and MMP14. In some embodiments, the CM comprises two or more substrates for the same MMP. In some embodiments, the CM comprises at least two or more MMP9 substrates. In some embodiments, the CM comprises at least two or more MMP14 substrates.

[0020] In some embodiments, the CM is a substrate for an MMP and includes the sequence ISSGLLSS (SEQ ID NO: 14); QNQALRMA (SEQ ID NO: 15); AQNLLGMV (SEQ ID NO: 16); STFPFGMF (SEQ ID NO: 17); PVGYTSSL

(SEQ ID NO: 18); DWLYWPGI (SEQ ID NO: 19); MIAPVAYR (SEQ ID NO: 20); RPSPMWAY (SEQ ID NO: 21); WATPRPMR (SEQ ID NO: 22); FRLLDWQW (SEQ ID NO: 23); LKAAPRWA (SEQ ID NO: 24); GPSHLVLT (SEQ ID NO: 25); LPGLSPW (SEQ ID NO: 26); MGLFSEAG (SEQ ID NO: 27); SPLPLRVP (SEQ ID NO: 28); RMHRLRSLG (SEQ ID NO: 29); LAAPLGLL (SEQ ID NO: 30); AVGLLAPP (SEQ ID NO: 31); LLAPSHRA (SEQ ID NO: 32); PAGLWLDP (SEQ ID NO: 33); and/or ISSGLSS (SEQ ID NO: 159).

[0021] In some embodiments, the CM comprises the amino acid sequence ISSGLLSS (SEQ ID NO: 14). In some embodiments, the CM comprises the amino acid sequence QNQALRMA (SEQ ID NO: 15). In some embodiments, the CM comprises the amino acid sequence AQNLLGMV (SEQ ID NO: 16). In some embodiments, the CM comprises the amino acid sequence STFPFGMF (SEQ ID NO: 17). In some embodiments, the CM comprises the amino acid sequence PVGYTSSL (SEQ ID NO: 18). In some embodiments, the CM comprises the amino acid sequence DWLYWPGI (SEQ ID NO: 19). In some embodiments, the CM comprises the amino acid sequence MIAPVAYR (SEQ ID NO: 20). In some embodiments, the CM comprises the amino acid sequence RPSPMWAY (SEQ ID NO: 21). In some embodiments, the CM comprises the amino acid sequence WATPRPMR (SEQ ID NO: 22). In some embodiments, the CM comprises the amino acid sequence FRLLDWQW (SEQ ID NO: 23). In some embodiments, the CM comprises the amino acid sequence LKAAPRWA (SEQ ID NO: 24). In some embodiments, the CM comprises the amino acid sequence GPSHLVLT (SEQ ID NO: 25). In some embodiments, the CM comprises the amino acid sequence LPGLSPW (SEQ ID NO: 26). In some embodiments, the CM comprises the amino acid sequence MGLFSEAG (SEQ ID NO: 27). In some embodiments, the CM comprises the amino acid sequence SPLPLRVP (SEQ ID NO: 28). In some embodiments, the CM comprises the amino acid sequence RMHRLRSLG (SEQ ID NO: 29). In some embodiments, the CM comprises the amino acid sequence LAAPLGLL (SEQ ID NO: 30). In some embodiments, the CM comprises the amino acid sequence AVGLLAPP (SEQ ID NO: 31). In some embodiments, the CM comprises the amino acid sequence LLAPSHRA (SEQ ID NO: 32). In some embodiments, the CM comprises the amino acid sequence PAGLWLDP (SEQ ID NO: 33). In some embodiments, the CM comprises the amino acid sequence ISSGLSS (SEQ ID NO: 159).

[0022] In some embodiments, the CM is a substrate for at least one matrix metalloprotease (MMP) and includes a motif sequence that is recognized by MMP9. In some embodiments, the CM is a substrate for at least one MMP and includes a motif sequence that is recognized by MMP14.

[0023] In some embodiments, the CM is a substrate for at least one MMP, and the CM polypeptide and/or the CM portion of any polypeptide that comprises the CM comprises a polypeptide having a length less than 50 amino acids, less than 40 amino acids, less than 30 amino acids, less than 25 amino acids, less than 20 amino acids, less than 19 amino acids, less than 18 amino acids, less than 17 amino acids, less than 16 amino acids, less than 15 amino acids long, less than 14 amino acids, less than 13 amino acids, less than 12 amino acids, less than 11 amino acids, or less than 10 amino acids long.

[0024] In some embodiments, the CM is a substrate for at least one MMP and comprises a polypeptide sequence that is

not substantially identical to any human polypeptide sequence that is naturally cleaved by the same MMP protease. In some embodiments, the CM is a substrate for at least one MMP and comprises a polypeptide sequence that is no more than 90% or more identical to any human polypeptide sequence that is naturally cleaved by the same MMP protease.

[0025] In some embodiments, the motif sequence is a substrate for at least MMP and includes a core CM consensus sequence shown in Tables 8A-8M below. In some embodiments, the motif sequence includes a subgenus, i.e., a subset, of the core CM consensus sequence shown in Tables 8A-8M below.

[0026] In some embodiments, the motif sequence is a substrate for at least MMP9 and includes a core CM consensus sequence shown in Tables 8A-8D. In some embodiments, the motif sequence is a substrate for at least MMP9 and includes a subgenus, i.e., a subset, of the core CM consensus sequence shown in Tables 8A-8D below.

[0027] In some embodiments, the motif sequence is a substrate for at least MMP14 and includes a core CM consensus sequence shown in Tables 8E-8M. In some embodiments, the motif sequence is a substrate for at least MMP14 and includes a subgenus, i.e., a subset, of the core CM consensus sequence shown in Tables 8E-8M below.

TABLE 8A

MMP9 Cleavable Core CM Consensus Sequence 1	
Core CM Consensus 1	Subgenus of Core CM Consensus 1
$X_{22}X_{23}X_{24}X_{25}X_{26}X_{27}X_{28}X_{29}$ (SEQ ID NO: 317), wherein X_{22} is A, C, D, G, H, L, P, R, or S; X_{23} is L, M, P, S, or T; X_{24} is A, D, F, G, L, M, N, P, R, S, T, or V; X_{25} is A, D, E, G, H, I, M, P, S, or V; X_{26} is A, C, D, G, L, M, N, R, V, W, or Y; X_{27} is C, F, G, H, P, Q, R, T, V, or W; X_{28} is A, D, G, L, M, S, T, V, or Y; and X_{29} is C, H, L, R, S, V, W, or Y.	Subgenus 1.1: $X_{22}X_{23}X_{24}X_{25}X_{26}X_{27}X_{28}X_{29}$ (SEQ ID NO: 318), wherein X_{22} is G, P, R, or S; X_{23} is P or S; X_{24} is L, M, P, or S; X_{25} is A, G, P, or S; X_{26} is L, M, or R; X_{27} is G or W; X_{28} is A, G, S, or Y; and X_{29} is L, R, V, or Y. Subgenus 1.2: $X_{22}X_{23}X_{24}X_{25}X_{26}X_{27}X_{28}X_{29}$ (SEQ ID NO: 319), wherein X_{22} is G, P or R; X_{23} is P; X_{24} is L, M, or S; X_{25} is G, P, or S; X_{26} is L, M, or R; X_{27} is W; X_{28} is A, G, or S; and X_{29} is R, V, or Y. Subgenus 1.3: $X_{22}X_{23}X_{24}X_{25}X_{26}X_{27}X_{28}X_{29}$ (SEQ ID NO: 320), wherein X_{22} is P or R; X_{23} is P; X_{24} is M or S; X_{25} is G or P; X_{26} is L, M, or R; X_{27} is W; X_{28} is A, G, or S; and X_{29} is R, V, or Y. Subgenus 1.4: $X_{22}X_{23}X_{24}X_{25}X_{26}X_{27}X_{28}X_{29}$ (SEQ ID NO: 321), wherein X_{22} is P or R; X_{23} is P; X_{24} is S; X_{25} is G or P; X_{26} is M, or R; X_{27} is W; X_{28} is A or S; and X_{29} is Y. Subgenus 1.5: $X_{22}X_{23}X_{24}X_{25}X_{26}X_{27}X_{28}X_{29}$ (SEQ ID NO: 322), wherein X_{22} is P or R; X_{23} is P; X_{24} is S; X_{25} is G or P; X_{26} is M, or R; X_{27} is W; X_{28} is A or S; and X_{29} is Y. Subgenus 1.6: $X_{22}X_{23}X_{24}X_{25}X_{26}X_{27}X_{28}X_{29}$ (SEQ ID NO: 323), wherein X_{22} is C, G, H, L, or R; X_{23} is P, S or T; X_{24} is N, R, S or T; X_{25} is P or S; X_{26} is C, M, R, V, or W; X_{27} is C, P, R, or W; X_{28} is A, D, or G; and X_{29} is C or Y.

TABLE 8B

MMP9 Cleavable Core CM Consensus Sequence 2	
Core CM Consensus 2	Subgenus of Core CM Consensus 2
$X_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}$ (SEQ ID NO: 324), wherein X_{32} is F, G, V, or W; X_{33} is A, D, L, M, P, R, T, or V; X_{34} is C, G, H, L, Q, S, T, W, X_{35} is D, G, L, P; X_{36} is E, G, I, L, N, P, R, or V; X_{37} is G, L, P, R, S, or V; X_{38} is A, I, L, M, T, or V; and X_{39} is A, G, L, P, Q, R, S, or V.	Subgenus 2.1: $X_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}$ (SEQ ID NO: 325), wherein X_{32} is W; X_{33} is D, P, or T; X_{34} is H, Q, or W; X_{35} is D or P; X_{36} is I or R; X_{37} is S; X_{38} is L, M, or V; and X_{39} is G, L, or S. Subgenus 2.2: $X_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}$ (SEQ ID NO: 326), wherein X_{32} is W; X_{33} is D; X_{34} is H, Q, or W; X_{35} is D or P; X_{36} is I or R; X_{37} is G, S, or V; X_{38} is L, M, or V; and X_{39} is G, L, or S. Subgenus 2.3: $X_{32}X_{33}X_{34}X_{35}X_{36}X_{37}X_{38}X_{39}$ (SEQ ID NO: 327), wherein X_{32} is W; X_{33} is D; X_{34} is H, Q, or W; X_{35} is P; X_{36} is I or R; X_{37} is S; X_{38} is L, M, or V; and X_{39} is L.

TABLE 8C

MMP9 Cleavable Core CM Consensus Sequence 3	
Core CM Consensus 3	Subgenus of Core CM Consensus 3
$X_{42}X_{43}X_{44}X_{45}X_{46}X_{47}X_{48}X_{49}$ (SEQ ID NO: 329), wherein X_{42} is G, I, L, M, P, R, S, T, or V; X_{43} is A, D, H, I, L, P, S, or T;	Subgenus 3.1: $X_{42}X_{43}X_{44}X_{45}X_{46}X_{47}X_{48}X_{49}$ (SEQ ID NO: 330), wherein X_{42} is I, L, M, or S; X_{43} is D, P, S, or T; X_{44} is F, L, S, or V; X_{45} is L, P, or S; X_{46} is A, F, R, S, or T; X_{47} is G, H, T or Y; X_{48} is G, I, M, V, or W; and X_{49} is F, L, or S. Subgenus 3.2: $X_{42}X_{43}X_{44}X_{45}X_{46}X_{47}X_{48}X_{49}$ (SEQ ID NO: 331), wherein X_{42} is L, M, or S; X_{43} is S or T; X_{44} is F or L; X_{45} is P; X_{46} is A, F, or T; X_{47} is G, H, T or Y; X_{48} is I, M, or W; and X_{49} is F.

TABLE 8C-continued

MMP9 Cleavable Core CM Consensus Sequence 3	
Core CM Consensus 3	Subgenus of Core CM Consensus 3
X_{44} is F, L, S, or V; X_{45} is H, L, M, P, Q, R, S, or T; X_{46} is A, D, F, G, L, M, R, S, T, or V; X_{47} is A, C, G, H, Q, T or Y; X_{48} is C, G, I, M, R, S, T, V, or W; and X_{49} is F, L, S, or Y.	Subgenus 3.3: $X_{42}X_{43}X_{44}X_{45}X_{46}X_{47}X_{48}X_{49}$ (SEQ ID NO: 332), wherein X_{42} is L, M, or S; X_{43} is S or T; X_{44} is F; X_{45} is P; X_{46} is A, F, or T; X_{47} is G, H, or Y; X_{48} is I, M, or W; and X_{49} is F. Subgenus 3.4: $X_{42}X_{43}X_{44}X_{45}X_{46}X_{47}X_{48}X_{49}$ (SEQ ID NO: 333), wherein X_{42} is L or M; X_{43} is S or T; X_{44} is F; X_{45} is P; X_{46} is A or T; X_{47} is H or Y; X_{48} is I or W; and X_{49} is F. Subgenus 3.5: $X_{42}X_{43}X_{44}X_{45}X_{46}X_{47}X_{48}X_{49}$ (SEQ ID NO: 334), wherein X_{42} is G, I, R, or S; X_{43} is H or T; X_{44} is F, L, S, or V; X_{45} is L, P, or R; X_{46} is F, L, or S; X_{47} is A, C, or G; X_{48} is I, M, or V; and X_{49} is F or L. Subgenus 3.6: $X_{42}X_{43}X_{44}X_{45}X_{46}X_{47}X_{48}X_{49}$ (SEQ ID NO: 335), wherein X_{42} is S; X_{43} is T; X_{44} is F or V; X_{45} is L or P; X_{46} is F or L; X_{47} is G; X_{48} is I or M; and X_{49} is F.

TABLE 8D

MMP9 Cleavable Core CM Consensus Sequence 4	
Core CM Consensus 4	Subgenus of Core CM Consensus 4
$X_{52}X_{53}X_{54}X_{55}X_{56}X_{57}X_{58}X_{59}$ (SEQ ID NO: 340), wherein X_{52} is D, G, H, L, N, P, Q, R, S, W, or Y; X_{53} is A, C, D, G, L, R, V, W, or Y; X_{54} is D, H, L, P, Q, R, S, or Y; X_{55} is D, F, H, I, L, M, P, S, or Y; X_{56} is A, C, E, F, G, K, M, R, S, V, or W; X_{57} is A, G, K L, M, N, P, R, S, or T; X_{58} is A, F, G, H, L, P, R, S, or T; and X_{59} is A, G, H, I, N, P, S, T, or Y.	Subgenus 4.1: $X_{52}X_{53}X_{54}X_{55}X_{56}X_{57}X_{58}X_{59}$ (SEQ ID NO: 341), wherein X_{52} is D, G, H, L, P, Q, S or Y; X_{53} is D, W, or Y; X_{54} is H, L, or R; X_{55} is H, L, M, P, or Y; X_{56} is E, F, G, M, R, or W; X_{57} is A, L, M, N, P, or R; X_{58} is G, L, P, R, or S; and X_{59} is G, I, P, S, T, or Y. Subgenus 4.2: $X_{52}X_{53}X_{54}X_{55}X_{56}X_{57}X_{58}X_{59}$ (SEQ ID NO: 342), wherein X_{52} is D or H; X_{53} is W or Y; X_{54} is H or L; X_{55} is H, L, or Y; X_{56} is G or W; X_{57} is P or R; X_{58} is G, L, or P; and X_{59} is G, I, S, or T. Subgenus 4.3: $X_{52}X_{53}X_{54}X_{55}X_{56}X_{57}X_{58}X_{59}$ (SEQ ID NO: 343), wherein X_{52} is H; X_{53} is W; X_{54} is H or L; X_{55} is H, L, or Y; X_{56} is G or W; X_{57} is P; X_{58} is L or P; and X_{59} is G, I, S or T. Subgenus 4.4: $X_{52}X_{53}X_{54}X_{55}X_{56}X_{57}X_{58}X_{59}$ (SEQ ID NO: 344), wherein X_{52} is H; X_{53} is W; X_{54} is H or L; X_{55} is L or Y; X_{56} is G; X_{57} is P; X_{58} is L or P; and X_{59} is G, I, S, or T. Subgenus 4.5: $X_{52}X_{53}X_{54}X_{55}X_{56}X_{57}X_{58}X_{59}$ (SEQ ID NO: 345), wherein X_{52} is H; X_{53} is W; X_{54} is H or L; X_{55} is L or Y; X_{56} is G; X_{57} is P; X_{58} is P; and X_{59} is T. Subgenus 4.6: $X_{52}X_{53}X_{54}X_{55}X_{56}X_{57}X_{58}X_{59}$ (SEQ ID NO: 346), wherein X_{52} is D, G, S, or Y; X_{53} is W; X_{54} is L or P; X_{55} is D or Y; X_{56} is C, E, G, or W; X_{57} is M or P; X_{58} is G, R, or S; and X_{59} is H, I, or Y. Subgenus 4.7: $X_{52}X_{53}X_{54}X_{55}X_{56}X_{57}X_{58}X_{59}$ (SEQ ID NO: 347), wherein X_{52} is D, G, or S; X_{53} is W; X_{54} is L; X_{55} is Y; X_{56} is E or W; X_{57} is M or P; X_{58} is G or S; and X_{59} is I or Y.

TABLE 8E

MMP14 Cleavable Core CM Consensus Sequence 5	
Core CM Consensus 5	Subgenus of Core CM Consensus 5
$X_{62}X_{63}X_{64}X_{65}X_{66}X_{67}X_{68}X_{69}$ (SEQ ID NO: 352), wherein X_{62} is A, I, G, L, M, P, Q, S, T, or V; X_{63} is A, D, L, P, Q, S, T, V, or Y; X_{64} is A, C, E, F, G, H, K, L, P, Q, R, S, or V; X_{65} is D, E, G, S, or V; X_{66} is A, I, L, M, or V; X_{67} is C, E, G, I, K, L, M, N, Q, R, or Y; X_{68} is A, F, H, I, L, M, N, P, R, S, or T; and X_{69} is A, C, G, H, I, L, N,	Subgenus 5.1: $X_{62}X_{63}X_{64}X_{65}X_{66}X_{67}X_{68}X_{69}$ (SEQ ID NO: 353), wherein X_{62} is A, G, I, P, Q, S, T, or V; X_{63} is A, L, Q, S, or V; X_{64} is A, E, L, R, or S; X_{65} is D or G; X_{66} is I or L; X_{67} is E, I, L, M, Q, R, or Y; X_{68} is F, H, L, M, R, or S; and X_{69} is A, G, H, L, N, P, Q, or S. Subgenus 5.2: $X_{62}X_{63}X_{64}X_{65}X_{66}X_{67}X_{68}X_{69}$ (SEQ ID NO: 354), wherein X_{62} is A, I, S or T; X_{63} is L, Q, S, or V; X_{64} is A, L, R, or S; X_{65} is G; X_{66} is I or L; X_{67} is E, L, R, or Y; X_{68} is F, H, L, R, or S; and X_{69} is H, L, P, or S. Subgenus 5.3: $X_{62}X_{63}X_{64}X_{65}X_{66}X_{67}X_{68}X_{69}$ (SEQ ID NO: 355), wherein X_{62} is A, I, S or T; X_{63} is L, S, or V; X_{64} is A, R or S; X_{65} is G; X_{66} is L; X_{67} is E, L or R; X_{68} is F, H, or S; and X_{69} is L, P, or S. Subgenus 5.4: $X_{62}X_{63}X_{64}X_{65}X_{66}X_{67}X_{68}X_{69}$ (SEQ ID NO: 356), wherein X_{62} is A, I, S or T; X_{63} is L, S, or V; X_{64} is R or S; X_{65} is

TABLE 8E-continued

MMP14 Cleavable Core CM Consensus Sequence 5	
Core CM Consensus 5	Subgenus of Core CM Consensus 5
P, Q, R, S, T, V, or W.	<p>G; X₆₆ is L; X₆₇ is L or R; X₆₈ is F, H, or S; and X₆₉ is P or S.</p> <p>Subgenus 5.5: X₆₂X₆₃X₆₄X₆₅X₆₆X₆₇X₆₈X₆₉ (SEQ ID NO: 357), wherein X₆₂ is A, I, S or T; X₆₃ is L, S, or V; X₆₄ is R or S; X₆₅ is G; X₆₆ is L; X₆₇ is L or R; X₆₈ is S; and X₆₉ is P or S.</p> <p>Subgenus 5.6: X₆₂X₆₃X₆₄X₆₅X₆₆X₆₇X₆₈X₆₉ (SEQ ID NO: 358), wherein X₆₂ is T; X₆₃ is L, S, or V; X₆₄ is S; X₆₅ is G; X₆₆ is L; X₆₇ is R; X₆₈ is S; and X₆₉ is P.</p> <p>Subgenus 5.7: X₆₂X₆₃X₆₄X₆₅X₆₆X₆₇X₆₈X₆₉ (SEQ ID NO: 359), wherein X₆₂ is A, G, I, M, P, S, T, or V; X₆₃ is L, Q, S, or V; X₆₄ is A, C, F, K, L, Q, R or S; X₆₅ is D, G, S, or V; X₆₆ is L or M; X₆₇ is G, I, L, M, N, Q, or R; X₆₈ is I, N, P, or S; and X₆₉ is A, H, I, N, Q, or S.</p> <p>Subgenus 5.8: X₆₂X₆₃X₆₄X₆₅X₆₆X₆₇X₆₈X₆₉ (SEQ ID NO: 360), wherein X₆₂ is A, I, or S; X₆₃ is L, Q, S, or V; X₆₄ is L, R or S; X₆₅ is G; X₆₆ is L; X₆₇ is M, or R; X₆₈ is S; and X₆₉ is A, H, N, Q, or S.</p> <p>Subgenus 5.9: X₆₂X₆₃X₆₄X₆₅X₆₆X₆₇X₆₈X₆₉ (SEQ ID NO: 361), wherein X₆₂ is A, I, or S; X₆₃ is L, Q, S, or V; X₆₄ is L, R or S; X₆₅ is G; X₆₆ is L; X₆₇ is L, M, or R; X₆₈ is S; and X₆₉ is A, H, N, Q, or S.</p> <p>Subgenus 5.10: X₆₂X₆₃X₆₄X₆₅X₆₆X₆₇X₆₈X₆₉ (SEQ ID NO: 362), wherein X₆₂ is A or S; X₆₃ is L or V; X₆₄ is L or S; X₆₅ is G; X₆₆ is L; X₆₇ is L or R; X₆₈ is S; and X₆₉ is H, or S.</p> <p>Subgenus 5.11: X₆₂X₆₃X₆₄X₆₅X₆₆X₆₇X₆₈X₆₉ (SEQ ID NO: 363), wherein X₆₂ is A or S; X₆₃ is L or V; X₆₄ is S; X₆₅ is G; X₆₆ is L; X₆₇ is L or R; X₆₈ is S; and X₆₉ is H, or S.</p>

TABLE 8F-1

MMP14 Cleavable Core CM Consensus Sequence 6	
Core CM Consensus 6	Subgenus of Core CM Consensus 6
X ₇₂ X ₇₃ X ₇₄ X ₇₅ X ₇₆ X ₇₇ X ₇₈ X ₇₉ (SEQ ID NO: 371), wherein X ₇₂ is A, C, D, E, F, G, H, I, K, L, M, N, P, Q, R, S, or V; X ₇₃ is A, C, E, F, H, L, N, R, S, or V; X ₇₄ is A, D, E, K, N, P, Q, S, T, or Y; X ₇₅ is A, E, G, H, K, L, N, P, R, S, or T; X ₇₆ is I, K, L, M, N, R, T, V or Y; X ₇₇ is A, D, E, I, K, L, P, Q, R, S, T, V or Y; X ₇₈ is A, C, D, E, G, I, L, M, Q, R, S, T, or V; and X ₇₉ is A, F, G, H, I, L, P, Q, R, S, T, or Y.	Subgenus 6.1: X ₇₂ X ₇₃ X ₇₄ X ₇₅ X ₇₆ X ₇₇ X ₇₈ X ₇₉ (SEQ ID NO: 372), wherein X ₇₂ is A, F, G, H, I, L, M, Q, R, or S; X ₇₃ is A, F, H, L, or N; X ₇₄ is A, E, N, Q, or S; X ₇₅ is A, E, K, N, S, or T; X ₇₆ is L or M; X ₇₇ is A, I, K, L, P, R, or V; X ₇₈ is A, D, I, L, M, R, T, or V; and X ₇₉ is A, F, G, H, I, L, P, Q, R, or S. Subgenus 6.2: X ₇₂ X ₇₃ X ₇₄ X ₇₅ X ₇₆ X ₇₇ X ₇₈ X ₇₉ (SEQ ID NO: 373), wherein X ₇₂ is G, L or R, or S; X ₇₃ is A or L; X ₇₄ is A, E, N, Q, or S; X ₇₅ is A, E, N, S, or T; X ₇₆ is L or M; X ₇₇ is L or R; X ₇₈ is A, L, or T; and X ₇₉ is F, G, L, R, or S. Subgenus 6.3: X ₇₂ X ₇₃ X ₇₄ X ₇₅ X ₇₆ X ₇₇ X ₇₈ X ₇₉ (SEQ ID NO: 374), wherein X ₇₂ is L; X ₇₃ is A or L; X ₇₄ is E, N, Q, or S; X ₇₅ is A or S; X ₇₆ is L or M; X ₇₇ is R; X ₇₈ is A or T; and X ₇₉ is F, L, or R. Subgenus 6.4: X ₇₂ X ₇₃ X ₇₄ X ₇₅ X ₇₆ X ₇₇ X ₇₈ X ₇₉ (SEQ ID NO: 375), wherein X ₇₂ is L; X ₇₃ is A or L; X ₇₄ is E, N, Q, or S; X ₇₅ is A or S; X ₇₆ is L or M; X ₇₇ is R; X ₇₈ is A; and X ₇₉ is L or R.

TABLE 8F-2

MMP14 Cleavable Core CM Consensus Sequence 6A	
Core CM Consensus 6A	Subgenus of Core CM Consensus 6A
X ₇₂ X ₇₃ X ₇₄ X ₇₅ X ₇₆ X ₇₇ X ₇₈ (SEQ ID NO: 485), wherein X ₇₂ is A, C, D, E, F, G, H, I, K, L, M, N, P, Q, R, S, or V; X ₇₃ is A, C, E, F, H, L, N, R, S, or V; X ₇₄ is A, D, E, K, N, P, Q, S, T, or Y; X ₇₅ is A, E, G, H, K, L, N, P, R, S, or T; X ₇₆ is I, K, L, M, N, R, T, V or Y;	Subgenus 6A.1: X ₇₂ X ₇₃ X ₇₄ X ₇₅ X ₇₆ X ₇₇ X ₇₈ (SEQ ID NO: 376), wherein X ₇₂ is A, E, L, N, P, or Q; X ₇₃ is F, H, L, N, or S; X ₇₄ is Q or Y; X ₇₅ is A; X ₇₆ is L, T, V or Y; X ₇₇ is D, E, P, Q, or R; and X ₇₈ is A, C, G, I, M, R, S, or T. Subgenus 6A.2: X ₇₂ X ₇₃ X ₇₄ X ₇₅ X ₇₆ X ₇₇ X ₇₈ (SEQ ID NO: 377), wherein X ₇₂ is A, E, L, or Q; X ₇₃ is F, H, or N; X ₇₄ is Q; X ₇₅ is A; X ₇₆ is L or T; X ₇₇ is Q or R; and X ₇₈ is I or M.

TABLE 8F-2-continued

MMP14 Cleavable Core CM Consensus Sequence 6A	
Core CM Consensus 6A	Subgenus of Core CM Consensus 6A
X ₇₇ is A, D, E, I, K, L, P, Q, R, S, T, V, or Y; and X ₇₈ is A, C, D, E, G, I, L, M, Q, R, S, Q; X ₇₉ is A, C, D, E, G, I, L, M, Q, R, S, Q; X ₇₅ is A; X ₇₆ is L; X ₇₇ is R; and X ₇₈ is M. T, or V.	Subgenus 6A.3: X ₇₂ X ₇₃ X ₇₄ X ₇₅ X ₇₆ X ₇₇ X ₇₈ (SEQ ID NO: 378), wherein X ₇₂ is A; X ₇₃ is F, H, or N; X ₇₄ is V; X ₇₅ is A; X ₇₆ is L; X ₇₇ is R; and X ₇₈ is M.

TABLE 8G

MMP14 Cleavable Core CM Consensus Sequence 7	
Core CM Consensus 7	Subgenus of Core CM Consensus 7
X ₈₂ X ₈₃ X ₈₄ X ₈₅ X ₈₆ X ₈₇ X ₈₈ X ₈₉ (SEQ ID NO: 394), wherein X ₈₂ is A, F, L, Q, S, T, or V; X ₈₃ is A, E, G, H, K, Q, R, V, or Y; X ₈₄ is A, G, I, K, L, M, N, S, T, or V; X ₈₅ is A, D, F, G, I, L, N, P, R, S, T, or V; X ₈₆ is A, P, or R; X ₈₇ is A, D, G, L, M, P, R, S, T, V, W, or Y; X ₈₈ is A, C, E, F, H, I, L, N, R, S, T, W, or Y; and X ₈₉ is A, F, G, I, L, M, R, S, T, or V.	Subgenus 7.1: X ₈₂ X ₈₃ X ₈₄ X ₈₅ X ₈₆ X ₈₇ X ₈₈ X ₈₉ (SEQ ID NO: 395), wherein X ₈₂ is L; X ₈₃ is H, K, Q, R, or V; X ₈₄ is A, L, M, S, T, or V; X ₈₅ is A, I, L, S, or V; X ₈₆ is P; X ₈₇ is A, F, G, L, S, or V; X ₈₈ is I, R, or W; and X ₈₉ is A, F, G, L, S, or V. Subgenus 7.2: X ₈₂ X ₈₃ X ₈₄ X ₈₅ X ₈₆ X ₈₇ X ₈₈ X ₈₉ (SEQ ID NO: 396), wherein X ₈₂ is L; X ₈₃ is H, K, R, or V; X ₈₄ is A, L, or V; X ₈₅ is A, I, or L; X ₈₆ is P; X ₈₇ is G, R, or V; X ₈₈ is T or W; and X ₈₉ is A, F, L, or S. Subgenus 7.3: X ₈₂ X ₈₃ X ₈₄ X ₈₅ X ₈₆ X ₈₇ X ₈₈ X ₈₉ (SEQ ID NO: 397), wherein X ₈₂ is L; X ₈₃ is K, R, or V; X ₈₄ is A; X ₈₅ is A or L; X ₈₆ is P; X ₈₇ is G, R, or V; X ₈₈ is W; and X ₈₉ is A or L. Subgenus 7.4: X ₈₂ X ₈₃ X ₈₄ X ₈₅ X ₈₆ X ₈₇ X ₈₈ X ₈₉ (SEQ ID NO: 398), wherein X ₈₂ is A, F, L, Q, or S; X ₈₃ is A, E, G, H, K, Q, or V; X ₈₄ is A, G, K, S, or V; X ₈₅ is A, I, L, P, or T; X ₈₆ is A, P, or R; X ₈₇ is A, L, M, R, V, or Y; X ₈₈ is C, H, R, T, or W; and X ₈₉ is A, F, L, R, S, or T. Subgenus 7.5: X ₈₂ X ₈₃ X ₈₄ X ₈₅ X ₈₆ X ₈₇ X ₈₈ X ₈₉ (SEQ ID NO: 399), wherein X ₈₂ is F or L; X ₈₃ is G, K, Q, or V; X ₈₄ is A, G, S, or V; X ₈₅ is A, I, or L; X ₈₆ is P; X ₈₇ is A, R, or V; X ₈₈ is R or W; and X ₈₉ is A, F, L, or R. Subgenus 7.6: X ₈₂ X ₈₃ X ₈₄ X ₈₅ X ₈₆ X ₈₇ X ₈₈ X ₈₉ (SEQ ID NO: 400), wherein X ₈₂ is L; X ₈₃ is K or V; X ₈₄ is A or S; X ₈₅ is A, I, or L; X ₈₆ is P; X ₈₇ is A, R, or V; X ₈₈ is W; and X ₈₉ is A or F. Subgenus 7.7: X ₈₂ X ₈₃ X ₈₄ X ₈₅ X ₈₆ X ₈₇ X ₈₈ X ₈₉ (SEQ ID NO: 401), wherein X ₈₂ is L; X ₈₃ is K or V; X ₈₄ is A; X ₈₅ is A or I; X ₈₆ is P; X ₈₇ is R or V; X ₈₈ is W; and X ₈₉ is A or F.

TABLE 8H-1

MMP14 Cleavable Core CM Consensus Sequence 8	
Core CM Consensus 8	Subgenus of Core CM Consensus 8
X ₉₂ X ₉₃ X ₉₄ X ₉₅ X ₉₆ X ₉₇ X ₉₈ (SEQ ID NO: 410), wherein X ₉₂ is A, D, F, G, H, I, L, M, N, P, Q, R, S, T, V, W; X ₉₃ is A, P, R, or T; X ₉₄ is A, E, F, G, H, I, K, L, N, P, Q, R, S, T, or V; X ₉₅ is A, D, E, G, H, K, M, N, P, R, S, or T; X ₉₆ is C, F, H, I, L, M, P, R, S, or T; X ₉₇ is A, F, L, M, P, Q, R, S, T, V, or Y; and X ₉₈ is A, D, E, G, H, K, M, N, P, R, S, or T; X ₉₉ is F, L, or S; X ₁₀₀ is P; X ₁₀₁ is A, E, H, K, N, Q, R, S, T, or V; X ₁₀₂ is A, G, H, N, P, or S; X ₁₀₃ is I, L, M, or V; X ₁₀₄ is F, I, L, R, T, V, or Y; and X ₁₀₅ is A, F, L, R, T, V, or Y; and X ₁₀₆ is C, F, H, I, L, M, P, R, S, or T; X ₁₀₇ is A, F, G, I, L, R, S, T, V, or Y; and X ₁₀₈ is A, F, H, K, N, Q, R, or S; X ₁₀₉ is A, G, H, or S; X ₁₁₀ is I, L, M, or V; X ₁₁₁ is F, L, R, S, T, V, or Y; and X ₁₁₂ is F, L, T, or V. Subgenus 8.2: X ₉₂ X ₉₃ X ₉₄ X ₉₅ X ₉₆ X ₉₇ X ₉₈ (SEQ ID NO: 412), wherein X ₉₂ is F, G, L, S, T, or V; X ₉₃ is P; X ₉₄ is A, E, H, K, N, Q, R, S, T, or V; X ₉₅ is A, G, H, N, P, or S; X ₉₆ is I, L, M, or V; X ₉₇ is F, I, L, R, S, T, V, or Y; and X ₉₈ is A, F, L, R, T, V, or Y. Subgenus 8.3: X ₉₂ X ₉₃ X ₉₄ X ₉₅ X ₉₆ X ₉₇ X ₉₈ (SEQ ID NO: 413), wherein X ₉₂ is F, L, or S; X ₉₃ is P; X ₉₄ is A, K, Q, R, or S; X ₉₅ is A, G, H, or S; X ₉₆ is I, L, M, or V; X ₉₇ is F, L, R, S, T, V, or Y; and X ₉₈ is F, L, T, or V. Subgenus 8.4: X ₉₂ X ₉₃ X ₉₄ X ₉₅ X ₉₆ X ₉₇ X ₉₈ (SEQ ID NO: 414), wherein X ₉₂ is F, L, or S; X ₉₃ is P; X ₉₄ is A, E, H, K, N, Q, R, S, T, or V; X ₉₅ is A, G, H, N, P, or S; X ₉₆ is I, L, M, or V; X ₉₇ is F, I, L, R, T, V, or Y; and X ₉₈ is A, F, L, R, T, V, or Y. Subgenus 8.5: X ₉₂ X ₉₃ X ₉₄ X ₉₅ X ₉₆ X ₉₇ X ₉₈ (SEQ ID NO: 415), wherein X ₉₂ is F, L, or S; X ₉₃ is P; X ₉₄ is A, Q or S; X ₉₅ is G; X ₉₆ is I, L, or M; X ₉₇ is L or V; and X ₉₈ is L. Subgenus 8.6: X ₉₂ X ₉₃ X ₉₄ X ₉₅ X ₉₆ X ₉₇ X ₉₈ (SEQ ID NO: 416), wherein X ₉₂ is F, L, or S; X ₉₃ is P; X ₉₄ is A or S; X ₉₅ is G; X ₉₆ is I, L, or M; X ₉₇ is L or V; and X ₉₈ is L. Subgenus 8.7: X ₉₂ X ₉₃ X ₉₄ X ₉₅ X ₉₆ X ₉₇ X ₉₈ (SEQ ID NO: 417), wherein X ₉₂ is F, G, L, M, P, S, V, or W; X ₉₃ is P; X ₉₄ is A, N, Q, or S; X ₉₅ is	

TABLE 8H-1-continued

MMP14 Cleavable Core CM Consensus Sequence 8	
Core CM Consensus 8	Subgenus of Core CM Consensus 8
	<p>A, D, G, H, M, N, P, or S; X₉₆ is F, I, L, M, or V; X₉₇ is A, I, L, M, S, or V; and X₉₈ is A, G, I, L, M, N, P, Q, R, S, T, or Y.</p> <p>Subgenus 8.8: X₉₂X₉₃X₉₄X₉₅X₉₆X₉₇X₉₈ (SEQ ID NO: 418), wherein X₉₂ is L, S, or V; X₉₃ is P; X₉₄ is A, N, Q, or S; X₉₅ is H, N, P, or S; X₉₆ is F, I, L, or M; X₉₇ is I, L, S, or V; and X₉₈ is A, L, or Q.</p> <p>Subgenus 8.9: X₉₂X₉₃X₉₄X₉₅X₉₆X₉₇X₉₈ (SEQ ID NO: 419), wherein X₉₂ is L; X₉₃ is P; X₉₄ is A, N, Q, or S; X₉₅ is H; X₉₆ is I or L; X₉₇ is V; and X₉₈ is L.</p>

TABLE 8H-2

MMP14 Cleavable Extended Core CM Consensus Sequence 8	
Extended Core CM Consensus 8A	Subgenus of Extended Core CM Consensus 8A
<p>X₉₂X₉₃X₉₄X₉₅X₉₆X₉₇X₉₈X₉₉ (SEQ ID NO: 486), wherein X₉₂ is A, D, F, G, H, I, L, M, N, P, Q, R, S, T, V, or W; X₉₃ is A, P, R, or T; X₉₄ is A, E, F, G, H, I, K, L, N, P, Q, R, S, T, or V; X₉₅ is A, D, E, G, H, K, M, N, P, R, S, or T; X₉₆ is C, F, H, I, L, M, P, R, S, V, W, or Y; X₉₇ is A, C, F, G, H, I, K, L, M, R, S, T, V, W, or Y; X₉₈ is A, D, E, F, G, H, I, K, L, M, N, P, Q, R, S, T, V, or Y; and X₉₉ is A, D, E, F, G, H, I, K, L, M, N, P, Q, R, S, T, V, W, or Y.</p>	<p>Subgenus 8A.1: X₉₂X₉₃X₉₄X₉₅X₉₆X₉₇X₉₈X₉₉ (SEQ ID NO: 487), wherein X₉₂ is A, F, G, I, L, M, N, S, T, V, or W; X₉₃ is P; X₉₄ is A, E, F, H, I, K, N, P, Q, R, S, T, or V; X₉₅ is A, D, E, G, H, N, P, or S; X₉₆ is C, F, I, L, M, R, S, or V; X₉₇ is C, F, G, I, L, R, S, T, V, or Y; X₉₈ is A, F, L, M, P, Q, R, S, T, V, or Y; and X₉₉ is A, D, E, G, H, I, L, N, P, Q, R, S, T, V, W, or Y.</p> <p>Subgenus 8A.2: X₉₂X₉₃X₉₄X₉₅X₉₆X₉₇X₉₈X₉₉ (SEQ ID NO: 488), wherein X₉₂ is F, G, L, S, T, or V; X₉₃ is P; X₉₄ is A, E, H, K, N, Q, R, S, T, or V; X₉₅ is A, G, H, N, P, or S; X₉₆ is I, L, M, or V; X₉₇ is F, I, L, R, S, T, V, or Y; X₉₈ is A, F, L, R, T, V, or Y; and X₉₉ is A, D, G, L, P, R, S, T, V, or Y.</p> <p>Subgenus 8A.3: X₉₂X₉₃X₉₄X₉₅X₉₆X₉₇X₉₈X₉₉ (SEQ ID NO: 489), wherein X₉₂ is F, L, or S; X₉₃ is P; X₉₄ is A, K, Q, R, or S; X₉₅ is A, G, H, or S; X₉₆ is I, L, M, or V; X₉₇ is F, L, R, S, T, V, or Y; X₉₈ is F, L, T, or V; and X₉₉ is A, D, G, L, R, T, or V.</p> <p>Subgenus 8A.4: X₉₂X₉₃X₉₄X₉₅X₉₆X₉₇X₉₈X₉₉ (SEQ ID NO: 490), wherein X₉₂ is F, L, or S; X₉₃ is P; X₉₄ is A, Q, or S; X₉₅ is G or S; X₉₆ is I, L, or M; X₉₇ is L, S, or V; X₉₈ is F, L, or T; and X₉₉ is A, R, or T.</p> <p>Subgenus 8A.5: X₉₂X₉₃X₉₄X₉₅X₉₆X₉₇X₉₈X₉₉ (SEQ ID NO: 491), wherein X₉₂ is F, L, or S; X₉₃ is P; X₉₄ is A, Q or S; X₉₅ is G; X₉₆ is I, L, or M; X₉₇ is L or V; X₉₈ is L; and X₉₉ is R.</p> <p>Subgenus 8A.6: X₉₂X₉₃X₉₄X₉₅X₉₆X₉₇X₉₈X₉₉ (SEQ ID NO: 492), wherein X₉₂ is F, L, or S; X₉₃ is P; X₉₄ is A or S; X₉₅ is G; X₉₆ is I, L, or M; X₉₇ is L or V; X₉₈ is L; and X₉₉ is R.</p> <p>Subgenus 8A.7: X₉₂X₉₃X₉₄X₉₅X₉₆X₉₇X₉₈X₉₉ (SEQ ID NO: 493), wherein X₉₂ is F, G, L, M, P, S, V, or W; X₉₃ is P; X₉₄ is A, N, Q, or S; X₉₅ is A, D, G, H, M, N, P, or S; X₉₆ is F, I, L, M, or V; X₉₇ is A, I, L, M, S, or V; X₉₈ is A, G, I, L, M, N, P, Q, R, S, T, or Y; and X₉₉ is A, F, H, I, L, Q, R, T, V, W, or Y.</p> <p>Subgenus 8A.8: X₉₂X₉₃X₉₄X₉₅X₉₆X₉₇X₉₈X₉₉ (SEQ ID NO: 494), wherein X₉₂ is L, S, or V; X₉₃ is P; X₉₄ is A, N, Q, or S; X₉₅ is H, N, P, or S; X₉₆ is F, I, L, or M; X₉₇ is I, L, S, or V; X₉₈ is A, L, or Q; and X₉₉ is L, T, V, or Y.</p> <p>Subgenus 8A.9: X₉₂X₉₃X₉₄X₉₅X₉₆X₉₇X₉₈X₉₉ (SEQ ID NO: 495), wherein X₉₂ is L; X₉₃ is P; X₉₄ is A, N, Q, or S; X₉₅ is H; X₉₆ is I, or L; X₉₇ is V; X₉₈ is L; and X₉₉ is L or V.</p>

TABLE 8I

MMP14 Cleavable Core CM Consensus Sequence 9	
Core CM Consensus 9	Subgenus of Core CM Consensus 9
<p>X₁₀₂X₁₀₃X₁₀₄X₁₀₅X₁₀₆X₁₀₇X₁₀₈X₁₀₉ (SEQ ID NO: 425), wherein X₁₀₂ is A, D, F, G, H, I, L, M, P, R, S, T, or V; X₁₀₃ is A, D, E, L, M, P, Q, R, S, T, V, or Y; X₁₀₄ is A, G, H, L, N, P, R, S, T, or V; and X₁₀₅ is A, G, H, L, M, N, P, Q, R, S, T, V, or Y.</p>	<p>Subgenus 9.1: X₁₀₂X₁₀₃X₁₀₄X₁₀₅X₁₀₆X₁₀₇X₁₀₈X₁₀₉ (SEQ ID NO: 426), wherein X₁₀₂ is A, D, F, G, H, I, R, or S; X₁₀₃ is D, E, L, M, P, R, S, T, V, or Y; X₁₀₄ is A, H, P, or S; X₁₀₅ is A, D, E, H, L, M, N, R, T, or V; X₁₀₆ is A, G, or R; X₁₀₇ is F, L, M, S, V, or W; X₁₀₈ is A, E, H, L, M, R, S, or V; and X₁₀₉ is A, G, L, P, R, S, or V.</p> <p>Subgenus 9.2: X₁₀₂X₁₀₃X₁₀₄X₁₀₅X₁₀₆X₁₀₇X₁₀₈X₁₀₉ (SEQ ID NO: 427), wherein X₁₀₂ is F, G, I, R, or S; X₁₀₃ is L, P, R,</p>

TABLE 8I-continued

MMP14 Cleavable Core CM Consensus Sequence 9

Core CM Consensus 9	Subgenus of Core CM Consensus 9
X_{105} is A, D, E, H, L, M, N, P, Q, R, S, T, or V;	or V; X_{104} is A or H; X_{105} is A, D, or R; X_{106} is A or G; X_{107} is L or V; X_{108} is H, L, M, R, S, or V; and X_{109} is A, L, S, or V.
X_{108} is A, G, R, S, or T;	Subgenus 9.3: $X_{102}X_{103}X_{104}X_{105}X_{106}X_{107}X_{108}X_{109}$ (SEQ ID NO: 428), wherein X_{102} is G, R or S; X_{103} is R or V; X_{104} is A or H; X_{105} is A, D, or R; X_{106} is A or G; X_{107} is L or V; X_{108} is H or R; and X_{109} is A, L, S, or V.
X_{107} is C, F, L, M, S, V, W, or Y;	Subgenus 9.4: $X_{102}X_{103}X_{104}X_{105}X_{106}X_{107}X_{108}X_{109}$ (SEQ ID NO: 429), wherein X_{102} is R; X_{103} is R; X_{104} is A or H; X_{105} is A or D; X_{106} is G; X_{107} is L or V; X_{108} is R; and X_{109} is A, S, or V.
X_{108} is A, E, F, G, H, I, L, M, N, Q, R, S, V, W, or Y; and	Subgenus 9.5: $X_{102}X_{103}X_{104}X_{105}X_{106}X_{107}X_{108}X_{109}$ (SEQ ID NO: 430), wherein X_{102} is D, F, G, I, L, R, S, or T; X_{103} is E, L, M, R, S, T, or V; X_{104} is H or N; X_{105} is A, D, L, M, R, or T; X_{106} is A, G, R, or T; X_{107} is C, L, M, S, V, or W; X_{108} is A, E, F, G, L, R, S, or W; and X_{109} is A, G, L, P, R, S, or V.
X_{109} is A, E, G, L, P, R, S, or V.	Subgenus 9.6: $X_{102}X_{103}X_{104}X_{105}X_{106}X_{107}X_{108}X_{109}$ (SEQ ID NO: 431), wherein X_{102} is F, I, R, or S; X_{103} is E, L, R, or V; X_{104} is H; X_{105} is D, M, R, or T; X_{106} is A or G; X_{107} is L, M, S, or V; X_{108} is E, R, or S; and X_{109} is A, P, S, or V.
	Subgenus 9.7: $X_{102}X_{103}X_{104}X_{105}X_{106}X_{107}X_{108}X_{109}$ (SEQ ID NO: 432), wherein X_{102} is I or R; X_{103} is E, R, or V; X_{104} is H; X_{105} is D, M, R, or T; X_{106} is A or G; X_{107} is L or V; X_{108} is R or S; and X_{109} is A, P, S, or V.
	Subgenus 9.8: $X_{102}X_{103}X_{104}X_{105}X_{106}X_{107}X_{108}X_{109}$ (SEQ ID NO: 433), wherein X_{102} is I or R; X_{103} is R; X_{104} is H; X_{105} is D; X_{106} is A or G; X_{107} is L or V; X_{108} is R or S; and X_{109} is A or S.

TABLE 8J

MMP14 Cleavable Core CM Consensus Sequence 10

Core CM Consensus 10	Subgenus of Core CM Consensus 10
$X_{112}X_{113}X_{114}X_{115}X_{116}X_{117}X_{118}X_{119}$ (SEQ ID NO: 436), wherein	Subgenus 10.1: $X_{112}X_{113}X_{114}X_{115}X_{116}X_{117}X_{118}X_{119}$ (SEQ ID NO: 437), wherein X_{112} is A, I, P, S, T, V, or Y; X_{113} is A, D, G, L, M, Q, R, S, V, or Y; X_{114} is A, H, K, L, N, S, or T; X_{115} is G, H, I, L, S, or V; X_{116} is I, L, or V; X_{117} is A, F, G, K, R, S, or W; X_{118} is D, H, L, M, N, Q, R, or V; and X_{119} is A, I, L, or V.
X_{112} is A, D, G, H, I, L, N, P, R, S, T, V, W, or Y;	Subgenus 10.2: $X_{112}X_{113}X_{114}X_{115}X_{116}X_{117}X_{118}X_{119}$ (SEQ ID NO: 438), wherein X_{112} is A, I, T, or V; X_{113} is A, L, M, Q, R, V, or Y; X_{114} is A, N, S, or T; X_{115} is G, L, S, or V; X_{116} is L or V; X_{117} is A, F, G, K, or S; X_{118} is M, N, Q, R, or V; and X_{119} is I, L, or V.
X_{113} is A, D, G, H, L, M, N, P, Q, R, S, V, or Y;	Subgenus 10.3: $X_{112}X_{113}X_{114}X_{115}X_{116}X_{117}X_{118}X_{119}$ (SEQ ID NO: 439), wherein X_{112} is A, I, T, or V; X_{113} is M, Q, or Y; X_{114} is A, N, or S; X_{115} is G, L, S, or V; X_{116} is L or V; X_{117} is A, F, G, or S; X_{118} is M, N, Q, or R; and X_{119} is I, L, or V.
X_{114} is A, H, K, L, N, P, Q, R, S, T, or V;	Subgenus 10.4: $X_{112}X_{113}X_{114}X_{115}X_{116}X_{117}X_{118}X_{119}$ (SEQ ID NO: 440), wherein X_{112} is A, I, or V; X_{113} is Y; X_{114} is N or S; X_{115} is G, L, or V; X_{116} is L; X_{117} is A, G, or S; X_{118} is M, Q, or R; and X_{119} is L or V.
X_{115} is A, D, F, G, H, I, L, P, R, S, V, or Y;	Subgenus 10.5: $X_{112}X_{113}X_{114}X_{115}X_{116}X_{117}X_{118}X_{119}$ (SEQ ID NO: 441), wherein X_{112} is A, I, or V; X_{113} is Y; X_{114} is N or S; X_{115} is G, L, or V; X_{116} is L; X_{117} is G or S; X_{118} is M or R; and X_{119} is L or V.
X_{116} is C, F, I, L, P, V, or Y;	Subgenus 10.6: $X_{112}X_{113}X_{114}X_{115}X_{116}X_{117}X_{118}X_{119}$ (SEQ ID NO: 442), wherein X_{112} is A, I, or V; X_{113} is Y; X_{114} is N or S; X_{115} is G, L, or V; X_{116} is L; X_{117} is S; X_{118} is M or R; and X_{119} is L or V.
X_{117} is A, D, E, F, G, I, K, M, N, R, S, T, V, or W;	Subgenus 10.7: $X_{112}X_{113}X_{114}X_{115}X_{116}X_{117}X_{118}X_{119}$ (SEQ ID NO: 443), wherein X_{112} is A; X_{113} is Y; X_{114} is N or S; X_{115} is G or L; X_{116} is L; X_{117} is S; X_{118} is R; and X_{119} is L or V.
X_{118} is A, D, E, F, H, K, L, M, N, Q, R, V, or Y; and	Subgenus 10.8: $X_{112}X_{113}X_{114}X_{115}X_{116}X_{117}X_{118}X_{119}$ (SEQ ID NO: 444), wherein X_{112} is A, D, G, I, L, N, P, S, T, V, W, or Y; X_{113} is A, D, G, L, M, Q, S, or V; X_{114} is H, K, N,
X_{119} is A, F, I, L, M, or V.	

TABLE 8J-continued

MMP14 Cleavable Core CM Consensus Sequence 10	
Core CM Consensus 10	Subgenus of Core CM Consensus 10
	P, Q, R, S, or T; X ₁₁₅ is H, I, L, R, or V; X ₁₁₆ is I, L, P, or V; X ₁₁₇ is A, D, E, G, I, K, M, N, S, or T; X ₁₁₈ is D, F, L, M, Q, R, or V; and X ₁₁₉ is A, F, I, L, or V.
	Subgenus 10.9: X ₁₁₂ X ₁₁₃ X ₁₁₄ X ₁₁₅ X ₁₁₆ X ₁₁₇ X ₁₁₈ X ₁₁₉ (SEQ ID NO: 445), wherein X ₁₁₂ is A, I, T, or V; X ₁₁₃ is A, D, G, L, M, Q, S, or V; X ₁₁₄ is H, K, N, S, or T; X ₁₁₅ is H, I, L, or V; X ₁₁₆ is L; X ₁₁₇ is A, G, K, or S; X ₁₁₈ is L, M, Q, R, or V; and X ₁₁₉ is A, L, or V.
	Subgenus 10.10: X ₁₁₂ X ₁₁₃ X ₁₁₄ X ₁₁₅ X ₁₁₆ X ₁₁₇ X ₁₁₈ X ₁₁₉ (SEQ ID NO: 446), wherein X ₁₁₂ is A or I; X ₁₁₃ is A, L, or Q; X ₁₁₄ is N, S, or T; X ₁₁₅ is L or V; X ₁₁₆ is L; X ₁₁₇ is A, G, K, or S; X ₁₁₈ is M, R, or V; and X ₁₁₉ is L or V.
	Subgenus 10.11: X ₁₁₂ X ₁₁₃ X ₁₁₄ X ₁₁₅ X ₁₁₆ X ₁₁₇ X ₁₁₈ X ₁₁₉ (SEQ ID NO: 447), wherein X ₁₁₂ is A or I; X ₁₁₃ is A, L, or Q; X ₁₁₄ is N or S; X ₁₁₅ is L or V; X ₁₁₆ is L; X ₁₁₇ is A or S; X ₁₁₈ is M or R; and X ₁₁₉ is L or V.
	Subgenus 10.12: X ₁₁₂ X ₁₁₃ X ₁₁₄ X ₁₁₅ X ₁₁₆ X ₁₁₇ X ₁₁₈ X ₁₁₉ (SEQ ID NO: 448), wherein X ₁₁₂ is I; X ₁₁₃ is A, L, or Q; X ₁₁₄ is N; X ₁₁₅ is L or V; X ₁₁₆ is L; X ₁₁₇ is A or S; X ₁₁₈ is M or R; and X ₁₁₉ is L or V.
	Subgenus 10.13: X ₁₁₂ X ₁₁₃ X ₁₁₄ X ₁₁₅ X ₁₁₆ X ₁₁₇ X ₁₁₈ X ₁₁₉ (SEQ ID NO: 449), wherein X ₁₁₂ is I; X ₁₁₃ is A, L, or Q; X ₁₁₄ is N; X ₁₁₅ is L or V; X ₁₁₆ is L; X ₁₁₇ is S; X ₁₁₈ is M; and X ₁₁₉ is L or V.

TABLE 8K

MMP14 Cleavable Core CM Consensus Sequence 11	
Core CM Consensus 11	Subgenus of Core CM Consensus 11
X ₁₂₂ X ₁₂₃ X ₁₂₄ X ₁₂₅ X ₁₂₆ X ₁₂₇ X ₁₂₈ X ₁₂₉ (SEQ ID NO: 453), wherein X ₁₂₂ is A, G, H, L, P, R, S, or V; X ₁₂₃ is A, G, R, S, T or V; X ₁₂₄ is A, G, P, R, S, or T; X ₁₂₅ is H, I, L, P, R, or V; X ₁₂₆ is L or W; X ₁₂₇ is F, H, L, M, Q, S, V, or Y; X ₁₂₈ is A, D, E, I, K, P, R, S, T, or V; and X ₁₂₉ is A, E, F, G, H, I, L, N, P, Q, R, or V.	Subgenus 11.1: X ₁₂₂ X ₁₂₃ X ₁₂₄ X ₁₂₅ X ₁₂₆ X ₁₂₇ X ₁₂₈ X ₁₂₉ (SEQ ID NO: 454), wherein X ₁₂₂ is A, G, P, R, or S; X ₁₂₃ is A, R, or S; X ₁₂₄ is G, P, S, or T; X ₁₂₅ is L or V; X ₁₂₆ is W; X ₁₂₇ is L, S, V, or Y; X ₁₂₈ is D, E, P, or T; and X ₁₂₉ is P, Q or V.
	Subgenus 11.2: X ₁₂₂ X ₁₂₃ X ₁₂₄ X ₁₂₅ X ₁₂₆ X ₁₂₇ X ₁₂₈ X ₁₂₉ (SEQ ID NO: 455), wherein X ₁₂₂ is G, P, R, or S; X ₁₂₃ is A or R; X ₁₂₄ is G, P, or S; X ₁₂₅ is L or V; X ₁₂₆ is W; X ₁₂₇ is L or Y; X ₁₂₈ is E or T; and X ₁₂₉ is Q.
	Subgenus 11.3: X ₁₂₂ X ₁₂₃ X ₁₂₄ X ₁₂₅ X ₁₂₆ X ₁₂₇ X ₁₂₈ X ₁₂₉ (SEQ ID NO: 456), wherein X ₁₂₂ is P; X ₁₂₃ is A; X ₁₂₄ is P or S; X ₁₂₅ is L or V; X ₁₂₆ is W; X ₁₂₇ is Y; X ₁₂₈ is T; and X ₁₂₉ is Q.

TABLE 8L

MMP14 Cleavable Core CM Consensus Sequence 12	
Core CM Consensus 12	Subgenus of Core CM Consensus 12
X ₂ X ₃ X ₄ X ₅ X ₆ X ₇ X ₈ X ₉ (SEQ ID NO: 458), wherein X ₂ is A, D, E, F, G, H, I, L, M, N, P, Q, R, S, T, V, or Y; X ₃ is A, E, F, G, H, I, K, L, M, P, Q, R, S, T, V, W, or Y; X ₄ is A, E, G, H, K, N, P, R, S, T, V, or Y; X ₅ is A, G, H, I, L, N, P, R, S, T, or V; X ₆ is I, L, M, Q, T, V, W, or Y; X ₇ is A, D, G, H, K, L, N, P, Q, R, S, T, or V; X ₈ is A, D, E, F, G, I, L, M, P, Q, R, S, T, or V; and X ₉ is A, E, G, H, I, K, L, P, Q, R, S, T, or V.	Subgenus 12.1: X ₂ X ₃ X ₄ X ₅ X ₆ X ₇ X ₈ X ₉ (SEQ ID NO: 459), wherein X ₂ is A, G, L, P, or S; X ₃ is A, E, G, H, L, P, Q, S, T, or V; X ₄ is G, N, R, or S; X ₅ is L, P, or S; X ₆ is I or L; X ₇ is A, G, N, Q, R, or S; X ₈ is D, F, G, I, L, M, P, S, or V; and X ₉ is F, G, L, P, Q, R, or S.
	Subgenus 12.2: X ₂ X ₃ X ₄ X ₅ X ₆ X ₇ X ₈ X ₉ (SEQ ID NO: 460), wherein X ₂ is A, P, or S; X ₃ is L or V; X ₄ is G, N, R, or S; X ₅ is L, P, or S; X ₆ is L; X ₇ is A, G, R, or S; X ₈ is L, P, or V; and X ₉ is F, L, P, or S.
	Subgenus 12.3: X ₂ X ₃ X ₄ X ₅ X ₆ X ₇ X ₈ X ₉ (SEQ ID NO: 461), wherein X ₂ is A, P, or S; X ₃ is L, S, or V; X ₄ is G, N, R, or S; X ₅ is L, P, or S; X ₆ is L; X ₇ is A, G, R, or S; X ₈ is L or P; and X ₉ is F, P, or S.
	Subgenus 12.4: X ₂ X ₃ X ₄ X ₅ X ₆ X ₇ X ₈ X ₉ (SEQ ID NO: 462), wherein X ₂ is A, P, or S; X ₃ is L or V; X ₄ is G, N, or S; X ₅ is L or S; X ₆ is L; X ₇ is A, G, R, or S; X ₈ is L or P; and X ₉ is P or S.
	Subgenus 12.5: X ₂ X ₃ X ₄ X ₅ X ₆ X ₇ X ₈ X ₉ (SEQ ID NO: 463), wherein X ₂ is A or S; X ₃ is L; X ₄ is G, N, or S; X ₅ is L or S; X ₆ is L; X ₇ is R or S; X ₈ is L; and X ₉ is P.
	Subgenus 12.6: X ₂ X ₃ X ₄ X ₅ X ₆ X ₇ X ₈ X ₉ (SEQ ID NO: 464), wherein X ₂ is A, E, G, H, I, L, M, P, or S; X ₃ is A, E, G, H, I, K, L, P, Q, R, S, T, or V.

TABLE 8L-continued

MMP14 Cleavable Core CM Consensus Sequence 12	
Core CM Consensus 12	Subgenus of Core CM Consensus 12
K, L, M, P, Q, R, S, V, W, or Y; and X ₉ is A, F, G, I, L, M, N, P, Q, R, S, T, V or Y.	S, T, V, W, or Y; X ₄ is A, G, N, R, S, T, or V; X ₅ is A, G, H, L, N, P, R, S, T, or V; X ₆ is I, L, M, or Q; X ₇ is A, D, G, K, L, N, Q, R, S, or V; X ₈ is A, D, E, F, G, I, K, L, M, P, R, V, W, or Y; and X ₉ is A, F, G, M, P, Q, R, S, V, or Y. Subgenus 12.7: X ₂ X ₃ X ₄ X ₅ X ₆ X ₇ X ₈ X ₉ (SEQ ID NO: 465), wherein X ₂ is A, P, or S; X ₃ is A, H, Q, S, or V; X ₄ is G, N, or S; X ₅ is L, P, or S; X ₆ is L; X ₇ is A, D, G, R, or S; X ₈ is F, I, L, M, or P; and X ₉ is F, P, Q, or R. Subgenus 12.8: X ₂ X ₃ X ₄ X ₅ X ₆ X ₇ X ₈ X ₉ (SEQ ID NO: 466), wherein X ₂ is A, P, or S; X ₃ is H, S, or V; X ₄ is G, N, or S; X ₅ is L, P, or S; X ₆ is L; X ₇ is A, G, R, or S; X ₈ is F, I, M, or P; and X ₉ is P or R. Subgenus 12.9: X ₂ X ₃ X ₄ X ₅ X ₆ X ₇ X ₈ X ₉ (SEQ ID NO: 467), wherein X ₂ is A, P, or S; X ₃ is S or V; X ₄ is G, N, or S; X ₅ is L; X ₆ is L; X ₇ is A, G or R; X ₈ is F, I, or P; and X ₉ is P. Subgenus 12.10: X ₂ X ₃ X ₄ X ₅ X ₆ X ₇ X ₈ X ₉ (SEQ ID NO: 468), wherein X ₂ is A, P, or S; X ₃ is S or V; X ₄ is G, N, or S; X ₅ is L; X ₆ is L; X ₇ is A or R; X ₈ is F or P; and X ₉ is P. Subgenus 12.11: X ₂ X ₃ X ₄ X ₅ X ₆ X ₇ X ₈ X ₉ (SEQ ID NO: 469), wherein X ₂ is A or P; X ₃ is S; X ₄ is G or N; X ₅ is L; X ₆ is L; X ₇ is R; X ₈ is F; and X ₉ is P.

TABLE 8M

MMP14 Cleavable Core CM Consensus Sequence 13	
Core CM Consensus 13	Subgenus of Core CM Consensus 13
X ₁₂ X ₁₃ X ₁₄ X ₁₅ X ₁₆ X ₁₇ X ₁₈ X ₁₉ (SEQ ID NO: 473), wherein X ₁₂ is F, I, L, M, R, S, T, or V; X ₁₃ is A, E, G, H, I, K, L, M, N, P, Q, R, S, T, V, W, or Y; X ₁₄ is A, D, E, F, G, H, I, K, L, M, N, P, Q, R, S, T, V, or Y; X ₁₅ is A, E, G, N, P, Q, S, T, V, or W; X ₁₆ is A, F, G, H, I, K, L, M, N, P, Q, R, S, T, V, or Y; X ₁₇ is A, D, E, F, G, H, I, L, M, N, P, Q, R, S, T, V, or Y; X ₁₈ is A, C, D, E, F, G, H, I, L, M, N, P, Q, R, S, T, V, or Y; and X ₁₉ is A, D, F, G, H, I, L, M, N, P, Q, R, S, T, V, W, or Y.	Subgenus 13.1: X ₁₂ X ₁₃ X ₁₄ X ₁₅ X ₁₆ X ₁₇ X ₁₈ X ₁₉ (SEQ ID NO: 475), wherein X ₁₂ is F, I, L, M, S, or V; X ₁₃ is A, E, H, K, L, M, N, Q, S, T, V, or Y; X ₁₄ is A, F, H, L, M, Q, S, T, or V; X ₁₅ is A, G, or P; X ₁₆ is A, F, G, H, I, L, M, N, R, S, V, or Y; X ₁₇ is A, E, G, H, L, M, N, R, S, V, or Y; and X ₁₈ is A, D, E, F, G, H, L, M, N, R, S, V, or Y; X ₁₉ is A, F, G, I, L, M, P, Q, R, S, W, or Y. Subgenus 13.2: X ₁₂ X ₁₃ X ₁₄ X ₁₅ X ₁₆ X ₁₇ X ₁₈ X ₁₉ (SEQ ID NO: 476), wherein X ₁₂ is L, M, or V; X ₁₃ is A, H, L, N, Q, S, or V; X ₁₄ is A, L, M, Q, S, T, or V; X ₁₅ is P; X ₁₆ is A, F, G, I, L, R, S, V, or Y; X ₁₇ is H, L, M, Q, or S; X ₁₈ is A, D, G, H, R, or S; and X ₁₉ is A, F, G, L, R, or S. Subgenus 13.3: X ₁₂ X ₁₃ X ₁₄ X ₁₅ X ₁₆ X ₁₇ X ₁₈ X ₁₉ (SEQ ID NO: 477), wherein X ₁₂ is L, M, or V; X ₁₃ is A or L; X ₁₄ is A, L, or S; X ₁₅ is P; X ₁₆ is L or V; X ₁₇ is H, L, or Q; X ₁₈ is G or S; and X ₁₉ is G, R, or S. Subgenus 13.4: X ₁₂ X ₁₃ X ₁₄ X ₁₅ X ₁₆ X ₁₇ X ₁₈ X ₁₉ (SEQ ID NO: 478), wherein X ₁₂ is L or V; X ₁₃ is A or L; X ₁₄ is L or S; X ₁₅ is P; X ₁₆ is L or V; X ₁₇ is H or L; X ₁₈ is G or S; and X ₁₉ is R or S. Subgenus 13.5: X ₁₂ X ₁₃ X ₁₄ X ₁₅ X ₁₆ X ₁₇ X ₁₈ X ₁₉ (SEQ ID NO: 479), wherein X ₁₂ is L or V; X ₁₃ is A or L; X ₁₄ is L or S; X ₁₅ is P; X ₁₆ is L; X ₁₇ is H or L; X ₁₈ is G; and X ₁₉ is S. Subgenus 13.6: X ₁₂ X ₁₃ X ₁₄ X ₁₅ X ₁₆ X ₁₇ X ₁₈ X ₁₉ (SEQ ID NO: 480), wherein X ₁₂ is F, I, L, M, S, T, or V; X ₁₃ is A, E, G, H, L, M, S, V, W, or Y; X ₁₄ is A, D, E, G, K, L, M, N, Q, R, S, T, or V; X ₁₅ is E, G, N, P, S, T, or V; X ₁₆ is A, F, G, L, N, P, Q, R, S, V, or Y; X ₁₇ is A, E, H, P, Q, or R; X ₁₈ is D, E, G, N, R, S, or T; and X ₁₉ is A, D, G, Q, S, T, or V. Subgenus 13.: X ₁₂ X ₁₃ X ₁₄ X ₁₅ X ₁₆ X ₁₇ X ₁₈ X ₁₉ (SEQ ID NO: 481), wherein X ₁₂ is L, M, or V; X ₁₃ is A or L; X ₁₄ is A, L, Q, or S; X ₁₅ is G, P, or T; X ₁₆ is A, S, or Y; X ₁₇ is H or P; X ₁₈ is D or G; and X ₁₉ is A, G or S. Subgenus 13.7: X ₁₂ X ₁₃ X ₁₄ X ₁₅ X ₁₆ X ₁₇ X ₁₈ X ₁₉ (SEQ ID NO: 482), wherein X ₁₂ is L or M; X ₁₃ is A or L; X ₁₄ is L; X ₁₅ is G or P; X ₁₆ is A or S; X ₁₇ is H; X ₁₈ is G; and X ₁₉ is A or G.

[0028] In some embodiments, the CM comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 352, 371, 394, 410, 425, 436, 453, 458, 473, 485, and 486. In some embodiments, the CM comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 353-363, 372-375, 376-378, 395-401, 411-419, 426-433,

437-449, 454-456, 459-469, 475-482, and 487-495. In some embodiments, the CM comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 353-363. In some embodiments, the CM comprises an amino acid sequence selected from the group consisting of 372-375. In some embodiments, the CM comprises an amino acid

[0036] In some embodiments, the CM comprises a core CM consensus 7 sequence comprising the amino acid sequence LKAAPRWA (SEQ ID NO: 24). In some embodiments, the CM comprises a core CM consensus 7 sequence comprising the amino acid sequence LKAAPVWA (SEQ ID NO: 403). In some embodiments, the CM comprises a core CM consensus 7 sequence comprising the amino acid sequence LKAAPRWF (SEQ ID NO: 404). In some embodiments, the CM comprises a core CM consensus 7 sequence comprising the amino acid sequence LKAAPVWF (SEQ ID NO: 405). In some embodiments, the CM comprises a core CM consensus 7 sequence comprising the amino acid sequence LYAAPRWA (SEQ ID NO: 406). In some embodiments, the CM comprises a core CM consensus 7 sequence comprising the amino acid sequence LYAAPVWA (SEQ ID NO: 407). In some embodiments, the CM comprises a core CM consensus 7 sequence comprising the amino acid sequence LYAAPRWF (SEQ ID NO: 408). In some embodiments, the CM comprises a core CM consensus 7 sequence comprising the amino acid sequence LYAAPVWF (SEQ ID NO: 409).

[0037] In some embodiments, the CM comprises a core CM consensus 8 sequence comprising the amino acid sequence GPSHLVLT (SEQ ID NO: 25). In some embodiments, the CM comprises a core CM consensus 8 sequence comprising the amino acid sequence LPAGLLL (SEQ ID NO: 402). In some embodiments, the CM comprises a core CM consensus 8 sequence comprising the amino acid sequence LPAGLLLR (SEQ ID NO: 420). In some embodiments, the CM comprises a core CM consensus 8 sequence comprising the amino acid sequence LP AHLVLL (SEQ ID NO: 421). In some embodiments, the CM comprises a core CM consensus 8 sequence comprising the amino acid sequence LPSHLVLL (SEQ ID NO: 422). In some embodiments, the CM comprises a core CM consensus 8 sequence comprising the amino acid sequence LP AHLVLV (SEQ ID NO: 423). In some embodiments, the CM comprises a core CM consensus 8 sequence comprising the amino acid sequence LPSHLVLV (SEQ ID NO: 424).

[0038] In some embodiments, the CM comprises a core CM consensus 9 sequence comprising the amino acid sequence RMHLRSLG (SEQ ID NO: 29). In some embodiments, the CM comprises a core CM consensus 9 sequence comprising the amino acid sequence RRHDGLRA (SEQ ID NO: 434). In some embodiments, the CM comprises a core CM consensus 9 sequence comprising the amino acid sequence RRHDGLRS (SEQ ID NO: 435).

[0039] In some embodiments, the CM comprises a core CM consensus 10 sequence comprising the amino acid sequence AQNLLGMV (SEQ ID NO: 16). In some embodiments, the CM comprises a core CM consensus 10 sequence comprising the amino acid sequence IANLLSMV (SEQ ID NO: 450). In some embodiments, the CM comprises a core CM consensus 10 sequence comprising the amino acid sequence ILNLLSMV (SEQ ID NO: 451). In some embodiments, the CM comprises a core CM consensus 10 sequence comprising the amino acid sequence IQNLLSMV (SEQ ID NO: 452).

[0040] In some embodiments, the CM comprises a core CM consensus 11 sequence comprising the amino acid sequence PAGLWLDP (SEQ ID NO: 33). In some embodiments, the CM comprises a core CM consensus 11 sequence comprising the amino acid sequence PASLWYTQ (SEQ ID NO: 457).

[0041] In some embodiments, the CM comprises a core CM consensus 12 sequence comprising the amino acid sequence ALGLLRLP (SEQ ID NO: 470). In some embodiments, the

CM comprises a core CM consensus 12 sequence comprising the amino acid sequence ALGLLSLP (SEQ ID NO: 471). In some embodiments, the CM comprises a core CM consensus 12 sequence comprising the amino acid sequence ASGLL-RFP (SEQ ID NO: 472). In some embodiments, the CM comprises a core CM consensus 12 sequence comprising the amino acid sequence AVGLLAPP (SEQ ID NO: 31).

[0042] In some embodiments, the CM comprises a core CM consensus 13 sequence comprising the amino acid sequence LAAPLGLL (SEQ ID NO: 30). In some embodiments, the CM comprises a core CM consensus 13 sequence comprising the amino acid sequence LLAPSHRA (SEQ ID NO: 32).

[0043] In some embodiments, the CM comprises a core CM consensus 13 sequence comprising the amino acid sequence LLLPAHGG (SEQ ID NO: 474). In some embodiments, the CM comprises a core CM consensus 13 sequence comprising the amino acid sequence LLLPLLGS (SEQ ID NO: 483).

[0044] In some embodiments, the CM is a substrate for at least two proteases. In some embodiments, at least one protease is an MMP and at least one protease is selected from the group consisting of those shown in Table 7.

TABLE 7

Exemplary Proteases and/or Enzymes
ADAMS, ADAMTS, e.g.
ADAM8
ADAM9
ADAM10
ADAM12
ADAM15
ADAM17/TACE
ADAMDEC1
ADAMTS1
ADAMTS4
ADAMTS5
Aspartate proteases, e.g.,
BACE
Renin
Aspartic cathepsins, e.g.,
Cathepsin D
Cathepsin E
Caspases, e.g.,
Caspase 1
Caspase 2
Caspase 3
Caspase 4
Caspase 5
Caspase 6
Caspase 7
Caspase 8
Caspase 9
Caspase 10
Caspase 14
Cysteine cathepsins, e.g.,
Cathepsin B
Cathepsin C
Cathepsin K
Cathepsin L
Cathepsin S
Cathepsin V/L2
Cathepsin X/Z/P
Cysteine proteinases, e.g.,
Cruzipain
Legumain
Otubain-2
KLKs, e.g.,
KLK4
KLK5
KLK6
KLK7
KLK8

TABLE 7-continued

Exemplary Proteases and/or Enzymes
KLK10
KLK11
KLK13
KLK14
Metallo proteinases, e.g.,
Mephrin
Neprilysin
PSMA
BMP-1
MMPs, e.g.,
MMP1
MMP2
MMP3
MMP7
MMP8
MMP9
MMP10
MMP11
MMP12
MMP13
MMP14
MMP15
MMP16
MMP17
MMP19
MMP20
MMP23
MMP24
MMP26
MMP27
Serine proteases, e.g.,
activated protein C
Cathepsin A
Cathepsin G
Chymase
coagulation factor proteases
(e.g., FVIIa, FIXa, FXa, FXIa, FXIIa)
Elastase
Granzyme B
Guanidinobenzoatase
HtrA1
Human Neutrophil Elastase
Lactoferrin
Marapsin
NS3/4A
PACE4
Plasmin
PSA
tPA
Thrombin
Tryptase
uPA
Type II Transmembrane
Serine Proteases (TTSPs), e.g.,
DESC1
DPP-4
FAP
Hepsin
Matriptase-2
MT-SP1/Matriptase
TMPRSS2
TMPRSS3
TMPRSS4

[0045] In some embodiments, the antibody includes at least a first CM and a second CM. In some embodiments, the first CM and the second CM are each polypeptides of no more than 15 amino acids long. In some embodiments, the first CM and the second CM in the antibody in the uncleaved state have the structural arrangement from N-terminus to C-terminus as follows: Agent-CM1-CM2-AB, AB-CM2-CM1-Agent, Agent-CM2-CM1-AB, or AB-CM1-CM2-Agent. In some

embodiments, the activatable antibody includes a linking peptide between the agent and CM1. In some embodiments, the activatable antibody includes a linking peptide between CM1 and CM2. In some embodiments, the activatable antibody includes a linking peptide between CM2 and AB. In some embodiments, the activatable antibody includes a linking peptide between agent and CM1 and a linking peptide between CM2 and AB. In some embodiments, the activatable antibody includes a linking peptide between agent and CM1 and a linking peptide between CM1 and CM2. In some embodiments, the activatable antibody includes a linking peptide between CM1 and CM2 and a linking peptide between CM2 and AB. In some embodiments, the activatable antibody includes a linking peptide between agent and CM1, a linking peptide between CM1 and CM2, and a linking peptide between CM2 and AB.

[0046] In some embodiments, the activatable antibody includes at least a first CM that includes a substrate for at least one matrix metalloprotease (MMP) and a second CM that includes a substrate sequence. Exemplary substrates for the second CM (CM2) include but are not limited to substrates cleavable by one or more of the following enzymes or proteases listed in Table 7.

[0047] In some embodiments, the CM2 is selected for use with a specific protease. In some embodiments, the CM2 is a substrate for at least one protease selected from the group consisting of a matrix metalloprotease (MMP), a neutrophil elastase, u-type plasminogen activator (uPA, also referred to as urokinase), legumain, matriptase (also referred to herein as MT-SP1 or MTSP1), thrombin, a cysteine protease such as a cathepsin, ADAM17, BMP-1, HtrA1, and a TMPRSS such as TMPRSS3 or TMPRSS4.

[0048] In some embodiments, the CM2 is a substrate for a neutrophil elastase. In some embodiments, the CM2 is a substrate for uPA. In some embodiments, the CM2 is a substrate for legumain. In some embodiments, the CM2 is a substrate for matriptase. In some embodiments, the CM2 is a substrate for thrombin. In some embodiments, the CM2 is a substrate for a cysteine protease. In some embodiments, the CM2 is a substrate for a cathepsin. In some embodiments, the CM2 is a substrate for ADAM17. In some embodiments, the CM2 is a substrate for BMP-1. In some embodiments, the CM2 is a substrate for HtrA1. In some embodiments, the CM2 is a substrate for a TMPRSS. In some embodiments, the CM2 is a substrate for TMPRSS3. In some embodiments, the CM2 is a substrate for TMPRSS4.

[0049] For example, suitable CM2 are cleaved by at least one protease and include the sequence TGRGPSWV (SEQ ID NO: 34); SARGPSRW (SEQ ID NO: 35); TARGPSFK (SEQ ID NO: 36); LSGRSDNH (SEQ ID NO: 37); GGWHT-GRN (SEQ ID NO: 38); HTGRSGAL (SEQ ID NO: 39); PLTGRSGG (SEQ ID NO: 40); AARGPAIH (SEQ ID NO: 41); RGPAFNPM (SEQ ID NO: 42); SSRGPAYL (SEQ ID NO: 43); RGPATPIM (SEQ ID NO: 44); RGPA (SEQ ID NO: 45); GGQPSGMWGW (SEQ ID NO: 46); FPRPLGITGL (SEQ ID NO: 47); VHMPPLGFLGP (SEQ ID NO: 48); SPLTGRSG (SEQ ID NO: 49); SAGFSLPA (SEQ ID NO: 126); LAPLGLQRR (SEQ ID NO: 50); SGGPLGV (SEQ ID NO: 51); PLGL (SEQ ID NO: 52); GPRSFGL (SEQ ID NO: 315) and/or GPRSFGL (SEQ ID NO: 316).

[0050] In some embodiments, the CM2 comprises the amino acid sequence TGRGPSWV (SEQ ID NO: 34). In some embodiments, the CM2 comprises the amino acid sequence SARGPSRW (SEQ ID NO: 35). In some embodi-

ments, the CM2 comprises the amino acid sequence TARGPSFK (SEQ ID NO: 36). In some embodiments, the CM2 comprises the amino acid sequence LSGRSRDNH (SEQ ID NO: 37). In some embodiments, the CM2 comprises the amino acid sequence GGWHTGRN (SEQ ID NO: 38). In some embodiments, the CM2 comprises the amino acid sequence HTGRSGAL (SEQ ID NO: 39). In some embodiments, the CM2 comprises the amino acid sequence PLTGRSGG (SEQ ID NO: 40). In some embodiments, the CM2 comprises the amino acid sequence AARGPAIH (SEQ ID NO: 41). In some embodiments, the CM2 comprises the amino acid sequence RGPAFNPM (SEQ ID NO: 42). In some embodiments, the CM2 comprises the amino acid sequence SSRGPAYL (SEQ ID NO: 43). In some embodiments, the CM2 comprises the amino acid sequence RGPATPIM (SEQ ID NO: 44). In some embodiments, the CM2 comprises the amino acid sequence RGPA (SEQ ID NO: 45). In some embodiments, the CM2 comprises the amino acid sequence GGQPSGMWGW (SEQ ID NO: 46). In some embodiments, the CM2 comprises the amino acid sequence FPRPLGITGL (SEQ ID NO: 47). In some embodiments, the CM2 comprises the amino acid sequence VHMLGLFLGP (SEQ ID NO: 48). In some embodiments, the CM2 comprises the amino acid sequence SPLTGRSG (SEQ ID NO: 49). In some embodiments, the CM2 comprises the amino acid sequence LAPLGLQRR (SEQ ID NO: 50). In some embodiments, the CM2 comprises the amino acid sequence SGGPLGVR (SEQ ID NO: 51). In some embodiments, the CM2 comprises the amino acid sequence PLGL (SEQ ID NO: 52). In some embodiments, the CM2 comprises the amino acid sequence GPRSFG (SEQ ID NO: 315). In some embodiments, the CM2 comprises the amino acid sequence GPRSFG (SEQ ID NO: 316).

[0051] In some embodiments, the CM2 is a substrate for at least one MMP. In some embodiments, the CM2 is a substrate for at least one MMP listed in the Table 7. In some embodiments, the CM2 is a substrate for MMP9. In some embodiments, the CM2 is a substrate for MMP14. In some embodiments, CM1 is substrate for a first MMP, and CM2 is a substrate for a second MMP, where the first MMP and the second MMP are different MMPs. In some embodiments, CM1 is a first substrate sequence for a MMP, and CM2 is a second substrate for the same MMP, where the CM1 and CM2 have different substrate sequences. In some embodiments, the CM2 is a substrate for two or more MMPs. In some embodiments, the CM2 is a substrate for at least MMP9 or MMP14. In some embodiments, the CM2 is a substrate for two or more MMPs. In some embodiments, the CM2 is a substrate for at least MMP9 and MMP14. In some embodiments, CM1 and CM2 are both substrates for MMP9. In some embodiments, CM1 and CM2 are both substrates for MMP14. In some embodiments, CM1 is a substrate for MMP9 and CM2 is a substrate for MMP14. In some embodiments, CM1 is a substrate for MMP14 and CM2 is a substrate for MMP9.

[0052] In some embodiments, at least one of CM1 and/or CM2 is a substrate for an MMP and includes the sequence ISSGLLSS (SEQ ID NO: 14); QNQALRMA (SEQ ID NO: 15); AQNLLGMV (SEQ ID NO: 16); STFPFGMF (SEQ ID NO: 17); PVGYTSSL (SEQ ID NO: 18); DWLYWPGI (SEQ ID NO: 19); MIAPVAYR (SEQ ID NO: 20); RPSPMWAY (SEQ ID NO: 21); WATPRPMR (SEQ ID NO: 22); FRLLDWQW (SEQ ID NO: 23); LKAAPRWA (SEQ ID NO: 24); GPSHLVLT (SEQ ID NO: 25); LPGGLSPW (SEQ ID NO: 26); MGLFSEAG (SEQ ID NO: 27); SPLPLRVP (SEQ ID

NO: 28); RMHLRSLG (SEQ ID NO: 29); LAAPLGLL (SEQ ID NO: 30); AVGLLAPP (SEQ ID NO: 31); LLAPSHRA (SEQ ID NO: 32); PAGLWLDP (SEQ ID NO: 33); and/or ISSGLLSS (SEQ ID NO: 159).

[0053] In some embodiments, the first cleaving agent and the second cleaving agent are the same protease, and the first CM and the second CM are different substrates for the enzyme. In some embodiments, the first cleaving agent and the second cleaving agent are different proteases. In some embodiments, the first cleaving agent and the second cleaving agent are co-localized in the target tissue. In some embodiments, the first CM and the second CM are cleaved by at least one cleaving agent in the target tissue.

[0054] In some embodiments, the agent conjugated to the AB is a therapeutic agent. In some embodiments, the agent is an antineoplastic agent. In some embodiments, the agent is a toxin or fragment thereof. As used herein, a fragment of a toxin is a fragment that retains toxic activity. In some embodiments, the agent is conjugated to the AB via a cleavable linker. In some embodiments, the agent is conjugated to the AB via a linker that includes at least one MMP-cleavable substrate sequence. In some embodiments, the agent is conjugated to the AB via a noncleavable linker. In some embodiments, the agent is a microtubule inhibitor. In some embodiments, the agent is a nucleic acid damaging agent, such as a DNA alkylator or DNA intercalator, or other DNA damaging agent. In some embodiments, the agent is an agent selected from the group listed in Table 3. In some embodiments, the agent is a dolastatin. In some embodiments, the agent is an auristatin or derivative thereof. In some embodiments, the agent is auristatin E or a derivative thereof. In some embodiments, the agent is monomethyl auristatin E (MMAE). In some embodiments, the agent is monomethyl auristatin D (MMAD). In some embodiments, the agent is a maytansinoid or maytansinoid derivative. In some embodiments, the agent is DM1 or DM4. In some embodiments, the agent is a duocarmycin or derivative thereof. In some embodiments, the agent is a calicheamicin or derivative thereof. In some embodiments, the agent is a pyrrolobenzodiazepine.

[0055] In some embodiments, the agent is an anti-inflammatory agent.

[0056] In some embodiments, the antibody also includes a detectable moiety. In some embodiments, the detectable moiety is a diagnostic agent.

[0057] In some embodiments, the conjugated antibody and/or conjugated activatable antibody includes a detectable label. In some embodiments, the detectable label includes an imaging agent, a contrasting agent, an enzyme, a fluorescent label, a chromophore, a dye, one or more metal ions, or a ligand-based label. In some embodiments, the imaging agent comprises a radioisotope. In some embodiments, the radioisotope is indium or technetium. In some embodiments, the contrasting agent comprises iodine, gadolinium or iron oxide. In some embodiments, the enzyme comprises horseradish peroxidase, alkaline phosphatase, or β -galactosidase. In some embodiments, the fluorescent label comprises yellow fluorescent protein (YFP), cyan fluorescent protein (CFP), green fluorescent protein (GFP), modified red fluorescent protein (mRFP), red fluorescent protein tdimer2 (RFP tdimer2), HCRED, or a europium derivative. In some embodiments, the luminescent label comprises an N-methylacridinium derivative. In some embodiments, the label comprises an Alexa Fluor® label, such as Alexa Fluor® 680 or

Alexa Fluor® 750. In some embodiments, the ligand-based label comprises biotin, avidin, streptavidin or one or more haptens.

[0058] In some embodiments, the AB of the antibody naturally contains one or more disulfide bonds. In some embodiments, the AB can be engineered to include one or more disulfide bonds.

[0059] In some embodiments, the antibody and/or conjugated antibody is monospecific. In some embodiments, the antibody and/or conjugated antibody is multispecific, referred to herein as multispecific antibodies and/or conjugated multispecific antibodies. In some embodiments, the multispecific antibody and/or conjugated multispecific antibody is bispecific or trifunctional. In some embodiments, the antibody and/or conjugated antibody is formulated as part of a pro-Bispecific T Cell Engager (pro-BITE) molecule. In some embodiments, the antibody and/or conjugated antibody is formulated as part of a pro-Chimeric Antigen Receptor (pro-CAR) modified T cell or other engineered receptor.

[0060] In some embodiments, the activatable antibody and/or conjugated activatable antibody is monospecific. In some embodiments, the activatable antibody and/or conjugated activatable antibody is multispecific, referred to herein as multispecific activatable antibodies and/or conjugated multispecific activatable antibodies. As used herein, terms such as "activatable antibody" and all grammatical variations thereof, unless otherwise noted, are intended to encompass, but are not limited to embodiments where the activatable antibody is a multispecific activatable antibody of the disclosure. As used herein, terms such as "conjugated activatable antibody" and all grammatical variations thereof, unless otherwise noted, are intended to encompass, but are not limited to embodiments where the conjugated activatable antibody is a conjugated multispecific activatable antibody of the disclosure. In some embodiments, the multispecific activatable antibody and/or conjugated multispecific activatable antibody is bispecific or trifunctional. In some embodiments, the activatable antibody and/or conjugated activatable antibody is formulated as part of a pro-Bispecific T Cell Engager (pro-BITE) molecule. In some embodiments, the activatable antibody and/or conjugated activatable antibody is formulated as part of a pro-Chimeric Antigen Receptor (pro-CAR) modified T cell or other engineered receptor.

[0061] In some embodiments, the activatable antibodies, conjugated activatable antibodies, multispecific activatable antibodies, and/or conjugated multispecific activatable antibodies described herein are used in conjunction with one or more additional agents or a combination of additional agents. Suitable additional agents include current pharmaceutical and/or surgical therapies for an intended application, such as, for example, cancer. For example, the activatable antibodies, conjugated activatable antibodies, multispecific activatable antibodies, and/or conjugated multispecific activatable antibodies can be used in conjunction with an additional chemotherapeutic or anti-neoplastic agent.

[0062] The activatable antibodies described herein in an activated state bind a given target and include (i) an antibody or an antigen binding fragment thereof (AB) that specifically binds to the target; (ii) a masking moiety (MM) that inhibits the binding of the AB to the target in an uncleaved state; and (c) a cleavable moiety (CM) coupled to the AB, wherein the CM is a polypeptide that functions as a substrate for a matrix metalloprotease.

[0063] In some embodiments, the activatable antibody in the uncleaved state has the structural arrangement from N-terminus to C-terminus as follows: MM-CM-AB or AB-CM-MM.

[0064] In some embodiments, the activatable antibody comprises a linking peptide between the MM and the CM.

[0065] In some embodiments, the activatable antibody comprises a linking peptide between the CM and the AB.

[0066] In some embodiments, the activatable antibody comprises a first linking peptide (LP1) and a second linking peptide (LP2), and the activatable antibody in the uncleaved state has the structural arrangement from N-terminus to C-terminus as follows: MM-LP1-CM-LP2-AB or AB-LP2-CM-LP1-MM.

[0067] In some embodiments, each of LP1 and LP2 is a peptide of about 1 to 20 amino acids in length.

[0068] In some embodiments, the two linking peptides need not be identical to each other.

[0069] In some embodiments, at least one of LP1 or LP2 comprises an amino acid sequence selected from the group consisting of (GS)_n, (GGS)_n, (GSGGS)_n (SEQ ID NO: 1) and (GGGS)_n (SEQ ID NO: 2), where n is an integer of at least one.

[0070] In some embodiments, at least one of LP1 or LP2 comprises an amino acid sequence selected from the group consisting of GGSG (SEQ ID NO: 3), GGSGG (SEQ ID NO: 4), GSGSG (SEQ ID NO: 5), GSAGG (SEQ ID NO: 6), GGGSG (SEQ ID NO: 7), and GSSSG (SEQ ID NO: 8).

[0071] In some embodiments, LP1 comprises the amino acid sequence GSSGGSGGS (SEQ ID NO: 9), GSSGGSGGS (SEQ ID NO: 10), GSSGGSGGS (SEQ ID NO: 11), GSSGGSGGS (SEQ ID NO: 155), GSSGGSGGS (SEQ ID NO: 156), or GSSGGSGGS (SEQ ID NO: 157).

[0072] In some embodiments, LP2 comprises the amino acid sequence GSS, GGS, GGGS (SEQ ID NO: 158), GSSGT (SEQ ID NO: 12) or GSSG (SEQ ID NO: 13).

[0073] In some embodiments, the AB has an equilibrium dissociation constant of about 100 nM or less for binding to the target.

[0074] In some embodiments, the activatable antibody includes an antibody or antigen-binding fragment thereof that specifically binds a target. In some embodiments, the antibody or immunologically active fragment thereof that binds the target is a monoclonal antibody, domain antibody, single chain, Fab fragment, a F(ab)₂ fragment, a scFv, a scab, a dAb, a single domain heavy chain antibody, or a single domain light chain antibody. In some embodiments, such an antibody or immunologically active fragment thereof that binds the target is a mouse, other rodent, chimeric, humanized or fully human monoclonal antibody.

[0075] In some embodiments, the activatable antibody is a multispecific activatable antibody. The multispecific activatable antibodies provided herein are multispecific antibodies that recognize two or more different antigens or epitopes and that include at least one masking moiety (MM) linked to at least one antigen- or epitope-binding domain of the multispecific antibody such that coupling of the MM reduces the ability of the antigen- or epitope-binding domain to bind its target. In some embodiments, the MM is coupled to the antigen- or epitope-binding domain of the multispecific antibody via a cleavable moiety (CM) that functions as a substrate for at least one MMP protease. The activatable multispecific antibodies provided herein are stable in circulation, activated

at intended sites of therapy and/or diagnosis but not in normal, i.e., healthy tissue, and, when activated, exhibit binding to a target that is at least comparable to the corresponding, unmodified multispecific antibody.

[0076] In some embodiments, the activatable antibody and/or conjugated activatable antibody provided herein, including but not limited to a multispecific activatable antibody and/or conjugated multispecific activatable antibody of the disclosure, includes at least a first antibody or antigen binding fragment thereof (AB1) that specifically binds a Jagged target, e.g., Jagged 1 and/or Jagged 2, and that contains a combination of a VH CDR1 sequence, a VH CDR2 sequence, and a VH CDR3 sequence, wherein at least one of the VH CDR1 sequence, the VH CDR2 sequence, and the VH CDR3 sequence is selected from a VH CDR1 sequence that includes at least the amino acid sequence SYAMS (SEQ ID NO: 498); a VH CD2 sequence that includes at least the amino acid sequence SIDPEGRQTYYADSVKG (SEQ ID NO: 499); a VH CDR3 sequence that includes at least the amino acid sequence DIGGRSAFDY (SEQ ID NO: 500), and combinations thereof.

[0077] In some embodiments, the activatable antibody and/or conjugated activatable antibody provided herein, including but not limited to a multispecific activatable antibody and/or conjugated multispecific activatable antibody of the disclosure, includes at least a first antibody or antigen binding fragment thereof (AB1) that specifically binds a Jagged target, e.g., Jagged 1 and/or Jagged 2, and that contains a combination of a VL CDR1 sequence, a VL CDR2 sequence, and a VL CDR3 sequence, wherein at least one of the VL CDR1 sequence, the VL CDR2 sequence, and the VL CDR3 sequence is selected from a VL CDR1 sequence that includes at least the amino acid sequence RASQSISSY (SEQ ID NO: 501); a VL CDR2 sequence that includes at least the amino acid sequence AASSLQS (SEQ ID NO: 502); a VL CDR3 sequence that includes at least the amino acid sequence QQTVVAPPL (SEQ ID NO: 503), and combinations thereof.

[0078] In some embodiments, the activatable antibody and/or conjugated activatable antibody provided herein, including but not limited to a multispecific activatable antibody and/or conjugated multispecific activatable antibody of the disclosure, includes at least a first antibody or antigen binding fragment thereof (AB1) that specifically binds a Jagged target, e.g., Jagged 1 and/or Jagged 2, and that contains a combination of a VH CDR1 sequence, a VH CDR2 sequence, and a VH CDR3 sequence, wherein at least one of the VH CDR1 sequence, the VH CDR2 sequence, and the VH CDR3 sequence is selected from a VH CDR1 sequence that includes a sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to the amino acid sequence SYAMS (SEQ ID NO: 498); a VH CD2 sequence that includes a sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to the amino acid sequence SIDPEGRQTYYADSVKG (SEQ ID NO: 499); a VH CDR3 sequence that includes a sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to the amino acid sequence DIGGRSAFDY (SEQ ID NO: 500), and combinations thereof.

[0079] In some embodiments, the activatable antibody and/or conjugated activatable antibody provided herein, including but not limited to a multispecific activatable antibody and/or conjugated multispecific activatable antibody of the disclosure, includes at least a first antibody or antigen binding fragment thereof (AB1) that specifically binds a Jagged tar-

get, e.g., Jagged 1 and/or Jagged 2, and that contains a combination of a VL CDR1 sequence, a VL CDR2 sequence, and a VL CDR3 sequence, wherein at least one of the VL CDR1 sequence, the VL CDR2 sequence, and the VL CDR3 sequence is selected from a VL CDR1 sequence that includes a sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to the amino acid sequence RASQSISSY (SEQ ID NO: 501); a VL CDR2 sequence that includes a sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to the amino acid sequence AASSLQS (SEQ ID NO: 502); and a VL CDR3 sequence that includes a sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to the amino acid sequence QQTVVAPPL (SEQ ID NO: 503), and combinations thereof.

[0080] In some embodiments, the activatable antibody and/or conjugated activatable antibody provided herein, including but not limited to a multispecific activatable antibody and/or conjugated multispecific activatable antibody of the disclosure, includes at least a first antibody or antigen binding fragment thereof (AB1) that specifically binds a Jagged target, e.g., Jagged 1 and/or Jagged 2, and that contains a combination of a VH CDR1 sequence, a VH CDR2 sequence, a VH CDR3 sequence, a VL CDR1 sequence, a VL CDR2 sequence, and a VL CDR3 sequence, wherein the VH CDR1 sequence includes at least the amino acid sequence SYAMS (SEQ ID NO: 498); the VH CD2 sequence includes at least the amino acid sequence SIDPEGRQTYYADSVKG (SEQ ID NO: 499); the VH CDR3 sequence includes at least the amino acid sequence DIGGRSAFDY (SEQ ID NO: 500); the VL CDR1 sequence includes at least the amino acid sequence RASQSISSY (SEQ ID NO: 501); the VL CDR2 sequence includes at least the amino acid sequence AASSLQS (SEQ ID NO: 502); and the VL CDR3 sequence includes at least the amino acid sequence QQTVVAPPL (SEQ ID NO: 503).

[0081] In some embodiments, the activatable antibody and/or conjugated activatable antibody provided herein, including but not limited to a multispecific activatable antibody and/or conjugated multispecific activatable antibody of the disclosure, includes at least a first antibody or antigen binding fragment thereof (AB1) that specifically binds a Jagged target, e.g., Jagged 1 and/or Jagged 2, and that contains a combination of a VH CDR1 sequence, a VH CDR2 sequence, a VH CDR3 sequence, a VL CDR1 sequence, a VL CDR2 sequence, and a VL CDR3 sequence, wherein the VH CDR1 sequence includes a sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to the amino acid sequence SYAMS (SEQ ID NO: 498); the VH CD2 sequence includes a sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to the amino acid sequence SIDPEGRQTYYADSVKG (SEQ ID NO: 499); the VH CDR3 sequence includes a sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to the amino acid sequence DIGGRSAFDY (SEQ ID NO: 500); the VL CDR1 sequence includes a sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to the amino acid sequence RASQSISSY (SEQ ID NO: 501); the VL CDR2 sequence includes a sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to the amino acid sequence AASSLQS (SEQ ID NO: 502); and the VL CDR3 sequence includes a sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to the amino acid sequence QQTVVAPPL (SEQ ID NO: 503).

98%, 99% or more identical to the amino acid sequence QQTVVAPPL (SEQ ID NO: 503).

[0082] In some embodiments, the activatable antibody and/or conjugated activatable antibody provided herein, including but not limited to a multispecific activatable antibody and/or conjugated multispecific activatable antibody of the disclosure, includes at least a first antibody or antigen binding fragment thereof (AB1) that specifically binds Epidermal Growth Factor Receptor (EGFR) and that contains a combination of a VH CDR1 sequence, a VH CDR2 sequence, and a VH CDR3 sequence, wherein at least one of the VH CDR1 sequence, the VH CDR2 sequence, and the VH CDR3 sequence is selected from a VH CDR1 sequence that includes at least the amino acid sequence NYGVH (SEQ ID NO: 504); a VH CD2 sequence that includes at least the amino acid sequence VIWSGGNTDYNTPFTS (SEQ ID NO: 505); a VH CDR3 sequence that includes at least the amino acid sequence ALTYYDYEFAY (SEQ ID NO: 506); and combinations thereof.

[0083] In some embodiments, the activatable antibody and/or conjugated activatable antibody provided herein, including but not limited to a multispecific activatable antibody and/or conjugated multispecific activatable antibody of the disclosure, includes at least a first antibody or antigen binding fragment thereof (AB1) that specifically binds EGFR and that contains a combination of a VL CDR1 sequence, a VL CDR2 sequence, and a VL CDR3 sequence, wherein at least one of the VL CDR1 sequence, the VL CDR2 sequence, and the VL CDR3 sequence is selected from a VL CDR1 sequence that includes at least the amino acid sequence RASQSIGTNIH (SEQ ID NO: 507); a VL CDR2 sequence that includes at least the amino acid sequence KYASESIS (SEQ ID NO: 508); and a VL CDR3 sequence that includes at least the amino acid sequence QQNNNWPTT (SEQ ID NO: 509), and combinations thereof.

[0084] In some embodiments, the activatable antibody and/or conjugated activatable antibody provided herein, including but not limited to a multispecific activatable antibody and/or conjugated multispecific activatable antibody of the disclosure, includes at least a first antibody or antigen binding fragment thereof (AB1) that specifically binds EGFR and that contains a combination of a VH CDR1 sequence, a VH CDR2 sequence, and a VH CDR3 sequence, wherein at least one of the VH CDR1 sequence, the VH CDR2 sequence, and the VH CDR3 sequence is selected from a VH CDR1 sequence that includes a sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to the amino acid sequence NYGVH (SEQ ID NO: 504); a VH CD2 sequence that includes a sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to the amino acid sequence VIWSGGNTDYNTPFTS (SEQ ID NO: 505); a VH CDR3 sequence that includes a sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to the amino acid sequence ALTYYDYEFAY (SEQ ID NO: 506); and combinations thereof.

[0085] In some embodiments, the activatable antibody and/or conjugated activatable antibody provided herein, including but not limited to a multispecific activatable antibody and/or conjugated multispecific activatable antibody of the disclosure, includes at least a first antibody or antigen binding fragment thereof (AB1) that specifically binds EGFR and that contains a combination of a VL CDR1 sequence, a VL CDR2 sequence, and a VL CDR3 sequence, wherein at least one of

the VL CDR1 sequence, the VL CDR2 sequence, and the VL CDR3 sequence is selected from a VL CDR1 sequence that includes a sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to the amino acid sequence RASQSIGTNIH (SEQ ID NO: 507); a VL CDR2 sequence that includes a sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to the amino acid sequence KYASESIS (SEQ ID NO: 508); and a VL CDR3 sequence that includes a sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to the amino acid sequence QQNNNWPTT (SEQ ID NO: 509), and combinations thereof.

[0086] In some embodiments, the activatable antibody and/or conjugated activatable antibody provided herein, including but not limited to a multispecific activatable antibody and/or conjugated multispecific activatable antibody of the disclosure, includes at least a first antibody or antigen binding fragment thereof (AB1) that specifically binds EGFR and that contains a combination of a VH CDR1 sequence, a VH CDR2 sequence, a VH CDR3 sequence, a VL CDR1 sequence, a VL CDR2 sequence, and a VL CDR3 sequence, wherein the VH CDR1 sequence includes at least the amino acid sequence NYGVH (SEQ ID NO: 504); the VH CD2 sequence includes at least the amino acid sequence VIWSGGNTDYNTPFTS (SEQ ID NO: 505); the VH CDR3 sequence includes at least the amino acid sequence ALTYYDYEFAY (SEQ ID NO: 506); the VL CDR1 sequence includes at least the amino acid sequence RASQSIGTNIH (SEQ ID NO: 507); the VL CDR2 sequence includes at least the amino acid sequence KYASESIS (SEQ ID NO: 508); and the VL CDR3 sequence includes at least the amino acid sequence QQNNNWPTT (SEQ ID NO: 509).

[0087] In some embodiments, the activatable antibody and/or conjugated activatable antibody provided herein, including but not limited to a multispecific activatable antibody and/or conjugated multispecific activatable antibody of the disclosure, includes at least a first antibody or antigen binding fragment thereof (AB1) that specifically binds EGFR and that contains a combination of a VH CDR1 sequence, a VH CDR2 sequence, a VH CDR3 sequence, a VL CDR1 sequence, a VL CDR2 sequence, and a VL CDR3 sequence, wherein the VH CDR1 sequence includes a sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to the amino acid sequence NYGVH (SEQ ID NO: 504); the VH CD2 sequence includes a sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to the amino acid sequence VIWSGGNTDYNTPFTS (SEQ ID NO: 505); the VH CDR3 sequence includes a sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to the amino acid sequence ALTYYDYEFAY (SEQ ID NO: 506); the VL CDR1 sequence includes a sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to the amino acid sequence RASQSIGTNIH (SEQ ID NO: 507); the VL CDR2 sequence includes a sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to the amino acid sequence KYASESIS (SEQ ID NO: 508); and the VL CDR3 sequence includes a sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to the amino acid sequence QQNNNWPTT (SEQ ID NO: 509).

[0088] In some embodiments, the activatable antibody and/or conjugated activatable antibody provided herein, including

but not limited to a multispecific activatable antibody and/or conjugated multispecific activatable antibody of the disclosure, includes at least a heavy chain amino acid sequence selected from the group consisting of SEQ ID NOs: 54, 56, 57, 58, 61, 63, 65, 68, 70, 72, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, and 114. In some embodiments, the activatable antibody and/or conjugated activatable antibody provided herein, including but not limited to a multispecific activatable antibody and/or conjugated multispecific activatable antibody of the disclosure, includes at least a light chain amino acid sequence selected from the group consisting of SEQ ID NOs: 55, 59, 60, 62, 64, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, and 113. In some embodiments, the activatable antibody and/or conjugated activatable antibody provided herein, including but not limited to a multispecific activatable antibody and/or conjugated multispecific activatable antibody of the disclosure, includes at least a heavy chain amino acid sequence selected from the group consisting of SEQ ID NOs: 54, 56, 57, 58, 61, 63, 65, 68, 70, 72, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, and 114 and a light chain amino acid sequence selected from the group consisting of SEQ ID NOs: 55, 59, 60, 62, 64, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, and 113.

[0089] In some embodiments, the activatable antibody and/or conjugated activatable antibody provided herein, including but not limited to a multispecific activatable antibody and/or conjugated multispecific activatable antibody of the disclosure, includes at least a heavy chain amino acid sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 54, 56, 57, 58, 61, 63, 65, 68, 70, 72, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, and 114. In some embodiments, the activatable antibody and/or conjugated activatable antibody provided herein, including but not limited to a multispecific activatable antibody and/or conjugated multispecific activatable antibody of the disclosure, includes at least a light chain amino acid sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 55, 59, 60, 62, 64, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, and 113. In some embodiments, the activatable antibody and/or conjugated activatable antibody provided herein, including but not limited to a multispecific activatable antibody and/or conjugated multispecific activatable antibody of the disclosure, includes at least a heavy chain amino acid sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 54, 56, 57, 58, 61, 63, 65, 68, 70, 72, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, and 114 and a light chain amino acid sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to an amino acid sequence selected from the group consisting of SEQ ID NOs: 55, 59, 60, 62, 64, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, and 113.

[0090] In some embodiments, the MM has an equilibrium dissociation constant for binding to the AB that is greater than the equilibrium dissociation constant of the AB to the target.

[0091] In some embodiments, the MM has an equilibrium dissociation constant for binding to the AB that is no more than the equilibrium dissociation constant of the AB to the target.

[0092] In some embodiments, the MM does not interfere or compete with the AB for binding to the target in a cleaved state.

[0093] In some embodiments, the MM is a polypeptide of about 2 to 40 amino acids in length. For example, the MM is a polypeptide of up to about 40 amino acids in length.

[0094] In some embodiments, the MM polypeptide sequence is different from that of any natural binding partner of the AB. In some embodiments, the MM polypeptide sequence is no more than 50% identical to any natural binding partner of the AB. In some embodiments, the MM polypeptide sequence is no more than 40%, 30%, 25%, 20%, 15%, or 10% identical to any natural binding partner of the AB.

[0095] In some embodiments, the coupling of the MM to the AB reduces the ability of the AB to bind its target such that the dissociation constant (K_d) of the AB when coupled to the MM towards the target is at least two times greater than the K_d of the AB when not coupled to the MM towards the target.

[0096] In some embodiments, the coupling of the MM to the AB reduces the ability of the AB to bind its target such that the dissociation constant (K_d) of the AB when coupled to the MM towards the target is at least three times greater than the K_d of the AB when not coupled to the MM towards the target.

[0097] In some embodiments, the coupling of the MM to the AB reduces the ability of the AB to bind its target such that the dissociation constant (K_d) of the AB when coupled to the MM towards the target is at least five times greater than the K_d of the AB when not coupled to the MM towards the target.

[0098] In some embodiments, the coupling of the MM to the AB reduces the ability of the AB to bind its target such that the dissociation constant (K_d) of the AB when coupled to the MM towards the target is at least 10 times greater than the K_d of the AB when not coupled to the MM towards the target.

[0099] In some embodiments, the coupling of the MM to the AB reduces the ability of the AB to bind its target such that the dissociation constant (K_d) of the AB when coupled to the MM towards the target is at least 20 times greater than the K_d of the AB when not coupled to the MM towards the target.

[0100] In some embodiments, the coupling of the MM to the AB reduces the ability of the AB to bind the target such that the dissociation constant (K_d) of the AB when coupled to the MM towards the target is at least 40 times greater than the K_d of the AB when not coupled to the MM towards the target.

[0101] In some embodiments, the coupling of the MM to the AB reduces the ability of the AB to bind the target such that the dissociation constant (K_d) of the AB when coupled to the MM towards the target is at least 100 times greater than the K_d of the AB when not coupled to the MM towards the target.

[0102] In some embodiments, the coupling of the MM to the AB reduces the ability of the AB to bind the target such that the dissociation constant (K_d) of the AB when coupled to the MM towards the target is at least 1000 times greater than the K_d of the AB when not coupled to the MM towards the target.

[0103] In some embodiments, the coupling of the MM to the AB reduces the ability of the AB to bind the target such that the dissociation constant (K_d) of the AB when coupled to

the MM towards the target is at least 10,000 times greater than the K_d of the AB when not coupled to the MM towards the target.

[0104] In some embodiments, the MMP protease is co-localized with the target in a tissue, and the MMP cleaves the CM in the activatable antibody when the activatable antibody is exposed to the MMP.

[0105] In some embodiments, in the presence of the target, the MM reduces the ability of the AB to bind the target by at least 90% when the CM is uncleaved, as compared to when the CM is cleaved when assayed in vitro using a target displacement assay such as, for example, the assay described in PCT Publication Nos. WO 2009/025846 and WO 2010/081173.

[0106] In some embodiments, the CM is positioned in the activatable antibody such that in the uncleaved state, binding of the activatable antibody to the target is reduced to occur with an equilibrium dissociation constant that is at least two-fold greater than the equilibrium dissociation constant of an unmodified AB binding to the target, whereas in the cleaved state (i.e., when the activatable antibody is in the cleaved state), the AB binds the target.

[0107] In some embodiments, the CM is positioned in the activatable antibody such that in the uncleaved state, binding of the activatable antibody to the target is reduced to occur with an equilibrium dissociation constant that is at least five-fold greater than the equilibrium dissociation constant of an unmodified AB binding to the target, whereas in the cleaved state (i.e., when the activatable antibody is in the cleaved state), the AB binds the target.

[0108] In some embodiments, the CM is positioned in the activatable antibody such that in the uncleaved state, binding of the activatable antibody to the target is reduced to occur with an equilibrium dissociation constant that is at least ten-fold greater than the equilibrium dissociation constant of an unmodified AB binding to the target, whereas in the cleaved state (i.e., when the activatable antibody is in the cleaved state), the AB binds the target.

[0109] In some embodiments, the CM is positioned in the activatable antibody such that in the uncleaved state, binding of the activatable antibody to the target is reduced to occur with an equilibrium dissociation constant that is at least 20-fold greater than the equilibrium dissociation constant of an unmodified AB binding to the target, whereas in the cleaved state (i.e., when the activatable antibody is in the cleaved state), the AB binds the target.

[0110] In some embodiments, the CM is positioned in the activatable antibody such that in the uncleaved state, binding of the activatable antibody to the target is reduced to occur with an equilibrium dissociation constant that is at least 40-fold greater than the equilibrium dissociation constant of an unmodified AB binding to the target, whereas in the cleaved state, the AB binds the target.

[0111] In some embodiments, the CM is positioned in the activatable antibody such that in the uncleaved state, binding of the activatable antibody to the target is reduced to occur with an equilibrium dissociation constant that is at least 50-fold greater than the equilibrium dissociation constant of an unmodified AB binding to the target, whereas in the cleaved state, the AB binds the target.

[0112] In some embodiments, the CM is positioned in the activatable antibody such that in the uncleaved state, binding of the activatable antibody to the target is reduced to occur with an equilibrium dissociation constant that is at least 100-

fold greater than the equilibrium dissociation constant of an unmodified AB binding to the target, whereas in the cleaved state, the AB binds the target.

[0113] In some embodiments, the CM is positioned in the activatable antibody such that in the uncleaved state, binding of the activatable antibody to the target is reduced to occur with an equilibrium dissociation constant that is at least 200-fold greater than the equilibrium dissociation constant of an unmodified AB binding to the target, whereas in the cleaved state, the AB binds the target.

[0114] In some embodiments, the CM is a polypeptide of up to 15 amino acids in length.

[0115] In some embodiments, the CM is a substrate for at least one matrix metalloprotease (MMP). Examples of MMPs include MMP1; MMP2; MMP3; MMP7; MMP8; MMP9; MMP10; MMP11; MMP12; MMP13; MMP14; MMP15; MMP16; MMP17; MMP19; MMP20; MMP23; MMP24; MMP26; and MMP27. In some embodiments, the CM is a substrate for MMP9, MMP14, MMP1, MMP3, MMP13, MMP17, MMP11, and MMP19. In some embodiments, the CM is a substrate for MMP9. In some embodiments, the CM is a substrate for MMP14. In some embodiments, the CM is a substrate for two or more MMPs. In some embodiments, the CM is a substrate for at least MMP9 and MMP14. In some embodiments, the CM comprises two or more substrates for the same MMP. In some embodiments, the CM comprises at least two or more MMP9 substrates. In some embodiments, the CM comprises at least two or more MMP14 substrates.

[0116] In some embodiments, the CM is a substrate for an MMP and includes the sequence ISSGLLSS (SEQ ID NO: 14); QNQALRMA (SEQ ID NO: 15); AQNLLGMV (SEQ ID NO: 16); STFPFGMF (SEQ ID NO: 17); PVGYTSSL (SEQ ID NO: 18); DWLYWPGI (SEQ ID NO: 19); MIAPVAYR (SEQ ID NO: 20); RPSPMWAY (SEQ ID NO: 21); WATPRPMR (SEQ ID NO: 22); FRLLDWQW (SEQ ID NO: 23); LKAAPRWA (SEQ ID NO: 24); GPSHLVLT (SEQ ID NO: 25); LPGLLSPW (SEQ ID NO: 26); MGLFSEAG (SEQ ID NO: 27); SPLPLRVP (SEQ ID NO: 28); RMHLRSLG (SEQ ID NO: 29); LAAPLGLL (SEQ ID NO: 30); AVGLLAPP (SEQ ID NO: 31); LLAPSHRA (SEQ ID NO: 32); PAGLWLDP (SEQ ID NO: 33); and/or ISSGLSS (SEQ ID NO: 159).

[0117] In some embodiments, the CM comprises the amino acid sequence ISSGLLSS (SEQ ID NO: 14). In some embodiments, the CM comprises the amino acid sequence QNQALRMA (SEQ ID NO: 15). In some embodiments, the CM comprises the amino acid sequence AQNLLGMV (SEQ ID NO: 16). In some embodiments, the CM comprises the amino acid sequence STFPFGMF (SEQ ID NO: 17). In some embodiments, the CM comprises the amino acid sequence PVGYTSSL (SEQ ID NO: 18). In some embodiments, the CM comprises the amino acid sequence DWLYWPGI (SEQ ID NO: 19). In some embodiments, the CM comprises the amino acid sequence MIAPVAYR (SEQ ID NO: 20). In some embodiments, the CM comprises the amino acid sequence RPSPMWAY (SEQ ID NO: 21). In some embodiments, the CM comprises the amino acid sequence WATPRPMR (SEQ ID NO: 22). In some embodiments, the CM comprises the amino acid sequence FRLLDWQW (SEQ ID NO: 23). In some embodiments, the CM comprises the amino acid sequence LKAAPRWA (SEQ ID NO: 24). In some embodiments, the CM comprises the amino acid sequence GPSHLVLT (SEQ ID NO: 25). In some embodiments, the

CM comprises the amino acid sequence LPGGLSPW (SEQ ID NO: 26). In some embodiments, the CM comprises the amino acid sequence MGLFSEAG (SEQ ID NO: 27). In some embodiments, the CM comprises the amino acid sequence SPLPLRVP (SEQ ID NO: 28). In some embodiments, the CM comprises the amino acid sequence RMHL-RSLG (SEQ ID NO: 29). In some embodiments, the CM comprises the amino acid sequence LAAPLGLL (SEQ ID NO: 30). In some embodiments, the CM comprises the amino acid sequence AVGLLAPP (SEQ ID NO: 31). In some embodiments, the CM comprises the amino acid sequence LLAPSHRA (SEQ ID NO: 32). In some embodiments, the CM comprises the amino acid sequence PAGLWLDP (SEQ ID NO: 33). In some embodiments, the CM comprises the amino acid sequence ISSGLSS (SEQ ID NO: 159).

[0118] In some embodiments, the CM is a substrate for at least two proteases. In some embodiments, at least one protease is an MMP and at least one protease is selected from the group consisting of those shown in Table 7.

[0119] In some embodiments, the activatable antibody includes at least a first CM and a second CM. In some embodiments, the first CM and the second CM are each polypeptides of no more than 15 amino acids long. In some embodiments, the first CM and the second CM in the activatable antibody have the structural arrangement from N-terminus to C-terminus as follows in the uncleaved state: MM-CM 1-CM2-AB, AB-CM2-CM 1-MM, MM-CM2-CM1-AB, or AB-CM1-CM2-MM. In some embodiments, the activatable antibody includes a linking peptide between MM and CM1. In some embodiments, the activatable antibody includes a linking peptide between CM1 and CM2. In some embodiments, the activatable antibody includes a linking peptide between CM2 and AB. In some embodiments, the activatable antibody includes a linking peptide between MM and CM1 and a linking peptide between CM2 and AB. In some embodiments, the activatable antibody includes a linking peptide between MM and CM1 and a linking peptide between CM1 and CM2. In some embodiments, the activatable antibody includes a linking peptide between CM1 and CM2 and a linking peptide between CM2 and AB. In some embodiments, the activatable antibody includes a linking peptide between MM and CM1, a linking peptide between CM1 and CM2, and a linking peptide between CM2 and AB.

[0120] In some embodiments, the activatable antibody includes at least a first CM that includes a substrate for at least one matrix metalloprotease (MMP) and a second CM that includes a substrate sequence. Exemplary substrates for the second CM (CM2) include but are not limited to substrates cleavable by one or more of the following enzymes or proteases listed in Table 7.

[0121] In some embodiments, the CM2 is selected for use with a specific protease. In some embodiments, the CM2 is a substrate for at least one protease selected from the group consisting of a matrix metalloprotease (MMP), a neutrophil elastase, u-type plasminogen activator (uPA, also referred to as urokinase), legumain, matriptase (MT-SP1), thrombin, a cysteine protease such as a cathepsin, ADAM17, BMP-1, HtrA1, and a TMPRSS such as TMPRSS3 or TMPRSS4.

[0122] In some embodiments, the CM2 is a substrate for a neutrophil elastase. In some embodiments, the CM2 is a substrate for uPA. In some embodiments, the CM2 is a substrate for legumain. In some embodiments, the CM2 is a substrate for matriptase. In some embodiments, the CM2 is a substrate for thrombin. In some embodiments, the CM2 is a

substrate for a cysteine protease. In some embodiments, the CM2 is a substrate for a cathepsin. In some embodiments, the CM2 is a substrate for ADAM17. In some embodiments, the CM2 is a substrate for BMP-1. In some embodiments, the CM2 is a substrate for HtrA1. In some embodiments, the CM2 is a substrate for a TMPRSS. In some embodiments, the CM2 is a substrate for TMPRSS3. In some embodiments, the CM2 is a substrate for TMPRSS4.

[0123] For example, suitable CM2 are cleaved by at least one protease and include the sequence TGRGPSWV (SEQ ID NO: 34); SARGPSRW (SEQ ID NO: 35); TARGPSFK (SEQ ID NO: 36); LSGRSDNH (SEQ ID NO: 37); GGWHTGRN (SEQ ID NO: 38); HTGRSGAL (SEQ ID NO: 39); PLTGRSGG (SEQ ID NO: 40); AARGPAIH (SEQ ID NO: 41); RGPAFNPM (SEQ ID NO: 42); SSRGPAYL (SEQ ID NO: 43); RGPATPIM (SEQ ID NO: 44); RGPA (SEQ ID NO: 45); GGQPSGMWGW (SEQ ID NO: 46); FPRPLGITGL (SEQ ID NO: 47); VHMPFLGP (SEQ ID NO: 48); SPLTGRSG (SEQ ID NO: 49); SAGFSLPA (SEQ ID NO: 126); LAPLGLQRR (SEQ ID NO: 50); SGGPLGVR (SEQ ID NO: 51); PLGL (SEQ ID NO: 52); GPRSFG (SEQ ID NO: 315) and/or GPRSFG (SEQ ID NO: 316).

[0124] In some embodiments, the CM2 comprises the amino acid sequence TGRGPSWV (SEQ ID NO: 34). In some embodiments, the CM2 comprises the amino acid sequence SARGPSRW (SEQ ID NO: 35). In some embodiments, the CM2 comprises the amino acid sequence TARGPSFK (SEQ ID NO: 36). In some embodiments, the CM2 comprises the amino acid sequence LSGRSDNH (SEQ ID NO: 37). In some embodiments, the CM2 comprises the amino acid sequence GGWHTGRN (SEQ ID NO: 38). In some embodiments, the CM2 comprises the amino acid sequence HTGRSGAL (SEQ ID NO: 39). In some embodiments, the CM2 comprises the amino acid sequence PLTGRSGG (SEQ ID NO: 40). In some embodiments, the CM2 comprises the amino acid sequence AARGPAIH (SEQ ID NO: 41). In some embodiments, the CM2 comprises the amino acid sequence RGPAFNPM (SEQ ID NO: 42). In some embodiments, the CM2 comprises the amino acid sequence SSRGPAYL (SEQ ID NO: 43). In some embodiments, the CM2 comprises the amino acid sequence RGPATPIM (SEQ ID NO: 44). In some embodiments, the CM2 comprises the amino acid sequence RGPA (SEQ ID NO: 45). In some embodiments, the CM2 comprises the amino acid sequence GGQPSGMWGW (SEQ ID NO: 46). In some embodiments, the CM2 comprises the amino acid sequence FPRPLGITGL (SEQ ID NO: 47). In some embodiments, the CM2 comprises the amino acid sequence VHMPFLGP (SEQ ID NO: 48). In some embodiments, the CM2 comprises the amino acid sequence SPLTGRSG (SEQ ID NO: 49). In some embodiments, the CM2 comprises the amino acid sequence LAPLGLQRR (SEQ ID NO: 50). In some embodiments, the CM2 comprises the amino acid sequence SGGPLGVR (SEQ ID NO: 51). In some embodiments, the CM2 comprises the amino acid sequence PLGL (SEQ ID NO: 52). In some embodiments, the CM2 comprises the amino acid sequence GPRSFG (SEQ ID NO: 315). In some embodiments, the CM2 comprises the amino acid sequence GPRSFG (SEQ ID NO: 316)

[0125] In some embodiments, the CM2 is a substrate for at least one MMP. In some embodiments, the CM2 is a substrate for at least one MMP listed in the Table 7. In some embodiments, the CM2 is a substrate for MMP9. In some embodiments, the CM2 is a substrate for MMP14. In some embodi-

ments, CM1 is substrate for a first MMP, and CM2 is a substrate for a second MMP, where the first MMP and the second MMP are different MMPs. In some embodiments, CM1 is a first substrate sequence for a MMP, and CM2 is a second substrate for the same MMP, where the CM1 and CM2 have different substrate sequences. In some embodiments, the CM2 is a substrate for two or more MMPs. In some embodiments, the CM2 is a substrate for at least MMP9 or MMP14. In some embodiments, the CM2 is a substrate for two or more MMPs. In some embodiments, the CM2 is a substrate for at least MMP9 and MMP14. In some embodiments, CM1 and CM2 are both substrates for MMP9. In some embodiments, CM1 and CM2 are both substrates for MMP14. In some embodiments, CM1 is a substrate for MMP9 and CM2 is a substrate for MMP14. In some embodiments, CM1 is a substrate for MMP14 and CM2 is a substrate for MMP9.

[0126] In some embodiments, at least one of CM1 and/or CM2 is a substrate for an MMP and includes the sequence ISSGLLSS (SEQ ID NO: 14); QNQALRMA (SEQ ID NO: 15); AQNLLGMV (SEQ ID NO: 16); STFPFGMF (SEQ ID NO: 17); PVGYTSSL (SEQ ID NO: 18); DWLYWPGI (SEQ ID NO: 19); MIAPVAYR (SEQ ID NO: 20); RPSPMWAY (SEQ ID NO: 21); WATPRPRMR (SEQ ID NO: 22); FRLLD-WQW (SEQ ID NO: 23); LKAAPRWA (SEQ ID NO: 24); GPSHLVLT (SEQ ID NO: 25); LPGLSPW (SEQ ID NO: 26); MGLFSEAG (SEQ ID NO: 27); SPLPLRVP (SEQ ID NO: 28); RMHRLRSLG (SEQ ID NO: 29); LAAPLGLL (SEQ ID NO: 30); AVGLLAPP (SEQ ID NO: 31); LLAPSHRA (SEQ ID NO: 32); PAGLWLDP (SEQ ID NO: 33); and/or ISSGLSS (SEQ ID NO: 159).

[0127] In some embodiments, the first cleaving agent and the second cleaving agent are the same matrix metalloprotease, and the first CM and the second CM are different substrates for the enzyme. In some embodiments, the first cleaving agent and the second cleaving agent are different proteases, where at least one protease is an MMP. In some embodiments, the first cleaving agent and the second cleaving agent are co-localized in the target tissue. In some embodiments, the first CM and the second CM are cleaved by at least one cleaving agent in the target tissue.

[0128] In some embodiments, the activatable antibody is exposed to and cleaved by a MMP such that, in the activated or cleaved state, the activated antibody includes a light chain amino acid sequence that includes at least a portion of LP2 and/or CM sequence after the MMP has cleaved the CM.

[0129] In some embodiments, the CM comprises the non-prime side of the protease cleavage site; that is, the CM comprises at least the P1 and P2 amino acids, and in some embodiments, comprises the P1, P2 and P3 amino acids and in some embodiments, comprises the P1, P2, P3, and P4 amino acids. In some embodiments, the CM comprises the non-prime side and the prime side of the protease cleavage site. In some embodiments, the CM comprises the non-prime side but lacks at least part of the prime side of the protease cleavage site. In some embodiments, the CM comprises the non-prime side but lacks the prime side of the protease cleavage site. Such a CM can be linked directly or through a linker to an antibody or other molecule as disclosed herein, such as, but not limited to, a detection moiety.

[0130] In some embodiments, the activatable antibody is an anti-EGFR activatable antibody that includes at least an AB that is or is derived from cetuximab or panitumumab; a MM comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 160, 167-200, and 497; and a CM

comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 14-33, and 159. In some embodiments, the activatable antibody is an anti-EGFR activatable antibody that includes at least an AB that is or is derived from cetuximab or panitumumab; a MM comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 160, 167-200, and 497; and a CM comprising an amino acid sequence selected from the group consisting of the sequences presented in Tables 8A-8M. In some embodiments, the anti-EGFR activatable antibody also includes a first linking peptide (LP1) and a second linking peptide (LP2), and the activatable antibody in the uncleaved state has the structural arrangement from N-terminus to C-terminus as follows: MM-LP1-CM-LP2-AB or AB-LP2-CM-LP1-MM. In some embodiments, each of LP1 and LP2 is a peptide of about 1 to 20 amino acids in length. In some embodiments, the two linking peptides need not be identical to each other. In some embodiments, at least one of LP1 or LP2 comprises an amino acid sequence selected from the group consisting of (GS)_n, (GGS)_n, (GSGGS)_n (SEQ ID NO: 1) and (GGGS)_n (SEQ ID NO: 2), where n is an integer of at least one. In some embodiments, at least one of LP1 or LP2 comprises an amino acid sequence selected from the group consisting of GGSG (SEQ ID NO: 3), GGS GG (SEQ ID NO: 4), GSGSG (SEQ ID NO: 5), GSGGG (SEQ ID NO: 6), GGGSG (SEQ ID NO: 7), and GSSSG (SEQ ID NO: 8). In some embodiments, LP1 comprises the amino acid sequence GSSGGSGGS (SEQ ID NO: 9), GSSGGSGGS (SEQ ID NO: 10), GSSGGSGGS (SEQ ID NO: 11), GSSGGSGGS (SEQ ID NO: 155), GSSGGSGGS (SEQ ID NO: 156), or GSSGGSGGS (SEQ ID NO: 157). In some embodiments, LP2 comprises the amino acid sequence GSS, GGS, GGGS (SEQ ID NO: 158), GSSGT (SEQ ID NO: 12) or GSSG (SEQ ID NO: 13).

[0131] In some embodiments, the activatable antibody is an anti-EGFR activatable antibody that includes at least an AB comprising a heavy chain amino acid sequence comprising the VH CDR1 sequence of SEQ ID NO: 504, the VH CDR2 sequence of SEQ ID NO: 505, the VH CDR3 sequence of SEQ ID NO: 506, the VL CDR1 sequence of SEQ ID NO: 507, the VL CDR2 sequence of SEQ ID NO: 508, and the VL CDR3 sequence of SEQ ID NO: 509; a MM comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 160, 167-200, and 497; and a CM comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 14-33, and 159. In some embodiments, the activatable antibody is an anti-EGFR activatable antibody that includes at least an AB comprising a heavy chain amino acid sequence comprising the VH CDR1 sequence of SEQ ID NO: 504, the VH CDR2 sequence of SEQ ID NO: 505, the VH CDR3 sequence of SEQ ID NO: 506, the VL CDR1 sequence of SEQ ID NO: 507, the VL CDR2 sequence of SEQ ID NO: 508, and the VL CDR3 sequence of SEQ ID NO: 509; a MM comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 160, 167-200, and 497; and a CM comprising an amino acid sequence selected from the group consisting of the sequences presented in Tables 8A-8M. In some embodiments, the anti-EGFR activatable antibody also includes a first linking peptide (LP1) and a second linking peptide (LP2), and the activatable antibody in the uncleaved state has the structural arrangement from N-terminus to C-terminus as follows: MM-LP1-CM-LP2-AB or AB-LP2-CM-LP1-MM. In some embodiments, each of LP1 and LP2 is a peptide of about 1 to 20 amino acids in length. In some

embodiments, the two linking peptides need not be identical to each other. In some embodiments, at least one of LP1 or LP2 comprises an amino acid sequence selected from the group consisting of (GS)_n, (GGS)_n, (GSGGS)_n (SEQ ID NO: 1) and (GGGS)_n (SEQ ID NO: 2), where n is an integer of at least one. In some embodiments, at least one of LP1 or LP2 comprises an amino acid sequence selected from the group consisting of GGSG (SEQ ID NO: 3), GGS GG (SEQ ID NO: 4), GSG SG (SEQ ID NO: 5), GSG GG (SEQ ID NO: 6), GGG SG (SEQ ID NO: 7), and GSS SG (SEQ ID NO: 8). In some embodiments, LP1 comprises the amino acid sequence GSSGGSGGGSG (SEQ ID NO: 9), GSSGGSGGGSG (SEQ ID NO: 10), GSSGGSGGGSGGS (SEQ ID NO: 11), GSSGGSGGGSGGGSG (SEQ ID NO: 155), GSSGGSGGGSG (SEQ ID NO: 156), or GSSGGSGGGSGS (SEQ ID NO: 157). In some embodiments, LP2 comprises the amino acid sequence GSS, GGS, GGGS (SEQ ID NO: 158), GSSGT (SEQ ID NO: 12) or GSSG (SEQ ID NO: 13).

[0132] In some embodiments, the activatable antibody is an anti-EGFR activatable antibody that includes at least an AB comprising the heavy chain amino acid sequence of SEQ ID NO: 56, 57 or 58 and the light chain amino acid sequence of SEQ ID NO: 59; a MM comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 160, 167-200, and 497; and a CM comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 14-33, and 159. In some embodiments, the activatable antibody is an anti-EGFR activatable antibody that includes at least an AB comprising the heavy chain amino acid sequence of SEQ ID NO: 56, 57 or 58 and the light chain amino acid sequence of SEQ ID NO: 59; a MM comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 160, 167-200, and 497; and a CM comprising an amino acid sequence selected from the group consisting of the sequences presented in Tables 8A-8M. In some embodiments, the anti-EGFR activatable antibody also includes a first linking peptide (LP1) and a second linking peptide (LP2), and the activatable antibody in the uncleaved state has the structural arrangement from N-terminus to C-terminus as follows: MM-LP1-CM-LP2-AB or AB-LP2-CM-LP1-MM. In some embodiments, each of LP1 and LP2 is a peptide of about 1 to 20 amino acids in length. In some embodiments, the two linking peptides need not be identical to each other. In some embodiments, at least one of LP1 or LP2 comprises an amino acid sequence selected from the group consisting of (GS)_n, (GGS)_n, (GSGGS)_n (SEQ ID NO: 1) and (GGGS)_n (SEQ ID NO: 2), where n is an integer of at least one. In some embodiments, at least one of LP1 or LP2 comprises an amino acid sequence selected from the group consisting of GGSG (SEQ ID NO: 3), GGS GG (SEQ ID NO: 4), GSG SG (SEQ ID NO: 5), GSG GG (SEQ ID NO: 6), GGG SG (SEQ ID NO: 7), and GSS SG (SEQ ID NO: 8). In some embodiments, LP1 comprises the amino acid sequence GSSGGSGGGSG (SEQ ID NO: 9), GSSGGSGGGSG (SEQ ID NO: 10), GSSGGSGGGSGGS (SEQ ID NO: 11), GSSGGSGGGSGGS (SEQ ID NO: 155), GSSGGSGGGSG (SEQ ID NO: 156), or GSSGGSGGGSGS (SEQ ID NO: 157). In some embodiments, LP2 comprises the amino acid sequence GSS, GGS, GGGS (SEQ ID NO: 158), GSSGT (SEQ ID NO: 12) or GSSG (SEQ ID NO: 13).

[0133] In some embodiments, the activatable antibody is an anti-EGFR activatable antibody that includes at least an AB comprising the heavy chain amino acid sequence of SEQ ID NO: 56 and the light chain amino acid sequence of SEQ ID

NO: 59; a MM comprising the amino acid sequence of SEQ ID NO: 160; and a CM comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 14-33, and 159. In some embodiments, the activatable antibody is an anti-EGFR activatable antibody that includes at least an AB comprising the heavy chain amino acid sequence of SEQ ID NO: 56 and the light chain amino acid sequence of SEQ ID NO: 59; a MM comprising the amino acid sequence of SEQ ID NO: 160; and a CM comprising an amino acid sequence selected from the group consisting of the sequences presented in Tables 8A-8M. In some embodiments, the anti-EGFR activatable antibody also includes a first linking peptide (LP1) and a second linking peptide (LP2), and the activatable antibody in the uncleaved state has the structural arrangement from N-terminus to C-terminus as follows: MM-LP1-CM-LP2-AB or AB-LP2-CM-LP1-MM. In some embodiments, each of LP1 and LP2 is a peptide of about 1 to 20 amino acids in length. In some embodiments, the two linking peptides need not be identical to each other. In some embodiments, at least one of LP1 or LP2 comprises an amino acid sequence selected from the group consisting of (GS)_n, (GGS)_n, (GSGGS)_n (SEQ ID NO: 1) and (GGGS)_n (SEQ ID NO: 2), where n is an integer of at least one. In some embodiments, at least one of LP1 or LP2 comprises an amino acid sequence selected from the group consisting of GGSG (SEQ ID NO: 3), GGS GG (SEQ ID NO: 4), GSG SG (SEQ ID NO: 5), GSG GG (SEQ ID NO: 6), GGG SG (SEQ ID NO: 7), and GSS SG (SEQ ID NO: 8). In some embodiments, LP1 comprises the amino acid sequence GSSGGSGGGSG (SEQ ID NO: 9), GSSGGSGGGSG (SEQ ID NO: 10), GSSGGSGGGSGGS (SEQ ID NO: 11), GSSGGSGGGSGGS (SEQ ID NO: 155), GSSGGSGGGSG (SEQ ID NO: 156), or GSSGGSGGGSGS (SEQ ID NO: 157). In some embodiments, LP2 comprises the amino acid sequence GSS, GGS, GGGS (SEQ ID NO: 158), GSSGT (SEQ ID NO: 12) or GSSG (SEQ ID NO: 13).

[0134] In some embodiments, the activatable antibody is an anti-EGFR activatable antibody that includes at least an AB comprising a heavy chain amino acid sequence comprising the VH CDR1 sequence of SEQ ID NO: 504, the VH CDR2 sequence of SEQ ID NO: 505, the VH CDR3 sequence of SEQ ID NO: 506, the VL CDR1 sequence of SEQ ID NO: 507, the VL CDR2 sequence of SEQ ID NO: 508, and the VL CDR2 sequence of SEQ ID NO: 509; a MM comprising the amino acid sequence of SEQ ID NO: 160; and a CM comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 14-33, and 159. In some embodiments, the activatable antibody is an anti-EGFR activatable antibody that includes at least an AB comprising a heavy chain amino acid sequence comprising the VH CDR1 sequence of SEQ ID NO: 504, the VH CDR2 sequence of SEQ ID NO: 505, the VH CDR3 sequence of SEQ ID NO: 506, the VL CDR1 sequence of SEQ ID NO: 507, the VL CDR2 sequence of SEQ ID NO: 508, and the VL CDR2 sequence of SEQ ID NO: 509; a MM comprising the amino acid sequence of SEQ ID NO: 160; and a CM comprising an amino acid sequence selected from the group consisting of the sequences presented in Tables 8A-8M. In some embodiments, the anti-EGFR activatable antibody also includes a first linking peptide (LP1) and a second linking peptide (LP2), and the activatable antibody in the uncleaved state has the structural arrangement from N-terminus to C-terminus as follows: MM-LP1-CM-LP2-AB or AB-LP2-CM-LP1-MM. In some embodiments, each of LP1 and LP2 is a peptide of about 1 to 20 amino acids in length. In

some embodiments, the two linking peptides need not be identical to each other. In some embodiments, at least one of LP1 or LP2 comprises an amino acid sequence selected from the group consisting of (GS)_n, (GGS)_n, (GSGGS)_n (SEQ ID NO: 1) and (GGGS)_n (SEQ ID NO: 2), where n is an integer of at least one. In some embodiments, at least one of LP1 or LP2 comprises an amino acid sequence selected from the group consisting of GGSG (SEQ ID NO: 3), GGS GG (SEQ ID NO: 4), GSG SG (SEQ ID NO: 5), GSG GG (SEQ ID NO: 6), GGG SG (SEQ ID NO: 7), and GSS SG (SEQ ID NO: 8). In some embodiments, LP1 comprises the amino acid sequence GSS GG SG SG SG (SEQ ID NO: 9), GSS GG SG SG SG (SEQ ID NO: 10), GSS GG SG SG SG (SEQ ID NO: 11), GSS GG SG SG SG SG (SEQ ID NO: 155), GSS GG SG SG SG (SEQ ID NO: 156), or GSS GG SG SG SG (SEQ ID NO: 157). In some embodiments, LP2 comprises the amino acid sequence GSS, GGS, GGGS (SEQ ID NO: 158), GSS GT (SEQ ID NO: 12) or GSSG (SEQ ID NO: 13).

[0135] In some embodiments, the activatable antibody is an anti-Jagged activatable antibody that includes at least an AB comprising the heavy chain amino acid sequence of SEQ ID NO: 61, 63, 65, 68, 70, 72, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, or 114 and the light chain amino acid sequence of SEQ ID NO: 60, 62, 64, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, or 113; a MM comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 201-263, and 496; and a CM comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 14-33, and 159. In some embodiments, the activatable antibody is an anti-Jagged activatable antibody that includes at least an AB comprising the heavy chain amino acid sequence of SEQ ID NO: 61, 63, 65, 68, 70, 72, 76, 78, 80, 82, 84, 86, 88, 90, 92, 94, 96, 98, 100, 102, 104, 106, 108, 110, 112, or 114 and the light chain amino acid sequence of SEQ ID NO: 60, 62, 64, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91, 93, 95, 97, 99, 101, 103, 105, 107, 109, 111, or 113; a MM comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 201-263, and 496; and a CM comprising an amino acid sequence selected from the group consisting of the sequences presented in Tables 8A-8M. In some embodiments, the anti-Jagged activatable antibody also includes a first linking peptide (LP1) and a second linking peptide (LP2), and the activatable antibody in the uncleaved state has the structural arrangement from N-terminus to C-terminus as follows: MM-LP1-CM-LP2-AB or AB-LP2-CM-LP1-MM. In some embodiments, each of LP1 and LP2 is a peptide of about 1 to 20 amino acids in length. In some embodiments, the two linking peptides need not be identical to each other. In some embodiments, at least one of LP1 or LP2 comprises an amino acid sequence selected from the group consisting of (GS)_n, (GGS)_n, (GSGGS)_n (SEQ ID NO: 1) and (GGGS)_n (SEQ ID NO: 2), where n is an integer of at least one. In some embodiments, at least one of LP1 or LP2 comprises an amino acid sequence selected from the group consisting of GGSG (SEQ ID NO: 3), GGS GG (SEQ ID NO: 4), GSG SG (SEQ ID NO: 5), GSG GG (SEQ ID NO: 6), GGG SG (SEQ ID NO: 7), and GSS SG (SEQ ID NO: 8). In some embodiments, LP1 comprises the amino acid sequence GSS GG SG SG SG (SEQ ID NO: 9), GSS GG SG SG SG (SEQ ID NO: 11), GSS GG SG SG SG SG (SEQ ID NO: 155), GSS GG SG SG SG (SEQ ID NO: 156), or GSS GG SG SG SG (SEQ ID NO: 157). In some embodiments, LP2 comprises the amino acid sequence GSS, GGS, GGGS (SEQ ID NO: 158), GSS GT (SEQ ID NO: 12) or GSSG (SEQ ID NO: 13).

amino acid sequence GSS, GGS, GGGS (SEQ ID NO: 158), GSS GT (SEQ ID NO: 12) or GSSG (SEQ ID NO: 13).

[0136] In some embodiments, the activatable antibody is an anti-Jagged activatable antibody that includes at least an AB comprising the heavy chain amino acid sequence of SEQ ID NO: 112 and the light chain amino acid sequence of SEQ ID NO: 111; a MM comprising the amino acid sequence selected of SEQ ID NO: 217; and a CM comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 14-33, and 159. In some embodiments, the activatable antibody is an anti-Jagged activatable antibody that includes at least an AB comprising the heavy chain amino acid sequence of SEQ ID NO: 112 and the light chain amino acid sequence of SEQ ID NO: 111; a MM comprising the amino acid sequence selected of SEQ ID NO: 217; and a CM comprising an amino acid sequence selected from the group consisting of the sequences presented in Tables 8A-8M. In some embodiments, the anti-Jagged activatable antibody also includes a first linking peptide (LP1) and a second linking peptide (LP2), and the activatable antibody in the uncleaved state has the structural arrangement from N-terminus to C-terminus as follows: MM-LP1-CM-LP2-AB or AB-LP2-CM-LP1-MM. In some embodiments, each of LP1 and LP2 is a peptide of about 1 to 20 amino acids in length. In some embodiments, the two linking peptides need not be identical to each other. In some embodiments, at least one of LP1 or LP2 comprises an amino acid sequence selected from the group consisting of (GS)_n, (GGS)_n, (GSGGS)_n (SEQ ID NO: 1) and (GGGS)_n (SEQ ID NO: 2), where n is an integer of at least one. In some embodiments, at least one of LP1 or LP2 comprises an amino acid sequence selected from the group consisting of GGSG (SEQ ID NO: 3), GGS GG (SEQ ID NO: 4), GSG SG (SEQ ID NO: 5), GSG GG (SEQ ID NO: 6), GGG SG (SEQ ID NO: 7), and GSS SG (SEQ ID NO: 8). In some embodiments, LP1 comprises the amino acid sequence GSS GG SG SG SG (SEQ ID NO: 9), GSS GG SG SG SG (SEQ ID NO: 11), GSS GG SG SG SG SG (SEQ ID NO: 155), GSS GG SG SG SG (SEQ ID NO: 156), or GSS GG SG SG SG (SEQ ID NO: 157). In some embodiments, LP2 comprises the amino acid sequence GSS, GGS, GGGS (SEQ ID NO: 158), GSS GT (SEQ ID NO: 12) or GSSG (SEQ ID NO: 13).

[0137] In some embodiments, the activatable antibody is an anti-Jagged activatable antibody that includes at least an AB comprising a heavy chain amino acid sequence comprising the VH CDR1 sequence of SEQ ID NO: 498, the VH CDR2 sequence of SEQ ID NO: 499, the VH CDR3 sequence of SEQ ID NO: 500, the VL CDR1 sequence of SEQ ID NO: 501, the VL CDR2 sequence of SEQ ID NO: 502, and the VL CDR2 sequence of SEQ ID NO: 503; a MM comprising the amino acid sequence selected from the group consisting of SEQ ID NO: 217; and a CM comprising an amino acid sequence selected from the group consisting of SEQ ID NO: 14-33, and 159. In some embodiments, the activatable antibody is an anti-Jagged activatable antibody that includes at least an AB comprising a heavy chain amino acid sequence comprising the VH CDR1 sequence of SEQ ID NO: 498, the VH CDR2 sequence of SEQ ID NO: 499, the VH CDR3 sequence of SEQ ID NO: 500, the VL CDR1 sequence of SEQ ID NO: 501, the VL CDR2 sequence of SEQ ID NO: 502, and the VL CDR2 sequence of SEQ ID NO: 503; a MM comprising the amino acid sequence selected from the group consisting of SEQ ID NO: 217; and a CM comprising an amino acid sequence selected from the group consisting of

the sequences presented in Tables 8A-8M. In some embodiments, the anti-Jagged activatable antibody also includes a first linking peptide (LP1) and a second linking peptide (LP2), and the activatable antibody in the uncleaved state has the structural arrangement from N-terminus to C-terminus as follows: MM-LP1-CM-LP2-AB or AB-LP2-CM-LP1-MM. In some embodiments, each of LP1 and LP2 is a peptide of about 1 to 20 amino acids in length. In some embodiments, the two linking peptides need not be identical to each other. In some embodiments, at least one of LP1 or LP2 comprises an amino acid sequence selected from the group consisting of (GS)_n, (GGS)_n, (GSGGS)_n (SEQ ID NO: 1) and (GGGS)_n (SEQ ID NO: 2), where n is an integer of at least one. In some embodiments, at least one of LP1 or LP2 comprises an amino acid sequence selected from the group consisting of GGSG (SEQ ID NO: 3), GGSGG (SEQ ID NO: 4), GSGSG (SEQ ID NO: 5), GSGGG (SEQ ID NO: 6), GGGSG (SEQ ID NO: 7), and GSSSG (SEQ ID NO: 8). In some embodiments, LP1 comprises the amino acid sequence GSSGGSGGS (SEQ ID NO: 9), GSSGGSGGS (SEQ ID NO: 10), GSSGGSGGS (SEQ ID NO: 11), GSSGGSGGS (SEQ ID NO: 155), GSSGGSGGS (SEQ ID NO: 156), or GSSGGSGGS (SEQ ID NO: 157). In some embodiments, LP2 comprises the amino acid sequence GSS, GGS, GGGS (SEQ ID NO: 158), GSSGT (SEQ ID NO: 12) or GSSG (SEQ ID NO: 13).

[0138] In some embodiments, the activatable antibody also includes an agent conjugated to the AB. In some embodiments, the agent is a therapeutic agent. In some embodiments, the agent is an antineoplastic agent. In some embodiments, the agent is a toxin or a fragment thereof. In some embodiments, the agent is conjugated to the AB via a linker. In some embodiments, the linker is a cleavable linker. In some embodiments, the agent is a microtubule inhibitor. In some embodiments, the agent is a nucleic acid damaging agent, such as a DNA alkylator or DNA intercalator, or other DNA damaging agent. In some embodiments, the linker is a cleavable linker. In some embodiments, the agent is conjugated to the AB via a linker that includes at least one MMP-cleavable substrate sequence. In some embodiments, the agent is an agent selected from the group listed in Table 3. In some embodiments, the agent is a dolastatin. In some embodiments, the agent is an auristatin or derivative thereof. In some embodiments, the agent is auristatin E or a derivative thereof. In some embodiments, the agent is monomethyl auristatin E (MMAE). In some embodiments, the agent is monomethyl auristatin D (MMAD). In some embodiments, the agent is a maytansinoid or maytansinoid derivative. In some embodiments, the agent is DM1 or DM4. In some embodiments, the agent is a duocarmycin or derivative thereof. In some embodiments, the agent is a calicheamicin or derivative thereof. In some embodiments, the agent is a pyrrolobenzodiazepine.

[0139] In some embodiments, the agent is an anti-inflammatory agent.

[0140] In some embodiments, the activatable antibody also includes a detectable moiety. In some embodiments, the detectable moiety is a diagnostic agent.

[0141] In some embodiments, the conjugated antibody includes a detectable label. In some embodiments, the detectable label includes an imaging agent, a contrasting agent, an enzyme, a fluorescent label, a chromophore, a dye, one or more metal ions, or a ligand-based label. In some embodiments, the imaging agent comprises a radioisotope. In some embodiments, the radioisotope is indium or technetium. In

some embodiments, the contrasting agent comprises iodine, gadolinium or iron oxide. In some embodiments, the enzyme comprises horseradish peroxidase, alkaline phosphatase, or β -galactosidase. In some embodiments, the fluorescent label comprises yellow fluorescent protein (YFP), cyan fluorescent protein (CFP), green fluorescent protein (GFP), modified red fluorescent protein (mRFP), red fluorescent protein (dimer2 (RFP dimer2), HCRED, or a europium derivative. In some embodiments, the luminescent label comprises an N-methylacridinium derivative. In some embodiments, the label comprises an Alexa Fluor® label, such as Alex Fluor® 680 or Alexa Fluor® 750. In some embodiments, the ligand-based label comprises biotin, avidin, streptavidin or one or more haptens.

[0142] In some embodiments, the activatable antibody also includes a signal peptide. In some embodiments, the signal peptide is conjugated to the activatable antibody via a spacer. In some embodiments, the spacer is conjugated to the activatable antibody in the absence of a signal peptide. In some embodiments, the spacer is joined directly to the MM of the activatable antibody. In some embodiments, the spacer is joined directly to the MM of the activatable antibody in the structural arrangement from N-terminus to C-terminus of spacer-MM-CM-AB. An example of a spacer joined directly to the N-terminus of MM of the activatable antibody is QGQSGQ (SEQ ID NO: 53). In some embodiments, the spacer includes at least the amino acid sequence QGQSGQ (SEQ ID NO: 53).

[0143] In some embodiments, the AB of the activatable antibody naturally contains one or more disulfide bonds. In some embodiments, the AB can be engineered to include one or more disulfide bonds.

[0144] In some embodiments, the serum half-life of the activatable antibody is longer than that of the corresponding antibody; e.g., the pK of the activatable antibody is longer than that of the corresponding antibody. In some embodiments, the serum half-life of the activatable antibody is similar to that of the corresponding antibody. In some embodiments, the serum half-life of the activatable antibody is at least 15 days when administered to an organism. In some embodiments, the serum half-life of the activatable antibody is at least 12 days when administered to an organism. In some embodiments, the serum half-life of the activatable antibody is at least 11 days when administered to an organism. In some embodiments, the serum half-life of the activatable antibody is at least 10 days when administered to an organism. In some embodiments, the serum half-life of the activatable antibody is at least 9 days when administered to an organism. In some embodiments, the serum half-life of the activatable antibody is at least 8 days when administered to an organism. In some embodiments, the serum half-life of the activatable antibody is at least 7 days when administered to an organism. In some embodiments, the serum half-life of the activatable antibody is at least 6 days when administered to an organism. In some embodiments, the serum half-life of the activatable antibody is at least 5 days when administered to an organism. In some embodiments, the serum half-life of the activatable antibody is at least 4 days when administered to an organism. In some embodiments, the serum half-life of the activatable antibody is at least 3 days when administered to an organism. In some embodiments, the serum half-life of the activatable antibody is at least 2 days when administered to an organism. In some embodiments, the serum half-life of the activatable antibody is at least 24 hours when administered to an organism. In

some embodiments, the serum half-life of the activatable antibody is at least 20 hours when administered to an organism. In some embodiments, the serum half-life of the activatable antibody is at least 18 hours when administered to an organism. In some embodiments, the serum half-life of the activatable antibody is at least 16 hours when administered to an organism. In some embodiments, the serum half-life of the activatable antibody is at least 14 hours when administered to an organism. In some embodiments, the serum half-life of the activatable antibody is at least 12 hours when administered to an organism. In some embodiments, the serum half-life of the activatable antibody is at least 10 hours when administered to an organism. In some embodiments, the serum half-life of the activatable antibody is at least 8 hours when administered to an organism. In some embodiments, the serum half-life of the activatable antibody is at least 6 hours when administered to an organism. In some embodiments, the serum half-life of the activatable antibody is at least 4 hours when administered to an organism. In some embodiments, the serum half-life of the activatable antibody is at least 3 hours when administered to an organism.

[0145] In some embodiments, the activatable antibody and/or conjugated activatable antibody is monospecific. In some embodiments, the activatable antibody and/or conjugated activatable antibody is multispecific, e.g., by way of non-limiting example, bispecific or trifunctional. In some embodiments, the activatable antibody and/or conjugated activatable antibody is formulated as part of a pro-Bispecific T Cell Engager (pro-BITE) molecule. In some embodiments, the activatable antibody and/or conjugated activatable antibody is formulated as part of a pro-Chimeric Antigen Receptor (pro-CAR) modified T cell or other engineered receptor.

[0146] The disclosure also provides compositions and methods that include an activatable antibody that includes an antibody or antibody fragment (AB) that specifically binds a given target, where the AB is coupled to a masking moiety (MM) that decreases the ability of the AB to bind its target. In some embodiments, the activatable antibody further includes a cleavable moiety (CM) that is a substrate for at least one MMP. The compositions and methods provided herein enable the attachment of one or more agents to one or more cysteine residues in the AB without compromising the activity (e.g., the masking, activating or binding activity) of the activatable antibody. In some embodiments, the compositions and methods provided herein enable the attachment of one or more agents to one or more cysteine residues in the AB without reducing or otherwise disturbing one or more disulfide bonds within the MM. The compositions and methods provided herein produce an activatable antibody that is conjugated to one or more agents, e.g., any of a variety of therapeutic, diagnostic and/or prophylactic agents, for example, in some embodiments, without any of the agent(s) being conjugated to the MM of the activatable antibody. The compositions and methods provided herein produce conjugated activatable antibodies in which the MM retains the ability to effectively and efficiently mask the AB of the activatable antibody in an uncleaved state. The compositions and methods provided herein produce conjugated activatable antibodies in which the activatable antibody is still activated, i.e., cleaved, in the presence of a MMP that can cleave the CM.

[0147] The activatable antibodies have at least one point of conjugation for an agent, but in the methods and compositions provided herein less than all possible points of conjugation are available for conjugation to an agent. In some

embodiments, the one or more points of conjugation are sulfur atoms involved in disulfide bonds. In some embodiments, the one or more points of conjugation are sulfur atoms involved in interchain disulfide bonds. In some embodiments, the one or more points of conjugation are sulfur atoms involved in interchain sulfide bonds, but not sulfur atoms involved in intrachain disulfide bonds. In some embodiments, the one or more points of conjugation are sulfur atoms of cysteine or other amino acid residues containing a sulfur atom. Such residues may occur naturally in the antibody structure or may be incorporated into the antibody by site-directed mutagenesis, chemical conversion, or mis-incorporation of non-natural amino acids.

[0148] Also provided are methods of preparing a conjugate of an activatable antibody having one or more interchain disulfide bonds in the AB and one or more intrachain disulfide bonds in the MM, and a drug reactive with free thiols is provided. The method generally includes partially reducing interchain disulfide bonds in the activatable antibody with a reducing agent, such as, for example, TCEP; and conjugating the drug reactive with free thiols to the partially reduced activatable antibody. As used herein, the term partial reduction refers to situations where an activatable antibody is contacted with a reducing agent and less than all disulfide bonds, e.g., less than all possible sites of conjugation are reduced. In some embodiments, less than 99%, 98%, 97%, 96%, 95%, 90%, 85%, 80%, 75%, 70%, 65%, 60%, 55%, 50%, 45%, 40%, 35%, 30%, 25%, 20%, 15%, 10% or less than 5% of all possible sites of conjugation are reduced.

a range from about 8:1 to about 1:1. In some embodiments, the ratio is in a range of from about 2.5:1 to 1:1.

[0150] In some embodiments, a method of reducing inter-chain disulfide bonds in the AB of an activatable antibody and conjugating an agent, e.g., a thiol-containing agent such as a drug, to the resulting interchain thiols to selectively locate agent(s) on the AB is provided. The method generally includes partially reducing the AB with a reducing agent to form at least two interchain thiols without forming all possible interchain thiols in the activatable antibody; and conjugating the agent to the interchain thiols of the partially reduced AB. For example, the AB of the activatable antibody is partially reduced for about 1 hour at about 37° C. at a desired ratio of reducing agent:activatable antibody. In some embodiments, the ratio of reducing agent to activatable antibody will be in a range from about 20:1 to 1:1, from about 10:1 to 1:1, from about 9:1 to 1:1, from about 8:1 to 1:1, from about 7:1 to 1:1, from about 6:1 to 1:1, from about 5:1 to 1:1, from about 4:1 to 1:1, from about 3:1 to 1:1, from about 2:1 to 1:1, from about 20:1 to 1:1.5, from about 10:1 to 1:1.5, from about 9:1 to 1:1.5, from about 8:1 to 1:1.5, from about 7:1 to 1:1.5, from about 6:1 to 1:1.5, from about 5:1 to 1:1.5, from about 4:1 to 1:1.5, from about 3:1 to 1:1.5, from about 2:1 to 1:1.5, from about 1.5:1 to 1:1.5, or from about 1:1 to 1:1.5. In some embodiments, the ratio is in a range of from about 5:1 to 1:1. In some embodiments, the ratio is in a range of from about 5:1 to 1.5:1. In some embodiments, the ratio is in a range of from about 4:1 to 1:1. In some embodiments, the ratio is in a range from about 4:1 to 1.5:1. In some embodiments, the ratio is in a range from about 8:1 to about 1:1. In some embodiments, the ratio is in a range of from about 2.5:1 to 1:1.

[0151] The thiol-containing reagent can be, for example, cysteine or N-acetyl cysteine. The reducing agent can be, for example, TCEP. In some embodiments, the reduced activatable antibody can be purified prior to conjugation, using for example, column chromatography, dialysis, or diafiltration. In some embodiments, the reduced antibody is not purified after partial reduction and prior to conjugation.

[0152] The disclosure also provides partially reduced activatable antibodies in which at least one interchain disulfide bond in the activatable antibody has been reduced with a reducing agent without disturbing any intrachain disulfide bonds in the activatable antibody, wherein the activatable antibody includes an antibody or an antigen binding fragment thereof (AB) that specifically binds to the target, a masking moiety (MM) that inhibits the binding of the AB of the activatable antibody in an uncleaved state to the target, and a cleavable moiety (CM) coupled to the AB, wherein the CM is a polypeptide that functions as a substrate for at least one MMP. In some embodiments, the MM is coupled to the AB via the CM. In some embodiments, one or more intrachain disulfide bond(s) of the activatable antibody is not disturbed by the reducing agent. In some embodiments, one or more intrachain disulfide bond(s) of the MM within the activatable antibody is not disturbed by the reducing agent. In some embodiments, the activatable antibody in the uncleaved state has the structural arrangement from N-terminus to C-terminus as follows: MM-CM-AB or AB-CM-MM. In some embodiments, reducing agent is TCEP.

[0153] The disclosure also provides partially reduced activatable antibodies, including but not limited to multispecific activatable antibodies of the disclosure, in which at least one interchain disulfide bond in the activatable antibody has been

reduced with a reducing agent without disturbing or otherwise compromising the activity and/or efficacy of the activatable antibody, wherein the activatable antibody includes an antibody or an antigen binding fragment thereof (AB) that specifically binds to a target, a masking moiety (MM) that inhibits the binding of the AB of the activatable antibody in an uncleaved state to the target, and a cleavable moiety (CM) coupled to the AB, and the CM is a polypeptide that functions as a substrate for a protease. The activity and/or efficacy of the activatable antibody is, by way of nonlimiting example, masking activity, activation of the activatable antibody, and/or binding activity of the activated activatable antibody. In some embodiments, one or more intrachain disulfide bond(s) of the activatable antibody is not disturbed by the reducing agent. In some embodiments, one or more intrachain disulfide bond(s) of the MM within the activatable antibody is not disturbed by the reducing agent. In some embodiments, the activatable antibody in the uncleaved state has the structural arrangement from N-terminus to C-terminus as follows: MM-CM-AB or AB-CM-MM. In some embodiments, reducing agent is TCEP.

[0154] The disclosure also provides conjugated activatable antibodies that include an activatable antibody linked to monomethyl auristatin D (MMAD) payload, wherein the activatable antibody includes an antibody or an antigen binding fragment thereof (AB) that specifically binds to a target, a masking moiety (MM) that inhibits the binding of the AB of the activatable antibody in an uncleaved state to the target, and cleavable moiety (CM) coupled to the AB, and the CM is a polypeptide that functions as a substrate for at least one MMP protease.

[0155] In some embodiments, the MMAD-conjugated activatable antibody can be conjugated using any of several methods for attaching agents to ABs: (a) attachment to the carbohydrate moieties of the AB, or (b) attachment to sulphydryl groups of the AB, or (c) attachment to amino groups of the AB, or (d) attachment to carboxylate groups of the AB.

[0156] In some embodiments, the MMAD payload is conjugated to the AB via a linker. In some embodiments, the MMAD payload is conjugated to a cysteine in the AB via a linker. In some embodiments, the MMAD payload is conjugated to a lysine in the AB via a linker. In some embodiments, the MMAD payload is conjugated to another residue of the AB via a linker, such as those residues disclosed herein. In some embodiments, the linker is a thiol-containing linker. In some embodiments, the linker is a cleavable linker. In some embodiments, the linker is a non-cleavable linker. In some embodiments, the linker is selected from the group consisting of the linkers shown in Tables 5 and 6. In some embodiments, the activatable antibody and the MMAD payload are linked via a maleimide caproyl-valine-citrulline linker. In some embodiments, the activatable antibody and the MMAD payload are linked via a maleimide PEG-valine-citrulline linker. In some embodiments, the activatable antibody and the MMAD payload are linked via a maleimide caproyl-valine-citrulline-para-aminobenzylloxycarbonyl linker. In some embodiments, the activatable antibody and the MMAD payload are linked via a maleimide PEG-valine-citrulline-para-aminobenzylloxycarbonyl linker. In some embodiments, the MMAD payload is conjugated to the AB using the partial reduction and conjugation technology disclosed herein.

[0157] In some embodiments, the target is selected from the group of targets listed in Table 1. In some embodiments, the target is EGFR. In some embodiments, the target is a Jagged

protein, e.g., Jagged 1 and/or Jagged 2. In some embodiments, the target is interleukin 6 receptor (IL-6R). In some embodiments, the AB is or is derived from an antibody selected from the group of antibodies listed in Table 2. In some embodiments, the antigen binding fragment thereof is selected from the group consisting of a Fab fragment, a F(ab')₂ fragment, a scFv, a scAb, a dAb, a single domain heavy chain antibody, and a single domain light chain antibody. In some embodiments, the AB has an equilibrium dissociation constant of about 100 nM or less for binding to the target. In some embodiments, the MM has an equilibrium dissociation constant for binding to the AB that is greater than the equilibrium dissociation constant of the AB to the target. In some embodiments, the MM does not interfere or compete with the AB of the activatable antibody in a cleaved state for binding to the target. In some embodiments, the MM is a polypeptide of no more than 40 amino acids in length. In some embodiments, the MM polypeptide sequence is different from that of the target, and the MM polypeptide sequence is no more than 50% identical to any natural binding partner of the AB. In some embodiments, the MM does not include more than 25% amino acid sequence identity to the target. In some embodiments, the MM does not include more than 10% amino acid sequence identity to the target. In some embodiments, the CM is a polypeptide of up to 15 amino acids in length. In some embodiments, the MMP protease is co-localized with the target in a tissue, and the MMP protease cleaves the CM in the activatable antibody when the activatable antibody is exposed to the MMP protease. In some embodiments, the MMP protease is a MMP9 protease. In some embodiments, the MMP protease is a MMP14 protease. In some embodiments, the activatable antibody includes a linking peptide between the MM and the CM. In some embodiments, the activatable antibody includes a linking peptide between the CM and the AB. In some embodiments, the activatable antibody includes a first linking peptide (LP1) and a second linking peptide (LP2), and the activatable antibody in an uncleaved state has the structural arrangement from N-terminus to C-terminus as follows: MM-LP1-CM-LP2-AB or AB-LP2-CM-LP1-MM. In some embodiments, the two linking peptides need not be identical to each other. In some embodiments, each of LP1 and LP2 is a peptide of about 1 to 20 amino acids in length. In some embodiments, at least one of LP1 or LP2 includes an amino acid sequence selected from the group consisting of (GS)_n, (GGS)_n, (GSGG)_n (SEQ ID NO: 1) and (GGGS)_n (SEQ ID NO: 2), where n is an integer of at least one. In some embodiments, at least one of LP1 or LP2 includes an amino acid sequence selected from the group consisting of GGSG (SEQ ID NO: 3), GGS GG (SEQ ID NO: 4), GSGSG (SEQ ID NO: 5), GSGGG (SEQ ID NO: 6), GGGSG (SEQ ID NO: 7), and GSSSG (SEQ ID NO: 8). In some embodiments, the activatable antibody includes a second CM; in some embodiments, the second CM is a substrate for an enzyme selected from the group consisting of those shown in Table 7.

[0158] The disclosure also provides polypeptides and other larger molecules that include one or more of the MMP-cleavable substrate sequences presented herein. By way of non-limiting example, the MMP-cleavable substrate sequences presented herein are useful in prodrug compositions and methods of use thereof. These MMP-cleavable substrate sequences presented herein are also useful in probes and other detection agents and methods of use thereof. For example, the MMP-cleavable substrate sequences presented herein can be

used in conjunction with fluors and other quenchers to produce detection agents, such as imaging agents and/or other diagnostic agents. Those of ordinary skill in the art will appreciate that the MMP-cleavable substrate sequences presented herein are useful in any composition and/or method in the art that would use a substrate that is cleavable by one or more MMPs, such as MMP9 and/or MMP14.

[0159] The disclosure also provides an isolated nucleic acid molecule encoding an antibody and/or an activatable antibody described herein, as well as vectors that include these isolated nucleic acid sequences. The disclosure provides methods of producing an antibody and/or activatable antibody by culturing a cell under conditions that lead to expression of the antibody and/or activatable antibody, wherein the cell comprises such a vector.

[0160] The disclosure provides a method of manufacturing a conjugated antibody of the disclosure that bind a given target by (a) culturing a cell comprising a nucleic acid construct that encodes the antibody under conditions that lead to expression of the antibody, (i) wherein the antibody includes a cleavable moiety (CM), and (ii) wherein the CM is a polypeptide that functions as a substrate for a matrix metalloprotease; (b) recovering the antibody; and (c) conjugating the recovered antibody to one or more additional agents.

[0161] The disclosure also provides a method of manufacturing the activatable antibodies of the disclosure that bind in an activated state a given target by (a) culturing a cell comprising a nucleic acid construct that encodes the activatable antibody under conditions that lead to expression of the activatable antibody, wherein the activatable antibody comprises a masking moiety (MM), a cleavable moiety (CM), and an antibody or an antigen binding fragment thereof (AB) that specifically binds the target, (i) wherein the CM is a polypeptide that functions as a substrate for a MMP, and (ii) wherein the CM is positioned in the activatable antibody such that, in an uncleaved state, the MM interferes with specific binding of the AB to the target and in a cleaved state the MM does not interfere or compete with specific binding of the AB to the target; and (b) recovering the activatable antibody.

[0162] The disclosure provides methods of preventing, delaying the progression of, treating, alleviating a symptom of, or otherwise ameliorating a target-related disease in a subject by administering a therapeutically effective amount of a conjugated antibody, an activatable antibody and/or a conjugated activatable antibody described herein to a subject in need thereof.

[0163] The disclosure provides methods of preventing, delaying the progression of, treating, alleviating a symptom of, or otherwise ameliorating inflammation and/or an inflammatory disorder in a subject by administering a therapeutically effective amount of a conjugated antibody, an activatable antibody and/or a conjugated activatable antibody described herein to a subject in need thereof. The disclosure also provides methods of preventing, delaying the progression of, treating, alleviating a symptom of, or otherwise ameliorating cancer in a subject by administering a therapeutically effective amount of a conjugated antibody, an activatable antibody and/or a conjugated activatable antibody described herein to a subject in need thereof. The disclosure also provides methods of preventing, delaying the progression of, treating, alleviating a symptom of, or otherwise ameliorating an autoimmune disease in a subject by administering a therapeutically effective amount a conjugated antibody, an

activatable antibody and/or a conjugated activatable antibody described herein to a subject in need thereof.

[0164] A conjugated antibody, an activatable antibody and/or a conjugated activatable antibody used in any of the embodiments of these methods and uses can be administered at any stage of the disease. For example, such a conjugated antibody, activatable antibody and/or conjugated activatable antibody can be administered to a patient suffering cancer of any stage, from early to metastatic. The terms subject and patient are used interchangeably herein.

[0165] In some embodiments, the subject is a mammal, such as a human, non-human primate, companion animal (e.g., cat, dog, horse), farm animal, work animal, or zoo animal. In some embodiments, the subject is a rodent. In some embodiments, the subject is a human. In some embodiments, the subject is a companion animal. In some embodiments, the subject is an animal in the care of a veterinarian.

[0166] The conjugated antibody, activatable antibody and/or conjugated activatable antibody and therapeutic formulations thereof are administered to a subject suffering from or susceptible to a disease or disorder associated with aberrant target expression and/or activity. A subject suffering from or susceptible to a disease or disorder associated with aberrant target expression and/or activity is identified using any of a variety of methods known in the art. For example, subjects suffering from cancer or other neoplastic condition are identified using any of a variety of clinical and/or laboratory tests such as, physical examination and blood, urine and/or stool analysis to evaluate health status. For example, subjects suffering from inflammation and/or an inflammatory disorder are identified using any of a variety of clinical and/or laboratory tests such as physical examination and/or bodily fluid analysis, e.g., blood, urine and/or stool analysis, to evaluate health status.

[0167] Administration of a conjugated antibody, an activatable antibody and/or a conjugated activatable antibody to a patient suffering from a disease or disorder associated with aberrant target expression and/or activity is considered successful if any of a variety of laboratory or clinical objectives is achieved. For example, administration of a conjugated antibody, an activatable antibody and/or a conjugated activatable antibody to a patient suffering from a disease or disorder associated with aberrant target expression and/or activity is considered successful if one or more of the symptoms associated with the disease or disorder is alleviated, reduced, inhibited or does not progress to a further, i.e., worse, state. Administration of a conjugated antibody, an activatable antibody and/or a conjugated activatable antibody to a patient suffering from a disease or disorder associated with aberrant target expression and/or activity is considered successful if the disease or disorder enters remission or does not progress to a further, i.e., worse, state.

[0168] In some embodiments, the conjugated antibody, activatable antibody and/or conjugated activatable antibody is administered during and/or after treatment in combination with one or more additional agents such as, by way of non-limiting example, an anti-inflammatory agent, an immuno-suppressive agent, a chemotherapeutic agent, such as an alkylating agent, an anti-metabolite, an anti-microtubule agent, a topoisomerase inhibitor, a cytotoxic antibiotic, and/or any other nucleic acid damaging agent. In some embodiments, the additional agent is a taxane, such as paclitaxel (e.g., Abraxane®). In some embodiments, the additional agent is an anti-metabolite, such as gemcitabine. In some embodiments, the

additional agent is an alkylating agent, such as platinum-based chemotherapy, such as carboplatin or cisplatin. In some embodiments, the additional agent is a targeted agent, such as a kinase inhibitor, e.g., sorafenib or erlotinib. In some embodiments, the additional agent is a targeted agent, such as another antibody, e.g., a monoclonal antibody (e.g., bevacizumab), a bispecific antibody, or a multispecific antibody. In some embodiments, the additional agent is a proteosome inhibitor, such as bortezomib or carfilzomib. In some embodiments, the additional agent is an immune modulating agent, such as lenolidomide or IL-2. In some embodiments, the additional agent is radiation. In some embodiments, the additional agent is an agent considered standard of care by those skilled in the art. In some embodiments, the additional agent is a chemotherapeutic agent well known to those skilled in the art.

[0169] In some embodiments, the additional agent is an antibody, another conjugated antibody, another activatable antibody and/or another conjugated activatable antibody. In some embodiments, the conjugated antibody, activatable antibody and/or conjugated activatable antibody and the additional agent(s) are administered simultaneously. For example, the conjugated antibody, activatable antibody and/or conjugated activatable antibody and the additional agent(s) can be formulated in a single composition or administered as two or more separate compositions. In some embodiments, the conjugated antibody, activatable antibody and/or conjugated activatable antibody and the additional agent(s) are administered sequentially, or the antibody and/or conjugated antibodies and the additional agent are administered at different times during a treatment regimen. For example, the antibody and/or conjugated antibodies is administered prior to the administration of the additional agent, the antibody and/or conjugated antibodies is administered subsequent to the administration of the additional agent, or the antibody and/or conjugated antibodies and the additional agent are administered in an alternating fashion. As described herein, the antibody and/or conjugated antibodies and additional agent are administered in single doses or in multiple doses.

[0170] In some embodiments, the CM is linked or otherwise attached to an activatable antibody that includes an antibody or antigen-binding fragment thereof that specifically binds a given target coupled to a masking moiety (MM), such that coupling of the MM to the AB reduces the ability of the antibody or antigen-binding fragment thereof to bind the target. In some embodiments, the MM is coupled via the CM. Exemplary targets include, but are not limited to the targets shown in Table 1. Exemplary ABs include, but are not limited to, the targets shown in Table 2. The activatable antibodies provided herein are stable in circulation, activated at intended sites of therapy and/or diagnosis but not in normal, e.g., healthy tissue or other tissue not targeted for treatment and/or diagnosis, and, when activated, exhibit binding to the target that is at least comparable to the corresponding, unmodified antibody.

[0171] The disclosure also provides methods and kits for using the conjugated antibodies, activatable antibodies and/or conjugated activatable antibodies in a variety of diagnostic and/or prophylactic indications.

[0172] In some embodiments, the disclosure provides methods and kits for detecting presence or absence of a cleaving agent and a target of interest in a subject or a sample by (i) contacting a subject or sample with an activatable antibody, wherein the activatable antibody comprises a masking moiety

(MM), a cleavable moiety (CM) that is cleaved by the cleaving agent, and an antigen binding domain or fragment thereof (AB) that specifically binds the target of interest, wherein the activatable antibody in an uncleaved, non-activated state comprises a structural arrangement from N-terminus to C-terminus as follows: MM-CM-AB or AB-CM-MM; (a) wherein the MM is a peptide that inhibits binding of the AB to the target, and wherein the MM does not have an amino acid sequence of a naturally occurring binding partner of the AB and is not a modified form of a natural binding partner of the AB; and (b) wherein, in an uncleaved, non-activated state, the MM interferes with specific binding of the AB to the target, and in a cleaved, activated state the MM does not interfere or compete with specific binding of the AB to the target; and (ii) measuring a level of activated activatable antibody in the subject or sample, wherein a detectable level of activated activatable antibody in the subject or sample indicates that the cleaving agent and the target are present in the subject or sample and wherein no detectable level of activated activatable antibody in the subject or sample indicates that the cleaving agent, the target or both the cleaving agent and the target are absent in the subject or sample.

[0173] In some embodiments, the activatable antibody is an activatable antibody to which a therapeutic agent is conjugated. In some embodiments, the activatable antibody is not conjugated to an agent. In some embodiments, the activatable antibody comprises a detectable label. In some embodiments, the detectable label is positioned on the AB. In some embodiments, measuring the level of activatable antibody in the subject or sample is accomplished using a secondary reagent that specifically binds to the activated antibody, wherein the reagent comprises a detectable label. In some embodiments, the secondary reagent is an antibody comprising a detectable label.

[0174] In some embodiments of these methods and kits, the activatable antibody includes a detectable label. In some embodiments of these methods and kits, the detectable label includes an imaging agent, a contrasting agent, an enzyme, a fluorescent label, a chromophore, a dye, one or more metal ions, or a ligand-based label. In some embodiments of these methods and kits, the imaging agent comprises a radioisotope. In some embodiments of these methods and kits, the radioisotope is indium or technetium. In some embodiments of these methods and kits, the contrasting agent comprises iodine, gadolinium or iron oxide. In some embodiments of these methods and kits, the enzyme comprises horseradish peroxidase, alkaline phosphatase, or β -galactosidase. In some embodiments of these methods and kits, the fluorescent label comprises yellow fluorescent protein (YFP), cyan fluorescent protein (CFP), green fluorescent protein (GFP), modified red fluorescent protein (mRFP), red fluorescent protein tdimer2 (RFP tdimer2), HCRED, or a europium derivative. In some embodiments of these methods and kits, the luminescent label comprises an N-methylacrydium derivative. In some embodiments of these methods, the label comprises an Alexa Fluor[®] label, such as Alex Fluor[®] 680 or Alexa Fluor[®] 750. In some embodiments of these methods and kits, the ligand-based label comprises biotin, avidin, streptavidin or one or more haptens.

[0175] In some embodiments of these methods and kits, the subject is a mammal. In some embodiments of these methods, the subject is a human. In some embodiments, the subject is a non-human mammal, such as a non-human primate, companion animal (e.g., cat, dog, horse), farm animal, work animal,

or zoo animal. In some embodiments, the subject is a rodent. In some embodiments, the subject is a human. In some embodiments, the subject is a companion animal. In some embodiments, the subject is an animal in the care of a veterinarian.

[0176] In some embodiments of these methods and kits, the method is an in vivo method. In some embodiments of these methods, the method is an in situ method. In some embodiments of these methods, the method is an ex vivo method. In some embodiments of these methods, the method is an in vitro method.

[0177] In some embodiments of the methods and kits, the method is used to identify or otherwise refine a patient population suitable for treatment with an activatable antibody of the disclosure, followed by treatment by administering that activatable antibody and/or conjugated activatable antibody to a subject in need thereof. For example, patients that test positive for both the target and at least one MMP that cleaves the substrate in the cleavable moiety (CM) of the activatable antibody being tested in these methods are identified as suitable candidates for treatment with such an activatable antibody comprising such a CM, and the patient is then administered a therapeutically effective amount of the activatable antibody and/or conjugated activatable antibody that was tested. Likewise, patients that test negative for either or both of the target and the MMP that cleaves the substrate in the CM in the activatable antibody being tested using these methods might be identified as suitable candidates for another form of therapy. In some embodiments, such patients can be tested with other activatable antibodies until a suitable activatable antibody for treatment is identified (e.g., an activatable antibody comprising a CM that is cleaved by the patient at the site of disease). In some embodiments, the patient is then administered a therapeutically effective amount of the activatable antibody and/or conjugated for which the patient tested positive.

[0178] Pharmaceutical compositions according to the disclosure can include an antibody of the disclosure and a carrier. These pharmaceutical compositions can be included in kits, such as, for example, diagnostic kits.

BRIEF DESCRIPTION OF THE DRAWINGS

[0179] FIGS. 1A and 1B are a series of graphs depicting the ability of the activatable anti-EGFR antibody containing a masking moiety comprising amino acid sequence CISPRGCPDPYVVMY (SEQ ID NO: 160), a cleavage moiety comprising the MMP14 substrate 520 (also referred to herein as MN520) ISSGLLSS (SEQ ID NO: 14), and the heavy and light chains of the anti-EGFR antibody C225v5, where the entire activatable antibody construct is referred to herein as Pb-MN520, to inhibit tumor growth in the H292 xenograft lung cancer model.

[0180] FIGS. 2A and 2B are a series of graphs depicting cleavage of the substrate pool referred to herein as SMP87 by 5 nM MMP9.

[0181] FIGS. 3A and 3B are a series of graphs depicting cleavage of substrate sequence VAGRSMRP (SEQ ID NO: 484) by 5 nM MMP9.

[0182] FIG. 4 is a graph depicting correlation of substrate sequence frequency and function.

[0183] FIGS. 5A and 5B are a series of graphs depicting cleavage of the substrate pool SMP39 by 60 nM MMP14.

[0184] FIGS. 6A and 6B are a series of graphs depicting cleavage of the substrate sequence QNQALRMA (SEQ ID NO: 15) by 30 nM MMP14.

[0185] FIGS. 7A and 7B are a series of schematic representations of the peptide display platforms used in the working examples provided herein. FIG. 7A is a schematic representation of the sequence of the display platform referred to herein as "Display Platform CYTX-DP-XXXXXXX" or "CYTX-DP-XXXXXXX" (SEQ ID NO: 512). FIG. 7B is a schematic representation of the sequence of the display platform referred to herein as "Display Platform SP-CYTX-DP-XXXXXXX" or "SP-CYTX-DP-XXXXXXX" (SEQ ID NO: 513), where SP-CYTX-DP-XXXXXXX is the CYTX-DP-XXXXXXX platform with a signal peptide.

DETAILED DESCRIPTION OF THE INVENTION

[0186] The disclosure provides amino acid sequences that include a cleavable moiety (CM) that is a substrate for at least one matrix metalloprotease (MMP). These CMs are useful in a variety of therapeutic, diagnostic and prophylactic indications.

[0187] The working examples provided herein demonstrate that these CM, when displayed in a peptide display platform, exhibit a number of desirable cleavage characteristics when exposed to an MMP protease under specified conditions. For example, Table 9 depicts (a) the percentage of MMP9-selected substrates tested in the CYTX-DP display platform that exhibited at least 20% cleavage when incubated with 50 nM human MMP9 for 1 hour at 37° C. in 50 mM Tris-HCl, pH 7.4, supplemented with 150 mM NaCl, 10 mM CaCl₂, and 0.05% (w/v) Brij-35 (>20% Cleavage with 50 nM MMP9); (b) the percentage of MMP14-selected substrates tested in the CYTX-DP display platform that exhibited at least 20% cleavage when incubated with 50 nM human MMP14 for 1 hour at 37° C. in 50 mM HEPES, pH 6.8, supplemented with 10 mM CaCl₂, and 0.5 mM MgCl₂ (>20% Cleavage with 50 nM MMP14); and (c) the percentage of MMP9-selected or MMP14-selected substrates tested in the CYTX-DP display platform that exhibited less than 20% cleavage when incubated with 500 pM human plasmin for 1 hour at 37° C. in 50 mM Tris-HCl, pH 7.4, supplemented with 100 mM NaCl, 0.01% Tween20 and 1 mM EDTA (<20% cleavage with 500 pM plasmin).

[0188] In some embodiments, a MMP9 substrate when displayed in the CYTX-DP platform exhibits at least 20% cleavage when incubated with 50 nM human MMP9 for 1 hour at 37° C. in 50 mM Tris-HCl, pH 7.4, supplemented with 150 mM NaCl, 10 mM CaCl₂, and 0.05% (w/v) Brij-35. In some embodiments, a MMP9 substrate when displayed in the CYTX-DP platform exhibits less than 20% cleavage when incubated with 500 pM human plasmin for 1 hour at 37° C. in 50 mM Tris-HCl, pH 7.4, supplemented with 100 mM NaCl, 0.01% Tween20 and 1 mM EDTA. In some embodiments, a MMP9 substrate when displayed in the CYTX-DP platform exhibits at least 20% cleavage when incubated with 50 nM

human MMP9 for 1 hour at 37° C. in 50 mM Tris-HCl, pH 7.4, supplemented with 150 mM NaCl, 10 mM CaCl₂, and 0.05% (w/v) Brij-35 and exhibits less than 20% cleavage when incubated with 500 pM human plasmin for 1 hour at 37° C. in 50 mM Tris-HCl, pH 7.4, supplemented with 100 mM NaCl, 0.01% Tween20 and 1 mM EDTA.

[0189] In some embodiments a MMP14 substrate exhibits at least 20% cleavage when incubated with 50 nM human MMP14 for 1 hour at 37° C. in 50 mM HEPES, pH 6.8, supplemented with 10 mM CaCl₂, and 0.5 mM MgCl₂. In some embodiments, a MMP14 substrate when displayed in the CYTX-DP platform exhibits less than 20% cleavage when incubated with 500 pM human plasmin for 1 hour at 37° C. in 50 mM Tris-HCl, pH 7.4, supplemented with 100 mM NaCl, 0.01% Tween20 and 1 mM EDTA. In some embodiments a MMP14 substrate exhibits at least 20% cleavage when incubated with 50 nM human MMP14 for 1 hour at 37° C. in 50 mM HEPES, pH 6.8, supplemented with 10 mM CaCl₂, and 0.5 mM MgCl₂ and exhibits less than 20% cleavage when incubated with 500 pM human plasmin for 1 hour at 37° C. in 50 mM Tris-HCl, pH 7.4, supplemented with 100 mM NaCl, 0.01% Tween20 and 1 mM EDTA.

[0190] In some embodiments, the observed k_{cat}/K_M value of a substrate in an activatable antibody for MMP9 is greater than 100 M⁻¹ s⁻¹. In some embodiments, the observed k_{cat}/K_M value of a substrate in an activatable antibody for MMP9 is greater than 1,000 M⁻¹ s⁻¹. In some embodiments, the observed k_{cat}/K_M value of a substrate in an activatable antibody for MMP9 is greater than 10,000 M⁻¹ s⁻¹.

[0191] In some embodiments, the observed k_{cat}/K_M value of a substrate in an activatable antibody for MMP14 is greater than 100 M⁻¹ s⁻¹. In some embodiments, the observed k_{cat}/K_M value of a substrate in an activatable antibody for MMP14 is greater than 1,000 M⁻¹ s⁻¹. In some embodiments, the observed k_{cat}/K_M value of a substrate in an activatable antibody for MMP14 is greater than 10,000 M⁻¹ s⁻¹.

[0192] The disclosure also provides antibodies that include one or more of these MMP-cleavable substrates. For example, these MMP-cleavable substrates are useful when conjugating antibodies to one or more additional agents to produce conjugated antibodies. These MMP-cleavable are useful in activatable antibody constructs.

[0193] The conjugated antibodies and/or activatable antibodies include an antibody or antigen-binding fragment thereof (AB) that specifically binds a target. Exemplary classes of targets of an AB include, but are not necessarily limited to, cell surface receptors and secreted binding proteins (e.g., growth factors), soluble enzymes, structural proteins (e.g. collagen, fibronectin) and the like. In some embodiments, conjugated antibodies and/or activatable antibodies have an AB that binds an extracellular target, usually an extracellular protein target. In some embodiments, conjugated antibodies and/or activatable antibodies are designed for cellular uptake and are switchable inside a cell.

[0194] As a non-limiting example, the AB is a binding partner for any target listed in Table 1.

TABLE 1

Exemplary Targets					
1-92-LFA-3	CD52	DL44	HVEM	LIF-R	STEAP1
Alpha-4 integrin	CD56	DLK1	Hyaluronidase	Lewis X	STEAP2

TABLE 1-continued

Exemplary Targets					
Alpha-V integrin	CD64	DLL4	ICOS	LIGHT	TAG-72
alpha4beta1 integrin	CD70	DPP-4	IFNalpha	LRP4	TAPA1
alpha4beta7 integrin	CD71	DSG1	IFNbta	LRRC26	TGFbeta
AGR2	CD74	EGFR	IFNgamma	MCSP	TIGIT
Anti-Lewis-Y		EGFRviii	IgE	Mesothelin	TIM-3
Apelin J receptor	CD80	Endothelin B receptor (ETBR)	IgE Receptor (FeeRI)	MRP4	TLR2
APRIL	CD81	ENPP3	IGF	MUC1	TLR4
B7-H4	CD86	EpCAM	IGF1R	Mucin-16 (MUC16, CA-125)	TLR6
BAFF	CD95	EPHA2	IL1B	Na/K ATPase	TLR7
BTLA	CD117	EPHB2	IL1R	Neutrophil elastase	TLR8
C5 complement	CD125	ERBB3	IL2	NGF	TLR9
C-242	CD132 (IL-2RG)	F protein of RSV	IL11	Nicastrin	TMEM31
CA9	CD133	FAP	IL12	Notch Receptors	TNFalpha
CA19-9 (Lewis a)	CD137	FGF-2	IL12p40	Notch 1	TNFR
Carbonic anhydrase 9	CD138	FGF8	IL-12R, IL-12Rbeta1	Notch 2	TNFRS12A
CD2	CD166	FGFR1	IL13	Notch 3	TRAIL-R1
CD3	CD172A	FGFR2	IL13R	Notch 4	TRAIL-R2
CD6	CD248	FGFR3	IL15	NOV	Transferrin
CD9	CDH6	FGFR4	IL17	OSM-R	Transferrin receptor
CD11a	CEACAM5 (CEA)	Folate receptor	IL18	OX-40	TRK-A
CD19	CEACAM6 (NCA-90)	GAL3ST1	IL21	PAR2	TRK-B
CD20	CLAUDIN-3	G-CSF	IL23	PDGF-AA	uPAR
CD22	CLAUDIN-4	G-CSFR	IL23R	PDGF-BB	VAP1
CD24	cMet	GD2	IL27/IL27R (wsx1)	PDGFRalpha	VCAM-1
CD25	Collagen	GITR	IL29	PDGFRbeta	VEGF
CD27	Cripto	GLUT1	IL-31R	PD-1	VEGF-A
CD28	CSFR	GLUT4	IL31/IL31R	PD-L1	VEGF-B
CD30	CSFR-1	GM-CSF	IL2R	PD-L2	VEGF-C
CD33	CTLA-4	GM-CSFR	IL4	Phosphatidyl-serine	VEGF-D
CD38	CTGF	GP IIb/IIIa receptors	IL4R	P1GF	VEGFR1
CD40	CXCL10	Gp130	IL6, IL6R	PSCA	VEGFR2
CD40L	CXCL13	GPIIb/IIIa	Insulin Receptor	PSMA	VEGFR3
CD41	CXCR1	GPNMB	Jagged Ligands	RAAG12	VISTA
CD44	CXCR2	GRP78	Jagged 1	RAGE	WISP-1
CD44v6		HER2/neu	Jagged 2	SLC44A4	WISP-2
CD47	CXCR4	HGF	LAG-3	Sphingosine 1 Phosphate	WISP-3
CD51	CYR61	hGH			

[0195] As a non-limiting example, the AB is or is derived from an antibody listed in Table 2.

TABLE 2

Exemplary sources for Abs	
Antibody Trade Name (antibody name)	Target
Avastin™ (bevacizumab)	VEGF
Lucentis™ (ranibizumab)	VEGF
Erbtitux™ (cetuximab)	EGFR

TABLE 2-continued

Exemplary sources for Abs	
Antibody Trade Name (antibody name)	Target
Vectibix™ (panitumumab)	EGFR
Remicade™ (infliximab)	TNFalpha
Humira™ (adalimumab)	TNFalpha
Tysabri™ (natalizumab)	Integrinalpha4
Simulect™ (basiliximab)	IL2R
Soliris™ (eculizumab)	Complement C5
Raptiva™ (efalizumab)	CD11a
Bexxar™ (tositumomab)	CD20

TABLE 2-continued

Exemplary sources for Abs	
Antibody Trade Name (antibody name)	Target
Zevalin™ (ibritumomab tiuxetan)	CD20
Rituxan™ (rituximab)	CD20
Ocrelizumab	CD20
Arzerra™ (ofatumumab)	CD20
Obinutuzumab	CD20
Zenapax™ (daclizumab)	CD25
Adcetris™ (brentuximab vedotin)	CD30
Myelotarg™ (gemtuzumab)	CD33
Mylotarg™ (gemtuzumab ozogamicin)	CD33
Campath™ (alemtuzumab)	CD52
ReoPro™ (abiximab)	Glycoprotein receptor IIb/IIIa
Xolair™ (omalizumab)	IgE
Herceptin™ (trastuzumab)	Her2
Kadcyla™ (trastuzumab emtansine)	Her2
Synagis™ (palivizumab)	F protein of RSV
(ipilimumab)	CTLA-4
(tremelimumab)	CTLA-4
Hu5c8	CD40L
(pertuzumab)	Her2-neu
(ertumaxomab)	CD3/Her2-neu
Orencia™ (abatacept)	CTLA-4
(tanazumab)	NGF
(bavituximab)	Phosphatidylserine
(zalutumumab)	EGFR
(mapatumumab)	EGFR
(matuzumab)	EGFR
(nimotuzumab)	EGFR
ICR62	EGFR
mAb 528	EGFR
CH806	EGFR
MDX-447	EGFR/CD64
(edrecolomab)	EpCAM
RAV12	RAAG12
huJ591	PSMA
Enbrel™ (etanercept)	TNF-R
Amevive™ (alefacept)	1-92-LFA-3
Antril™, Kineret™ (ankinra)	IL-1Ra
GC1008	TGFbeta
(adecatumumab)	Notch, e.g., Notch 1
(figitumumab)	Jagged 1 or Jagged 2
(tocilizumab)	EpCAM
Stelara™ (ustekinumab)	IGF1R
Prolia™ (denosumab)	IL-6 receptor
	IL-12/IL-23
	RANKL

[0196] Exemplary conjugated antibodies and/or activatable antibodies of the disclosure include, for example, antibodies that bind interleukin 6 receptor (IL-6R) and that include a heavy chain and a light chain that are, or are derived from, the antibody referred to herein as the "Av1" antibody, which binds interleukin-6 receptor (IL-6R). The amino acid sequences for the Av1 heavy chain and the Av1 light chain are shown below in SEQ ID NO: 54 and SEQ ID NO: 55, respectively.

Av1 Antibody Heavy Chain Amino Acid Sequence:

[0197]

(SEQ ID NO: 54)

QVQLQESGPGLVRPSQTLSLTCTVSGYSITSDHAWSWVRQPGRGLEWIG
YISYSGITTYNPSLKSRTVISRDNSKNTLYLQMNSLRAEDTAVYYCARSLS
ARTTAMDYWGQGSLTVSSASTKGPSVFPLAPSSKTSGGTAALGCLVKD
YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGTQTY

-continued

ICNVNHKPSNTKVDKKVEPKSCDKTHCPCPAPELLGGPSVFLPPKPK
DTLMISRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTKPREEQYNS
TYRVSVSLTVLHQDWLNGKEYKCKVSNKALPAPIEKTIKAKGQPREPVQ
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVVL
DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

Av1 Antibody Light Chain Amino Acid Sequence:

[0198]

(SEQ ID NO: 55)

DIQMTQSPSSLSASVGDRVTITCRASQDISSYLNWYQQKPGKAPKLLIYY
TSRLHSGVPSRFSGSGSGTDFTFTISSLQPEDIAITYYCQQGNTLPYTFGQ
GTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCLLNNFYPREAKVQWKV
DNALQSGNSQESVTEQDSKDSTYLSSTLTLSKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

[0199] Exemplary conjugated antibodies and/or activatable antibodies of the disclosure include, for example, antibodies that bind interleukin 6 receptor (IL-6R) and that include a heavy chain and a light chain that are, or are derived from, the Av1 antibody and a masking moiety. Exemplary conjugated antibodies and/or activatable antibodies of the disclosure include an amino acid sequence attached to the N-terminus of the Av1 light chain. These N-terminal amino acid sequences include, for example, YGSCSWNYVHIFMDC (SEQ ID NO: 161); QGQDFDIPFPAHWVPIT (SEQ ID NO: 162); MGVPAGCVWNYAHIFMDC (SEQ ID NO: 163); QGQS-GQYGSWSWNYVHIFMDC (SEQ ID NO: 164); QGQS-GQGDFDIPFPAHWVPIT (SEQ ID NO: 165); or QGQS-GQMGVPAGCVWNYAHIFMDC (SEQ ID NO: 166). It is also to be appreciated that such amino acid sequences can be attached to the N-terminus of the Av1 heavy chain or to the C-terminus of the Av1 heavy or light chain.

[0200] Exemplary activatable antibodies of the disclosure include, for example, antibodies that bind Epidermal Growth Factor Receptor (EGFR) and that include a heavy chain and a light chain that are, or are derived from, an antibody selected from the group consisting of the antibody referred to herein as the "c225v5" antibody, the antibody referred to herein as the "c225v4" antibody, and the antibody referred to herein as the "c225v6" antibody, each of which binds EGFR. The c225v5 antibody, the c225v4 antibody, and the c225v6 antibody share the same light chain sequence, referred to herein as "c225 light chain." The amino acid sequences for the c225v5 heavy chain, the c225v4 antibody, the c225v6 antibody, and the c225 light chain are shown below.

C225v5 Antibody Heavy Chain Amino Acid Sequence:

[0201]

(SEQ ID NO: 56)

QVQLKQSGPGLVQPSQSLITCTVSGFSLTNYGVHWRQSPGKGLELGV
IWSGGNTDYNTPTSRSLINKDNKSQVFFKMNSLQSQDTAIYYCARALT
YYDYEFAVWGQGTLVTVSAASTKGPSVFPLAPSSKTSGGTAALGCLVKD

- continued

YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY
 ICNVNHKPSNTKVDKKVEPKSCDKTHTCPCPAPELLGGPSVLFPPKPK
 DTLmisRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAAKTPREEQYNS
 TYRvvsvltvlhQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
 YTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVVL
 DSDGSFFLYSKLTVDKSRWQOGNVFSCSVMHEALHNHYTQKSLSLSPGK*

C225v4 Antibody Heavy Chain Amino Acid Sequence:

[0202]

(SEQ ID NO: 57)
 QVQLKQSGPGLVQPSQSLSICTVSGFSLTNYGVHWRQSPGKGLELGV
 IWSGGNTDYNTPFTSRLSINKDNSKSQVFFKMNSLQSNDTAIYYCARALT
 YYDYEFAWQGQTLTVSAASTKGPSVFLAPSSKSTSGGTAALGCLVKD
 YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY
 ICNVNHKPSNTKVDKKVEPKSCDKTHTCPCPAPELLGGPSVLFPPKPK
 DTLmisRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAAKTPREEQYNS
 TYRvvsvltvlhQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
 YTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVVL
 DSDGSFFLYSKLTVDKSRWQOGNVFSCSVMHEALHNHYTQKSLSLSPGK*

C225v6 Antibody Heavy Chain Amino Acid Sequence:

[0203]

(SEQ ID NO: 58)
 QVQLKQSGPGLVQPSQSLSICTVSGFSLTNYGVHWRQSPGKGLELGV
 IWSGGNTDYNTPFTSRLSINKDNSKSQVFFKMNSLQSQDTAIYYCARALT

- continued

YYDYEFAWQGQTLTVSAASTKGPSVFLAPSSKSTSGGTAALGCLVKD
 YFPEPVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY
 ICNVNHKPSNTKVDKKVEPKSCDKTHTCPCPAPELLGGPSVLFPPKPK
 DTLmisRTPEVTCVVVDVSHEDPEVKFNWYVDGVEVHNAAKTPREEQYAS
 TYRvvsvltvlhQDWLNGKEYKCKVSNKALPAPIEKTISKAKGQPREPQV
 YTLPPSRDELTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPVVL
 DSDGSFFLYSKLTVDKSRWQOGNVFSCSVMHEALHNHYTQKSLSLSPGK*

C225 Antibody Light Chain Amino Acid Sequence:

[0204]

(SEQ ID NO: 59)
 QILLTQSPVILSVSPGERVSFSCRASQSIGTNIHWYQQRTNGSPRLLIKY
 ASESiSGiPSRFSGSGSGTDFTLSINSVESEDIADYYCQQNNNWPTTFGA
 GTKLELKRTVAAPSVFIFPPSDEQLKSGTASVVCLNNFYPREAKVQWKV
 DNALQSGNSQESVTEQDSKDSTYSLSTTLSKADYEKHKVYACEVTHQG
 LSSPVTKSFNRGEC*

[0205] Exemplary conjugated antibodies and/or activatable antibodies of the disclosure include, for example, antibodies that bind a Jagged target, e.g., Jagged-1, Jagged-2 and/or both Jagged-1 and Jagged-2, and that include a combination of a variable heavy chain region and a variable light chain region that are, or are derived from, the variable heavy chain and variable light chain sequences shown below.

Variable Light Chain Amino Sequence Lc4

(SEQ ID NO: 60)
 DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYASSLQSGVPSRFSG
 SGSGTDFTLTISLQPEDFATYYCQQSVVAPLTFGQGKTVKEIKR

Variable Heavy Chain Amino Sequence Hc4

(SEQ ID NO: 61)
 EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWSVRQAPGKGLEWVSSIEQMGWQTYYADSV
 KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDIGGRSAFDYWGQGTLTVSS

Variable Light Chain Amino Sequence Lc5

(SEQ ID NO: 62)
 DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYASSLQSGVPSRFSG
 SGSGTDFTLTISLQPEDFATYYCQQSVVAPLTFGQGKTVKEIKR

Variable Heavy Chain Amino Sequence Hc5

(SEQ ID NO: 63)
 EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWSVRQAPGKGLEWVSSIEQMGWQTYYADSV
 KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSPPYHGQFDYWGQGTLTVSS

Variable Light Chain Amino Sequence Lc7

(SEQ ID NO: 64)
 DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYASSLQSGVPSRFSG
 SGSGTDFTLTISLQPEDFATYYCQQSVVAPLTFGQGKTVKEIKR

-Continued

Variable Heavy Chain Amino Sequence Hc7

(SEQ ID NO: 65)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSSI EQMGWQTYYADSV
KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSPPFFQFDYWGQGTLVTVSS

Variable Light Chain Amino Sequence Lc8

(SEQ ID NO: 67)

DIQMTQSPSSLASVGDRVITTCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSG
SGSGTDFTLTISSLQPEDFATYYCQQSVVAPLTFGQGTKEIKR

Variable Heavy Chain Amino Sequence Hc8

(SEQ ID NO: 68)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSSI EQMGWQTYYADSV
KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKHIGRTNPFDYWGQGTLVTVSS

Variable Light Chain Amino Sequence Lc13

(SEQ ID NO: 69)

DIQMTQSPSSLASVGDRVITTCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSG
SGSGTDFTLTISSLQPEDFATYYCQQSVVAPLTFGQGTKEIKR

Variable Heavy Chain Amino Sequence Hc13

(SEQ ID NO: 70)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSSI EQMGWQTYYADSV
KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSAAAIFDYWGQGTLVTVSS

Variable Light Chain Amino Sequence Lc16

(SEQ ID NO: 71)

DIQMTQSPSSLASVGDRVITTCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSG
SGSGTDFTLTISSLQPEDFATYYCQQSVVAPLTFGQGTKEIKR

Variable Heavy Chain Amino Sequence Hc16

(SEQ ID NO: 72)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSSI EQMGWQTYYADSV
KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSPPYYYGQFDYWGQGTLVTVSS

Variable Light Chain Amino Sequence Lc19

(SEQ ID NO: 73)

DIQMTQSPSSLASVGDRVITTCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSG
SGSGTDFTLTISSLQPEDFATYYCQQSVVAPLTFGQGTKEIKR

Variable Heavy Chain Amino Sequence Hc19

(SEQ ID NO: 74)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSSI EQMGWQTYYADSV
KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSPPFFGQFDYWGQGTLVTVSS

Variable Light Chain Amino Sequence Lc21

(SEQ ID NO: 75)

DIQMTQSPSSLASVGDRVITTCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSG
SGSGTDFTLTISSLQPEDFATYYCQQSVVAPLTFGQGTKEIKR

Variable Heavy Chain Amino Sequence Hc21

(SEQ ID NO: 76)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSSI EQMGWQTYYADSV
KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDIGGRSAFDYWGQGTLVTVSS

Variable Light Chain Amino Sequence Lc24

(SEQ ID NO: 77)

DIQMTQSPSSLASVGDRVITTCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSG
SGSGTDFTLTISSLQPEDFATYYCQQSVVAPLTFGQGTKEIKR

Variable Heavy Chain Amino Sequence Hc24

(SEQ ID NO: 78)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSSI EEMGWQTLYADSV
KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSAAAIFDYWGQGTLVTVSS

Variable Light Chain Amino Sequence Lc26

(SEQ ID NO: 79)

DIQMTQSPSSLASVGDRVITTCRASQSISSYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSG
SGSGTDFTLTISSLQPEDFATYYCQQSVVAPLTFGQGTKEIKR

Variable Heavy Chain Amino Sequence Hc26

(SEQ ID NO: 80)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSSI EQMGWQTYYADSV
KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDIGGRSAFDYWGQGTLVTVSS

-Continued

Variable Light Chain Amino Sequence Lc27

(SEQ ID NO: 81)

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYASSLQSGVPSRFSG
SGSGTDFTLTISSLQPEDFATYYCQQSVVAPLTFGQGTKVEIKR

Variable Heavy Chain Amino Sequence Hc27

(SEQ ID NO: 82)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSSIEQMGWQTYYADSV
KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSPPFYQGFDYWGQGTLVTVSS

Variable Light Chain Amino Sequence Lc28

(SEQ ID NO: 83)

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYASSLQSGVPSRFSG
SGSGTDFTLTISSLQPEDFATYYCQQSVVAPLTFGQGTKVEIKR

Variable Heavy Chain Amino Sequence Hc28

(SEQ ID NO: 84)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSSIEQMGWQTYYADSV
KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSPPFFGQFDYWGQGTLVTVSS

Variable Light Chain Amino Sequence Lc30

(SEQ ID NO: 85)

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYASSLQSGVPSRFSG
SGSGTDFTLTISSLQPEDFATYYCQQSVVAPLTFGQGTKVEIKR

Variable Heavy Chain Amino Sequence Hc30

(SEQ ID NO: 86)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSSIEEMGWQTLYADSV
KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYAKSAAAFDYWGQGTLVTVSS

Variable Light Chain Amino Sequence Lc31

(SEQ ID NO: 87)

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYASSLQSGVPSRFSG
SGSGTDFTLTISSLQPEDFATYYCQQSVVAPLTFGQGTKVEIKR

Variable Heavy Chain Amino Sequence Hc31

(SEQ ID NO: 88)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSSIEQMGWQTYYADSV
KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDIGGRSAFDYWGQGTLVTVSS

Variable Light Chain Amino Sequence Lc32

(SEQ ID NO: 89)

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYASSLQSGVPSRFSG
SGSGTDFTLTISSLQPEDFATYYCQQSVVAPLTFGQGTKVEIKR

Variable Heavy Chain Amino Sequence Hc32

(SEQ ID NO: 90)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSSIDPEGWQTYYADSV
KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSAAAFDYWGQGTLVTVSS

Variable Light Chain Amino Sequence Lc37

(SEQ ID NO: 91)

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYASSLQSGVPSRFSG
SGSGTDFTLTISSLQPEDFATYYCQQSVVAPLTFGQGTKVEIKR

Variable Heavy Chain Amino Sequence Hc37

(SEQ ID NO: 92)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSSIEQMGWQTYYADSV
KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSPPHNGQFDYWGQGTLVTVSS

Variable Light Chain Amino Sequence Lc39

(SEQ ID NO: 93)

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYASSLQSGVPSRFSG
SGSGTDFTLTISSLQPEDFATYYCQQSVVAPLTFGQGTKVEIKR

Variable Heavy Chain Amino Sequence Hc39

(SEQ ID NO: 94)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSSIEQMGWQTEYADSV
KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSAAAFDYWGQGTLVTVSS

Variable Light Chain Amino Sequence Lc40

(SEQ ID NO: 95)

DIQMTQSPSSLSASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYASSLQSGVPSRFSG
SGSGTDFTLTISSLQPEDFATYYCQQSVVAPLTFGQGTKVEIKR

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Heavy Chain Amino Sequence Hc40

(SEQ ID NO: 96)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSSIEMGWQTYYADSV
KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSPPFFQFDYWGQGTLVTVSS

Variable Light Chain Amino Sequence Lc47

(SEQ ID NO: 97)

DIQMTQSPSSLSASVGDRVITTCRASQSISYYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSG
SGSGTDFTLTISSLQPEDFATYYCQQSVVAPLTFGQGTLKVEIKR

Variable Heavy Chain Amino Sequence Hc47

(SEQ ID NO: 98)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSSIEMGWQTYYADSV
KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSAAAFDYWGQGTLVTVSS

Variable 4B2 Light Chain

(SEQ ID NO: 99)

DIQMTQSPSSLSASVGDRVITTCRASQSISYYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSG
SGSGTDFTLTISSLQPEDFATYYCQQTLDAPPQFGQGTLKVEIKR

Variable 4B2 Heavy Chain

(SEQ ID NO: 100)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSSIEMGWQTYYADSV
KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDIGGRSAFDYWGQGTLVTVSS

Variable 4D11 Light Chain

(SEQ ID NO: 101)

DIQMTQSPSSLSASVGDRVITTCRASQSISYYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSG
SGSGTDFTLTISSLQPEDFATYYCQQTVVAPPLFGQGTLKVEIKR

Variable 4D11 Heavy Chain

(SEQ ID NO: 102)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSSIEMGWQTYYADSV
KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDIGGRSAFDYWGQGTLVTVSS

Variable 4E7 Light Chain

(SEQ ID NO: 103)

DIQMTQSPSSLSASVGDRVITTCRASQSISYYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSG
SGSGTDFTLTISSLQPEDFATYYCQOSLVAPLTFGQGTLKVEIKR

Variable 4E7 Heavy Chain

(SEQ ID NO: 104)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSSIEMGWQTYYADSV
KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSAAAFDYWGQGTLVTVSS

Variable 4E11 Light Chain

(SEQ ID NO: 105)

DIQMTQSPSSLSASVGDRVITTCRASQSISYYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSG
SGSGTDFTLTISSLQPEDFATYYCQQALDAPLMFGQGTLKVEIKR

Variable 4E11 Heavy Chain

(SEQ ID NO: 106)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSSIEMGWQTYYADSV
KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDIGGRSAFDYWGQGTLVTVSS

Variable 6B7 Light Chain

(SEQ ID NO: 107)

DIQMTQSPSSLSASVGDRVITTCRASQSISYYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSG
SGSGTDFTLTISSLQPEDFATYYCQQALVAPLTFGQGTLKVEIKR

Variable 6B7 Heavy Chain

(SEQ ID NO: 108)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSSIEMGWQTYYADSV
KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSAAAFDYWGQGTLVTVSS

Variable 6F8 Light Chain

(SEQ ID NO: 109)

DIQMTQSPSSLSASVGDRVITTCRASQSISYYLNWYQQKPGKAPKLLIYAASSLQSGVPSRFSG
SGSGTDFTLTISSLQPEDFATYYCQQALVAPLTFGQGTLKVEIKR

Variable 6F8 Heavy Chain

(SEQ ID NO: 110)

EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSSIEMGWQTYYADSV
KGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKSAAAFDYWGQGTLVTVSS

[0206] Exemplary conjugated antibodies and/or activatable antibodies of the disclosure include, for example, antibodies that bind a Jagged target, e.g., Jagged-1, Jagged-2 and/or both Jagged-1 and Jagged-2, and that include a combination of a heavy chain region and a light chain region that are, or are derived from, the heavy chain and light chain sequences shown below.

4D11 Light Chain sequence:

(SEQ ID NO: 111)
DIQMTQSPSSLASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYA
ASSLQSGVPSRFSGSGSGTDFTLTISSLQFEDFATYYCQQTVVAPPFLFGQ
GKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCCLNNFYPREAKVQWKV
DNALQSGNSQESVTEQDSKDSITYSLSSTLTLKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

4D11 Heavy Chain sequence:

(SEQ ID NO: 112)
EVQLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSS
IDPEGRQTYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDI
GGRSAFDYWGQGTLVTVSSASTKGPSVFLAPLSSKSTSGGTAALGCLVKD
YFPPEVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY
ICNVNHPKSNNTKVDKKVEPKSCDKTHTCPPCAPELLGGPSVFLFPPKPK
DTLMISRTPETVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTPKREEQYNS
TYRVSVLTVLHQDWLNKEYKCKVSNKALPAPIEKTISAKQGPQEPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPPVL
DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

4D11v2 Heavy Chain sequence

(SEQ ID NO: 113)
EVHLLESGGGLVQPGGSLRLSCAASGFTFSSYAMSWVRQAPGKGLEWVSS
IDPEGRQTYADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKDI
GGRSAFDYWGQGTLVTVSSASTKGPSVFLAPLSSKSTSGGTAALGCLVKD
YFPPEVTVSWNSGALTSGVHTFPAVLQSSGLYSLSSVVTVPSSSLGTQTY
ICNVNHPKSNNTKVDKKVEPKSCDKTHTCPPCAPELLGGPSVFLFPPKPK
DTLMISRTPETVTCVVVDVSHEDPEVKFNWYVDGVEVHNAKTPKREEQYNS
TYRVSVLTVLHQDWLNKEYKCKVSNKALPAPIEKTISAKQGPQEPQV
YTLPPSREEMTKNQVSLTCLVKGFYPSDIAVEWESNGQPENNYKTPPPVL
DSDGSFFLYSKLTVDKSRWQQGNVFSCSVMHEALHNHYTQKSLSLSPGK

4D11v2 Light Chain Sequence

(SEQ ID NO: 114)
DIQMTQSPSSLASVGDRVTITCRASQSISSYLNWYQQKPGKAPKLLIYA
ASSLQSGVPSRFSGSGSGTDFTLTISSLQFEDFATYYCQQTVVAPPFLFGQ
GKVEIKRTVAAPSVFIFPPSDEQLKSGTASVVCCLNNFYPREAKVQWKV
DNALQSGNSQESVTEQDSKDSITYSLSSTLTLKADYEKHKVYACEVTHQG
LSSPVTKSFNRGEC

[0207] The activatable antibodies and activatable antibody compositions provided herein contain at least an antibody or antibody fragment thereof (collectively referred to as AB throughout the disclosure) that specifically binds a target, e.g., a human target, wherein the AB is modified by a masking moiety (MM).

[0208] In some embodiments, the masking moiety is selected for use with a specific antibody or antibody fragment. For example, suitable masking moieties for use with antibodies that bind EGFR include MMs that include the sequence CISPRG (SEQ ID NO: 167). By way of non-limiting examples, the MM can include a sequence such as CISPRGC (SEQ ID NO: 497); CISPRGCG (SEQ ID NO: 168); CISPRGCPDGPYVMY (SEQ ID NO: 160); CISPRGCPDGPYVM (SEQ ID NO: 169); CISPRGCEPG-TYVPT (SEQ ID NO: 170) and CISPRGCPQIWHP (SEQ ID NO: 171). Other suitable masking moieties include any of the EGFR-specific masks disclosed in PCT Publication No. WO 2010/081173, such as, by way of non-limiting example, GSHCLIPINMAGAPSC (SEQ ID NO: 172); CISPRGCGGSSASQSGQGHCLIPINMAGAPSC (SEQ ID NO: 173); CNHHYFYTCGCISPRGCPG (SEQ ID NO: 174); ADHVFWSYGCISPRGCPG (SEQ ID NO: 175);

CHHVYWGHCFCISPRGCPG (SEQ ID NO: 176); CPHFTTSCGCISPRGCPG (SEQ ID NO: 177); CNHHYHYY-CGCISPRGCPG (SEQ ID NO: 178); CPHVSGFCG-CISPRGCPG (SEQ ID NO: 179); CPYYTSLYCGCISPRGCPG (SEQ ID NO: 180); CNHVY-FGTCGCISPRGCPG (SEQ ID NO: 181); CNHFTLTTCG-CISPRGCPG (SEQ ID NO: 182); CHHFTLTTCG-CISPRGCPG (SEQ ID NO: 183); YNPCATPMCCISPRGCPG (SEQ ID NO: 184); CNHHY-FYTCGCISPRGCG (SEQ ID NO: 185); CNHHYHYYCG-CISPRGCG (SEQ ID NO: 186); CNHVYFGTCG-CISPRGCG (SEQ ID NO: 187); CHHVYWGHCFCISPRGCG (SEQ ID NO: 188); CPHFTTSCGCISPRGCG (SEQ ID NO: 189); CNHFTLTTCG-CISPRGCG (SEQ ID NO: 190); CHHFTLTTCG-CISPRGCG (SEQ ID NO: 191); CPYYTSLYCGCISPRGCG (SEQ ID NO: 192); CPHVSGFCG-CISPRGCG (SEQ ID NO: 193); ADHVFWSYGCISPRGCG (SEQ ID NO: 194); YNPCATPMCCISPRGCG (SEQ ID NO: 195); CHHVYWGHCFCISPRGCG (SEQ ID NO: 196); C(N/P)H(HN/F)(Y/T)(F/W/T/L)(Y/G/T/S)(T/S/Y/H)CGCISPRGCG (SEQ ID NO: 197); CISPRGCGQPIPSVK (SEQ ID NO: 198); CISPRGCTQPY-HVSR (SEQ ID NO: 199); and/or CISPRGCNAVGLGS (SEQ ID NO: 200).

[0209] Suitable masking moieties for use with antibodies that bind a Jagged target, e.g., Jagged 1 and/or Jagged 2, include, by way of non-limiting example, masking moieties that include a sequence such as QGQSGQCNIWLVGGDCRGWQG (SEQ ID NO: 496); QGQSGQQQQWCNI-WINGGDCRGWNG (SEQ ID NO: 201); PWCMQRQDFL-RCPQP (SEQ ID NO: 202); QLGLPAYMCTFECLR (SEQ ID NO: 203); CNLWVSGGDCGGLQG (SEQ ID NO: 204); SCSLWTSGSCLPHSP (SEQ ID NO: 205); YCLQLPHYM-QAMCGR (SEQ ID NO: 206); CFLYSCTDVSYWNNT (SEQ ID NO: 207); PWCMQRQDYLRCQP (SEQ ID NO: 208); CNLWISGGDCRGLAG (SEQ ID NO: 209); CNLWVSGGDCRGVQG (SEQ ID NO: 210); CNLWVSGGDCRGLRG (SEQ ID NO: 211); CNLWISGGDCRGLPG (SEQ ID NO: 212); CNLWVSGGDCRDAPW (SEQ ID NO: 213); CNLWVSGGDCRDLLG (SEQ ID NO: 214); CNLWVSGGDCRGLQG (SEQ ID NO: 215); CNLWLHGGDCRGWQG (SEQ ID NO: 216); CNIWLVGGDCRGWQG (SEQ ID NO: 217); CTTWFCGGDCGVMRG (SEQ ID NO: 218); CNIWGPSVDCGALLG (SEQ ID NO: 219); CNIWVNGGDCRSFEG (SEQ ID NO: 220); YCLNLPRYMQDMCWA (SEQ ID NO: 221); YCLALPHYMQADCAR (SEQ ID NO: 222); CFLYSCGDVSYWGS (SEQ ID NO: 223); CYLYSCTDSAFWNR (SEQ ID NO: 224); CYLYSCND-VSYWSNT (SEQ ID NO: 225); CFLYSCTDVSYW (SEQ ID NO: 226); CFLYSCTDVAYWNSA (SEQ ID NO: 227); CFLYSCTDVSYWGDT (SEQ ID NO: 228); CFLYSCTDVSYWGNS (SEQ ID NO: 229); CFLYSCTDVAYWNNT (SEQ ID NO: 230); CFLYSCGDVSYWGNPLS (SEQ ID NO: 231); CFLYSCTDVAYWSGL (SEQ ID NO: 232); CYLYSCTDGSYWNST (SEQ ID NO: 233); CFLYSCSD-VSYWGNI (SEQ ID NO: 234); CFLYSCTDVAYW (SEQ ID NO: 235); CFLYSCTDVSYWGST (SEQ ID NO: 236); CFLYSCTDVAYWGDT (SEQ ID NO: 237); GCNIWLN-GDCRGWVDPQLQG (SEQ ID NO: 238); GCNIWLVGGDCRGWIGDNTNG (SEQ ID NO: 239); GCNIWLVGGDCRGWIEDNSG (SEQ ID NO: 240); GCNIWANGGDCRGWIDNIIDG (SEQ ID NO: 241); GCNIWLVGGDCRGWLGEAVG (SEQ ID NO: 242);

GCNIWLVGGDCRGWLEEAVG (SEQ ID NO: 243); GGPALCNIWLNNGGDCRGWSG (SEQ ID NO: 244); GAPVFCNIWLNNGGDCRGWMG (SEQ ID NO: 245); GQQQWCNIWINGGDCRGWNG (SEQ ID NO: 246); GKSEFCNIWLNNGGDCRGWIG (SEQ ID NO: 247); GTPGGCNIWANGGDCRGWEG (SEQ ID NO: 248); GASQYCNLWINGGDCRGWRG (SEQ ID NO: 249); GCNIWLVGGDCRPVVEGG (SEQ ID NO: 250); GCNIWAVGGDCRPVFDGG (SEQ ID NO: 251); GCNIWLNNGDCRAWVDTG (SEQ ID NO: 252); GCNIWIVGGDCRPFINDG (SEQ ID NO: 253); GCNIWLNNGGDCRPVVFQGG (SEQ ID NO: 254); GCNIWLSGGDCRMFMNEG (SEQ ID NO: 255); GCNIWVNGGDCRSFVYSG (SEQ ID NO: 256); GCNIWLNNGGDCRGWEASG (SEQ ID NO: 257); GCNIWAHGGDCRGFIEPG (SEQ ID NO: 258); GCNIWLNNGDCRTFVASG (SEQ ID NO: 259); GCNIWAHGGDCRGFIEPG (SEQ ID NO: 260); GFLENCNIWLNNGGDCRTG (SEQ ID NO: 261); GIYENCNIWLNNGGDCRMG (SEQ ID NO: 262); and/or GIPDNCNIWINGGDCRYG (SEQ ID NO: 263).

[0210] Suitable masking moieties for use with antibodies that bind an interleukin 6 target, e.g., interleukin 6 receptor (IL-6R), include, by way of non-limiting example, masking moieties that include a sequence such as QGQSGQYQGSC-SWNYVHIFMDC (SEQ ID NO: 264); QGQSGQGDF-DIPFPAAHWVPIT (SEQ ID NO: 265); QGQSG-QMVGVPAGCVWNYAHIFMDC (SEQ ID NO: 266); YRSCNWNYVSIFLDC (SEQ ID NO: 267); PGAFDIPF-PAHWVPNT (SEQ ID NO: 268); ESSCVWNYVHIFMDC (SEQ ID NO: 269); YPGCKWNYDRIFLDC (SEQ ID NO: 270); YRTCSWNYVGIFLDC (SEQ ID NO: 271); YGSC-SWNYVHIFMDC (SEQ ID NO: 161); YGSCSWNYVHIFLDC (SEQ ID NO: 272); YGSCNWNYVHIFLDC (SEQ ID NO: 273); YTSCNWNYVHIFMDC (SEQ ID NO: 274); YPGCKWNYDRIFLDC (SEQ ID NO: 275); WRSCNWNYAHIFLDC (SEQ ID NO: 276); WSNCHWNYVHIFLDC (SEQ ID NO: 277); DRSCTWNYVRISYDC (SEQ ID NO: 278); SGSCKWDYVHIFLDC (SEQ ID NO: 279); SRSCI-WNYAHIFLDC (SEQ ID NO: 280); SMSCYWQYERIFLDC (SEQ ID NO: 281); YRSCNWNYVSIFLDC (SEQ ID NO: 282); SGSCKWDYVHIFLDC (SEQ ID NO: 283); YKSCHWDYVHIFLDC (SEQ ID NO: 284); YGSCTWNYVHIFMEC (SEQ ID NO: 285); FSSCN-WNYVHIFLDC (SEQ ID NO: 286); WRSCNWNYAHIFLDC (SEQ ID NO: 287); YGSCQWNYVHIFLDC (SEQ ID NO: 288); YRSCNWNYVHIFLDC (SEQ ID NO: 289); NMSCHWDYVHIFLDC (SEQ ID NO: 290); FGPCTWN-YARISWDC (SEQ ID NO: 291); XXsCXWXYvhIfXdc (SEQ ID NO: 292); MGVPAGCVWNYAHIFMDC (SEQ ID NO: 163); RDTGGQCRWDYVHIFMDC (SEQ ID NO: 293); AGVPAGCTWNYVHIFMEC (SEQ ID NO: 294); VGVPNGCVWNYAHIFMEC (SEQ ID NO: 295); DGG-PAGCSWNYVHIFMEC (SEQ ID NO: 296); AVGPAGCW-WNYVHIFMEC (SEQ ID NO: 297); CTWNYVHIFMD-CGEGEGP (SEQ ID NO: 298); GGVPEGCTWNYAHIFMEC (SEQ ID NO: 299); AEVPAGCWNYVHIFMEC (SEQ ID NO: 300); AGVPAGCTWNYVHIFMEC (SEQ ID NO: 301); SGASGGCKWNYVHIFMDC (SEQ ID NO: 302); TPGCR-WNYVHIFMECAL (SEQ ID NO: 303); VGVP-NGCVWNYAHIFMEC (SEQ ID NO: 304); PGAFDIPFPAHWVPNT (SEQ ID NO: 305); RGACDIPF-PAHWIPNT (SEQ ID NO: 306); QGDFDIPFPAHWVPIT (SEQ ID NO: 162); XGafDIPFPAHWVpNT (SEQ ID NO:

307); RGDGNDSDIPFPAHWVPRT (SEQ ID NO: 308); SGVGRDRDIPFPAHWVPRT (SEQ ID NO: 309); WAG-GNDCDIPFPAHWIPNT (SEQ ID NO: 310); WGDGMDV-DIPFPAHWVPVT (SEQ ID NO: 311); AGSGNDSDIPF-PAHWVPRT (SEQ ID NO: 312); ESRSGYADIPFPAHWVPRT (SEQ ID NO: 313); and/or RECGRCGDIIPFPAHWVPRT (SEQ ID NO: 314).

[0211] When the AB is modified with a MM and is in the presence of the target, specific binding of the AB to its target is reduced or inhibited, as compared to the specific binding of the AB not modified with an MM or the specific binding of the parental AB to the target.

[0212] The K_d of the AB modified with a MM towards the target is at least 5, 10, 25, 50, 100, 250, 500, 1,000, 2,500, 5,000, 10,000, 50,000, 100,000, 500,000, 1,000,000, 5,000, 000, 10,000,000, 50,000,000 or greater, or between 5-10, 10-100, 10-1,000, 10-10,000, 10-100,000, 10-1,000,000, 10-10,000,000, 100-1,000, 100-10,000, 100-100,000, 100-1,000,000, 100-10,000,000, 1,000-10,000, 1,000-100,000, 1,000-1,000,000, 1000-10,000,000, 10,000-100,000, 10,000-1,000,000, 10,000-10,000,000, 100,000-1,000,000, or 100,000-10,000,000 times greater than the K_d of the AB not modified with an MM or of the parental AB towards the target. Conversely, the binding affinity of the AB modified with a MM towards the target is at least 2, 3, 4, 5, 10, 20, 25, 40, 50, 100, 250, 500, 1,000, 2,500, 5,000, 10,000, 50,000, 100,000, 500,000, 1,000,000, 5,000,000, 10,000,000, 50,000, 000 or greater, or between 5-10, 10-100, 10-1,000, 10-10,000, 10-100,000, 10-1,000,000, 10-10,000, 100-1,000,000, 100-10,000, 100-100,000, 100-1,000,000, 100-10,000, 100-100,000, 1,000-1,000,000, 1,000-10,000,000, 10,000-100,000, 10,000-1,000,000, 10,000-10,000,000, 100,000-1,000,000, or 100,000-10,000,000 times lower than the binding affinity of the AB not modified with an MM or of the parental AB towards the target.

[0213] The dissociation constant (K_d) of the MM towards the AB is generally greater than the K_d of the AB towards the target. The K_d of the MM towards the AB can be at least 5, 10, 25, 50, 100, 250, 500, 1,000, 2,500, 5,000, 10,000, 100,000, 1,000,000 or even 10,000,000 times greater than the K_d of the AB towards the target. Conversely, the binding affinity of the MM towards the AB is generally lower than the binding affinity of the AB towards the target. The binding affinity of MM towards the AB can be at least 5, 10, 25, 50, 100, 250, 500, 1,000, 2,500, 5,000, 10,000, 100,000, 1,000,000 or even 10,000,000 times lower than the binding affinity of the AB towards the target.

[0214] When the AB is modified with a MM and is in the presence of the target specific binding of the AB to its target is reduced or inhibited, as compared to the specific binding of the AB not modified with an MM or the specific binding of the parental AB to the target. When compared to the binding of the AB not modified with an MM or the binding of the parental AB to the target the AB's ability to bind the target when modified with an MM can be reduced by at least 50%, 60%, 70%, 80%, 90%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% and even 100% for at least 2, 4, 6, 8, 12, 28, 24, 30, 36, 48, 60, 72, 84, or 96 hours, or 5, 10, 15, 30, 45, 60, 90, 120, 150, or 180 days, or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months or more when measured in vivo or in an in vitro assay.

[0215] The MM inhibits the binding of the AB to the target. The MM binds the antigen binding domain of the AB and inhibits binding of the AB to the target. The MM can sterically inhibit the binding of the AB to the target. The MM can

allosterically inhibit the binding of the AB to its target. In these embodiments when the AB is modified or coupled to a MM and in the presence of target there is no binding or substantially no binding of the AB to the target, or no more than 0.001%, 0.01%, 0.1%, 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, or 50% binding of the AB to the target, as compared to the binding of the AB not modified with an MM, the parental AB, or the AB not coupled to an MM to the target, for at least 2, 4, 6, 8, 12, 28, 24, 30, 36, 48, 60, 72, 84, or 96 hours, or 5, 10, 15, 30, 45, 60, 90, 120, 150, or 180 days, or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months or longer when measured in vivo or in an in vitro assay.

[0216] When an AB is coupled to or modified by a MM, the MM ‘masks’ or reduces or otherwise inhibits the specific binding of the AB to the target. When an AB is coupled to or modified by a MM, such coupling or modification can effect a structural change that reduces or inhibits the ability of the AB to specifically bind its target.

[0217] An AB coupled to or modified with an MM can be represented by the following formulae (in order from an amino (N) terminal region to carboxyl (C) terminal region:

(MM)-(AB)

(AB)-(MM)

(MM)-L-(AB)

(AB)-L-(MM)

where MM is a masking moiety, the AB is an antibody or antibody fragment thereof, and the L is a linker. In many embodiments, it may be desirable to insert one or more linkers, e.g., flexible linkers, into the composition so as to provide for flexibility.

[0218] In certain embodiments, the MM is not a natural binding partner of the AB. In some embodiments, the MM contains no or substantially no homology to any natural binding partner of the AB. In some embodiments, the MM is no more than 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, or 80% similar to any natural binding partner of the AB. In some embodiments, the MM is no more than 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, or 80% identical to any natural binding partner of the AB. In some embodiments, the MM is no more than 25% identical to any natural binding partner of the AB. In some embodiments, the MM is no more than 50% identical to any natural binding partner of the AB. In some embodiments, the MM is no more than 20% identical to any natural binding partner of the AB. In some embodiments, the MM is no more than 10% identical to any natural binding partner of the AB.

[0219] In some embodiments, the activatable antibodies include an AB that is modified by an MM and also includes one or more cleavable moieties (CM). Such activatable antibodies exhibit activatable/switchable binding, to the AB’s target. Activatable antibodies generally include an antibody or antibody fragment (AB), modified by or coupled to a masking moiety (MM) and a modifiable or cleavable moiety (CM). In some embodiments, the CM contains an amino acid sequence that serves as a substrate for at least one matrix metalloprotease of interest.

[0220] The elements of the activatable antibodies are arranged so that the MM and CM are positioned such that in a cleaved (or relatively active) state and in the presence of a

target, the AB binds a target while in an uncleaved (or relatively inactive) state in the presence of the target, specific binding of the AB to its target is reduced or inhibited. The specific binding of the AB to its target can be reduced due to the inhibition or masking of the AB’s ability to specifically bind its target by the MM.

[0221] The K_d of the AB modified with a MM and a CM towards the target is at least 5, 10, 20, 25, 40, 50, 100, 250, 500, 1,000, 2,500, 5,000, 10,000, 50,000, 100,000, 500,000, 1,000,000, 5,000,000, 10,000,000, 50,000,000 or greater, or between 5-10, 10-100, 10-1,000, 10-10,000, 10-100,000, 10-1,000,000, 10-10,000,000, 100-1,000, 100-10,000, 100-100,000, 100-1,000,000, 100-10,000,000, 1,000-10,000, 1,000-100,000, 1,000-1,000,000, 1,000-10,000,000, 1000-10,000,000, 10,000-10,000,000, 10,000-10,000,000, 100,000-1,000,000, 10,000-10,000,000, 100,000-1,000,000, or 100,000-10,000,000 times greater than the K_d of the AB not modified with an MM and a CM or of the parental AB towards the target. Conversely, the binding affinity of the AB modified with a MM and a CM towards the target is at least 2, 3, 4, 5, 10, 20, 25, 40, 50, 100, 250, 500, 1,000, 2,500, 5,000, 10,000, 50,000, 100,000, 500,000, 1,000,000, 5,000,000 or greater, or between 5-10, 10-100, 10-1,000, 10-10,000, 10-100,000, 10-1,000,000, 10-10,000,000, 100-1,000, 100-10,000, 100-100,000, 100-1,000,000, 100-10,000,000, 1,000-10,000, 1,000-100,000, 1,000-1,000,000, 1,000-10,000,000, 10,000-10,000,000, 10,000-1,000,000, 10,000-10,000,000, 100,000-1,000,000, or 100,000-10,000,000 times lower than the binding affinity of the AB not modified with an MM and a CM or of the parental AB towards the target.

[0222] When the AB is modified with a MM and a CM and is in the presence of the target but not in the presence of a modifying agent (for example a MMP), specific binding of the AB to its target is reduced or inhibited, as compared to the specific binding of the AB not modified with an MM and a CM or of the parental AB to the target. When compared to the binding of the parental AB or the binding of an AB not modified with an MM and a CM to its target, the AB’s ability to bind the target when modified with an MM and a CM can be reduced by at least 50%, 60%, 70%, 80%, 90%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% and even 100% for at least 2, 4, 6, 8, 12, 28, 24, 30, 36, 48, 60, 72, 84, or 96 hours or 5, 10, 15, 30, 45, 60, 90, 120, 150, or 180 days, or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months or longer when measured in vivo or in an in vitro assay.

[0223] As used herein, the term cleaved state refers to the condition of the activatable antibodies following modification of the CM by at least one matrix metalloprotease. The term uncleaved state, as used herein, refers to the condition of the activatable antibodies in the absence of cleavage of the CM by a MMP. As discussed above, the term “activatable antibodies” is used herein to refer to an activatable antibody in both its uncleaved (native) state, as well as in its cleaved state. It will be apparent to the ordinarily skilled artisan that in some embodiments, a cleaved activatable antibody may lack an MM due to cleavage of the CM by protease, resulting in release of at least the MM (e.g., where the MM is not joined to the activatable antibodies by a covalent bond (e.g., a disulfide bond between cysteine residues)).

[0224] By activatable or switchable is meant that the activatable antibody exhibits a first level of binding to a target when in an inhibited, masked or uncleaved state (i.e., a first conformation), and a second level of binding to the target in the uninhibited, unmasked and/or cleaved state (i.e., a second

conformation), where the second level of target binding is greater than the first level of binding. In general, the access of target to the AB of the activatable antibody is greater in the presence of a cleaving agent capable of cleaving the CM than in the absence of such a cleaving agent. Thus, when the activatable antibody is in the uncleaved state, the AB is inhibited from target binding and can be masked from target binding (i.e., the first conformation is such the AB cannot bind the target), and in the cleaved state the AB is not inhibited or is unmasked to target binding.

[0225] The CM and AB of the activatable antibodies are selected so that the AB represents a binding moiety for a given target, and the CM represents a substrate for a MMP that is co-localized with the target at a treatment site or diagnostic site in a subject. The activatable antibodies disclosed herein find particular use where, for example, a MMP capable of cleaving a site in the CM is present at relatively higher levels in target-containing tissue of a treatment site or diagnostic site than in tissue of non-treatment sites (for example in healthy tissue).

[0226] In some embodiments, activatable antibodies provide for reduced toxicity and/or adverse side effects that could otherwise result from binding of the AB at non-treatment sites if the AB were not masked or otherwise inhibited from binding to the target.

[0227] In general, an activatable antibody can be designed by selecting an AB of interest and constructing the remainder of the activatable antibody so that, when conformationally constrained, the MM provides for masking of the AB or reduction of binding of the AB to its target. Structural design criteria can be to be taken into account to provide for this functional feature.

[0228] Activatable antibodies exhibiting a switchable phenotype of a desired dynamic range for target binding in an inhibited versus an uninhibited conformation are provided. Dynamic range generally refers to a ratio of (a) a maximum detected level of a parameter under a first set of conditions to (b) a minimum detected value of that parameter under a second set of conditions. For example, in the context of an activatable antibody, the dynamic range refers to the ratio of (a) a maximum detected level of target protein binding to an activatable antibody in the presence of a MMP capable of cleaving the CM of the activatable antibodies to (b) a minimum detected level of target protein binding to an activatable antibody in the absence of the protease. The dynamic range of an activatable antibody can be calculated as the ratio of the equilibrium dissociation constant of an activatable antibody cleaving agent (e.g., enzyme) treatment to the equilibrium dissociation constant of the activatable antibodies cleaving agent treatment. The greater the dynamic range of an activatable antibody, the better the switchable phenotype of the activatable antibody. Activatable antibodies having relatively higher dynamic range values (e.g., greater than 1) exhibit more desirable switching phenotypes such that target protein binding by the activatable antibodies occurs to a greater extent (e.g., predominantly occurs) in the presence of a cleaving agent (e.g., enzyme) capable of cleaving the CM of the activatable antibodies than in the absence of a cleaving agent.

[0229] Activatable antibodies can be provided in a variety of structural configurations. Exemplary formulae for activatable antibodies are provided below. It is specifically contemplated that the N- to C-terminal order of the AB, MM and CM may be reversed within an activatable antibody. It is also

specifically contemplated that the CM and MM may overlap in amino acid sequence, e.g., such that the CM is contained within the MM.

[0230] For example, activatable antibodies can be represented by the following formula (in order from an amino (N) terminal region to carboxyl (C) terminal region:

(MM)-(CM)-(AB)

(AB)-(CM)-(MM)

where MM is a masking moiety, CM is a cleavable moiety, and AB is an antibody or fragment thereof. It should be noted that although MM and CM are indicated as distinct components in the formulae above, in all exemplary embodiments (including formulae) disclosed herein it is contemplated that the amino acid sequences of the MM and the CM could overlap, e.g., such that the CM is completely or partially contained within the MM. In addition, the formulae above provide for additional amino acid sequences that may be positioned N-terminal or C-terminal to the activatable antibodies elements.

[0231] In certain embodiments, the MM is not a natural binding partner of the AB. In some embodiments, the MM contains no or substantially no homology to any natural binding partner of the AB. In some embodiments, the MM is no more than 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, or 80% similar to any natural binding partner of the AB. In some embodiments, the MM is no more than 5%, 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, or 80% identical to any natural binding partner of the AB. In some embodiments, the MM is no more than 50% identical to any natural binding partner of the AB. In some embodiments, the MM is no more than 25% identical to any natural binding partner of the AB. In some embodiments, the MM is no more than 20% identical to any natural binding partner of the AB. In some embodiments, the MM is no more than 10% identical to any natural binding partner of the AB.

[0232] In many embodiments, it may be desirable to insert one or more linkers, e.g., flexible linkers, into the activatable antibody construct so as to provide for flexibility at one or more of the MM-CM junction, the CM-AB junction, or both. For example, the AB, MM, and/or CM may not contain a sufficient number of residues (e.g., Gly, Ser, Asp, Asn, especially Gly and Ser, particularly Gly) to provide the desired flexibility. As such, the switchable phenotype of such activatable antibody constructs may benefit from introduction of one or more amino acids to provide for a flexible linker. In addition, as described below, where the activatable antibody is provided as a conformationally constrained construct, a flexible linker can be operably inserted to facilitate formation and maintenance of a cyclic structure in the uncleaved activatable antibody.

[0233] For example, in certain embodiments, an activatable antibody comprises one of the following formulae (where the formula below represent an amino acid sequence in either N- to C-terminal direction or C- to N-terminal direction):

(MM)-L1-(CM)-(AB)

(MM)-(CM)-L2-(AB)

(MM)-L1-(CM)-L2-(AB)

wherein MM, CM, and AB are as defined above; wherein L1 and L2 are each independently and optionally present or

absent, are the same or different flexible linkers that include at least 1 flexible amino acid (e.g., Gly). In addition, the formulae above provide for additional amino acid sequences that may be positioned N-terminal or C-terminal to the activatable antibodies elements. Examples include, but are not limited to, targeting moieties (e.g., a ligand for a receptor of a cell present in a target tissue) and serum half-life extending moieties (e.g., polypeptides that bind serum proteins, such as immunoglobulin (e.g., IgG) or serum albumin (e.g., human serum albumin (HAS)).

[0234] The CM is specifically cleaved by at least one MMP at a rate of about $0.001\text{--}1500 \times 10^4 \text{M}^{-1} \text{S}^{-1}$ or at least 0.001, 0.005, 0.01, 0.05, 0.1, 0.5, 1, 2.5, 5, 7.5, 10, 15, 20, 25, 50, 75, 100, 125, 150, 200, 250, 500, 750, 1000, 1250, or $1500 \times 10^4 \text{M}^{-1} \text{S}^{-1}$.

[0235] For specific cleavage by an enzyme, contact between the enzyme and CM is made. When the activatable antibody comprising an AB coupled to a MM and a CM is in the presence of target and sufficient enzyme activity, the CM can be cleaved. Sufficient enzyme activity can refer to the ability of the enzyme to make contact with the CM and effect cleavage. It can readily be envisioned that an enzyme may be in the vicinity of the CM but unable to cleave because of other cellular factors or protein modification of the enzyme.

[0236] Linkers suitable for use in compositions described herein are generally ones that provide flexibility of the modified AB or the activatable antibodies to facilitate the inhibition of the binding of the AB to the target. Such linkers are generally referred to as flexible linkers. Suitable linkers can be readily selected and can be of any of a suitable of different lengths, such as from 1 amino acid (e.g., Gly) to 20 amino acids, from 2 amino acids to 15 amino acids, from 3 amino acids to 12 amino acids, including 4 amino acids to 10 amino acids, 5 amino acids to 9 amino acids, 6 amino acids to 8 amino acids, or 7 amino acids to 8 amino acids, and may be 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 amino acids in length.

[0237] Exemplary flexible linkers include glycine polymers (G)_n, glycine-serine polymers (including, for example, (GS)_n, (GSGGS)_n (SEQ ID NO: 1) and (GGGS)_n (SEQ ID NO: 2), where n is an integer of at least one), glycine-alanine polymers, alanine-serine polymers, and other flexible linkers known in the art. Glycine and glycine-serine polymers are relatively unstructured, and therefore may be able to serve as a neutral tether between components. Glycine accesses significantly more phi-psi space than even alanine, and is much less restricted than residues with longer side chains (see Scheraga, Rev. Computational Chem. 11173-142 (1992)). Exemplary flexible linkers include, but are not limited to Gly-Gly-Ser-Gly (SEQ ID NO: 3), Gly-Gly-Ser-Gly-Gly (SEQ ID NO: 4), Gly-Ser-Gly-Ser-Gly (SEQ ID NO: 5), Gly-Ser-Gly-Gly-Gly (SEQ ID NO: 6), Gly-Gly-Gly-Ser-Gly (SEQ ID NO: 7), Gly-Ser-Ser-Ser-Gly (SEQ ID NO: 8), and the like. The ordinarily skilled artisan will recognize that design of an activatable antibodies can include linkers that are all or partially flexible, such that the linker can include a flexible linker as well as one or more portions that confer less flexible structure to provide for a desired activatable antibodies structure.

[0238] In some embodiments, the activatable antibodies described herein also include an agent conjugated to the activatable antibody. In some embodiments, the conjugated agent is a therapeutic agent, such as an anti-inflammatory and/or an antineoplastic agent. In such embodiments, the agent is con-

jugated to a carbohydrate moiety of the activatable antibody, for example, in some embodiments, where the carbohydrate moiety is located outside the antigen-binding region of the antibody or antigen-binding fragment in the activatable antibody. In some embodiments, the agent is conjugated to a sulphydryl group of the antibody or antigen-binding fragment in the activatable antibody.

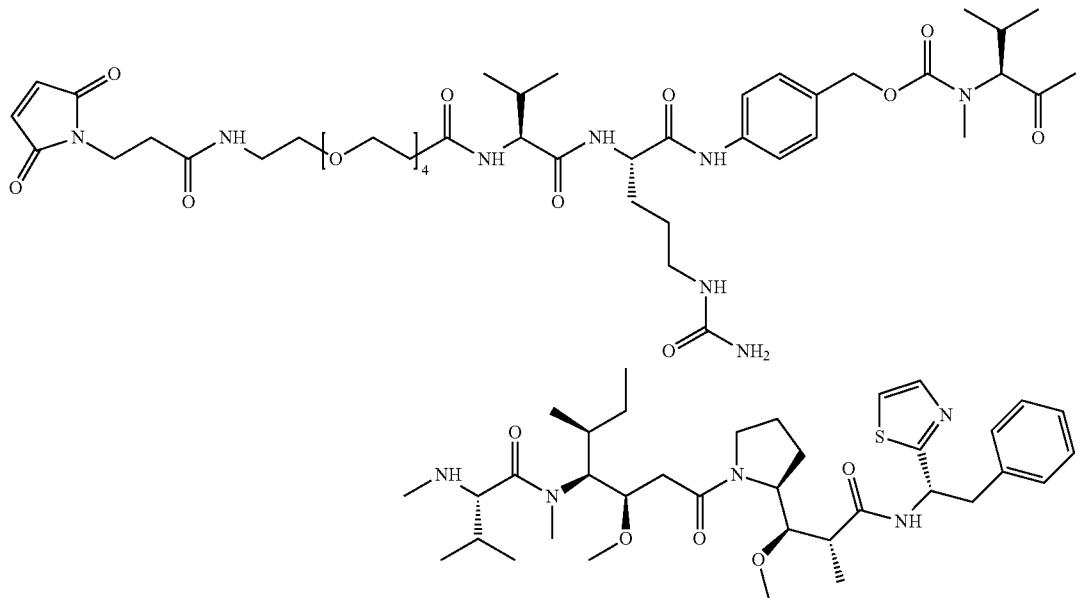
[0239] In some embodiments, the agent is a cytotoxic agent such as a toxin (e.g., an enzymatically active toxin of bacterial, fungal, plant, or animal origin, or fragments thereof), or a radioactive isotope (i.e., a radioconjugate).

[0240] In some embodiments, the agent is a detectable moiety such as, for example, a label or other marker. For example, the agent is or includes a radiolabeled amino acid, one or more biotinyl moieties that can be detected by marked avidin (e.g., streptavidin containing a fluorescent marker or enzymatic activity that can be detected by optical or calorimetric methods), one or more radioisotopes or radionuclides, one or more fluorescent labels, one or more enzymatic labels, and/or one or more chemiluminescent agents. In some embodiments, detectable moieties are attached by spacer molecules.

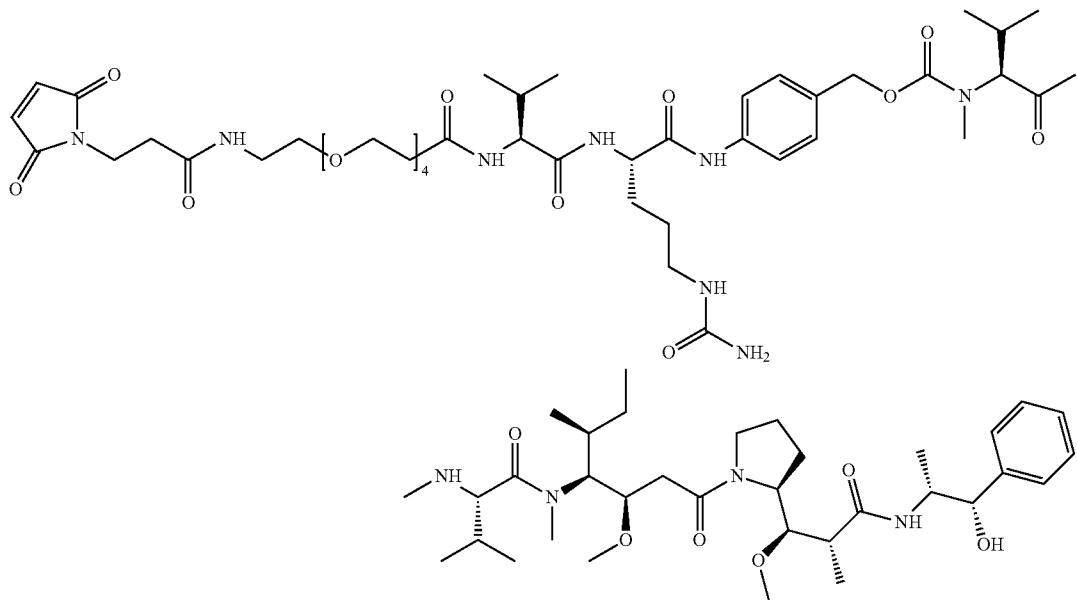
[0241] The disclosure also pertains to immunoconjugates comprising an antibody conjugated to a cytotoxic agent such as a toxin (e.g., an enzymatically active toxin of bacterial, fungal, plant, or animal origin, or fragments thereof), or a radioactive isotope (i.e., a radioconjugate). Suitable cytotoxic agents include, for example, dolastatins and derivatives thereof (e.g. auristatin E, AFP, MMAF, MMAE, MMAD, DMAF, DMAE). For example, the agent is monomethyl auristatin E (MMAE) or monomethyl auristatin D (MMAD). In some embodiments, the agent is an agent selected from the group listed in Table 3. In some embodiments, the agent is a dolastatin. In some embodiments, the agent is an auristatin or derivative thereof. In some embodiments, the agent is auristatin E or a derivative thereof. In some embodiments, the agent is monomethyl auristatin E (MMAE). In some embodiments, the agent is monomethyl auristatin D (MMAD). In some embodiments, the agent is a maytansinoid or maytansinoid derivative. In some embodiments, the agent is DM1 or DM4. In some embodiments, the agent is a duocarmycin or derivative thereof. In some embodiments, the agent is a calicheamicin or derivative thereof. In some embodiments, the agent is a pyrrolobenzodiazepine.

[0242] In some embodiments, the agent is linked to the AB using a maleimide caproyl-valine-citrulline linker or a maleimide PEG-valine-citrulline linker. In some embodiments, the agent is linked to the AB using a maleimide caproyl-valine-citrulline linker. In some embodiments, the agent is linked to the AB using a maleimide PEG-valine-citrulline linker. In some embodiments, the agent is monomethyl auristatin D (MMAD) linked to the AB using a maleimide PEG-valine-citrulline-para-aminobenzoyloxycarbonyl linker, and this linker payload construct is referred to herein as "vc-MMAD." In some embodiments, the agent is monomethyl auristatin E (MMAE) linked to the AB using a maleimide PEG-valine-citrulline-para-aminobenzoyloxycarbonyl linker, and this linker payload construct is referred to herein as "vc-MMAE." The structures of vc-MMAD and vc-MMAE are shown below:

vc-MMAD:



vc-MMAE:



[0243] Enzymatically active toxins and fragments thereof that can be used include diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from *Pseudomonas aeruginosa*), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, *Aleurites fordii* proteins, dianthin proteins, *Phytolaca americana* proteins (PAPI, PAPII, and PAP-S), *momordica charantia* inhibitor, curcin, crotin, *sapaonaria officinalis* inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin, and the trichothecenes. A variety of radionuclides are available for the production of radioconjugated antibodies. Examples include ^{212}Bi , ^{131}I , ^{131}In , ^{90}Y , and ^{186}Re .

[0244] Conjugates of the antibody and cytotoxic agent are made using a variety of bifunctional protein-coupling agents such as N-succinimidyl-3-(2-pyridylthio) propionate (SPDP), iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCL), active esters (such as disuccinimidyl suberate), aldehydes (such as glutaraldehyde), bis-azido compounds (such as bis(p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as tolyene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta et al., *Science* 238: 1098 (1987). Carbon-14-labeled

1-isothiocyanatobenzyl-3-methyldiethylene triaminepenaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the antibody. (See WO94/11026).

[0245] Table 3 lists some of the exemplary pharmaceutical agents that may be employed in the herein described disclosure but in no way is meant to be an exhaustive list.

TABLE 3

Exemplary Pharmaceutical Agents for Conjugation

<u>CYTOTOXIC AGENTS</u>	
Auristatins	
Auristatin E	
Monomethyl auristatin D (MMA D)	
Monomethyl auristatin E (MMA E)	
Desmethyl auristatin E (DMA E)	
Auristatin F	
Monomethyl auristatin F (MMA F)	
Desmethyl auristatin F (DMA F)	
Auristatin derivatives, e.g., amides thereof	
Auristatin tyramine	
Auristatin quinoline	
Dolastatins	
Dolastatin derivatives	
Dolastatin 16 DmJ	
Dolastatin 16 DpV	
Maytansinoids, e.g. DM-1; DM-4	
Maytansinoid derivatives	
Duocarmycin	
Duocarmycin derivatives	
Alpha-amanitin	
Anthracyclines	
Doxorubicin	
Daunorubicin	
Bryostatins	
Camptothecin	
Camptothecin derivatives	
7-substituted Camptothecin	
10,11-	
Difluoromethylenedioxycamptothecin	
Combretastatins	
Debromoaplysiatoxin	
Kahalalide-F	
Discodermolide	
Ecteinascidins	
<u>ANTIVIRALS</u>	
Acyclovir	
Vira A	
Symmetrel	
<u>ANTIFUNGALS</u>	
Nystatin	
<u>ADDITIONAL ANTI-NEOPLASTICS</u>	
Adriamycin	
Cerubidine	
Bleomycin	
Alkeran	
Velban	
Oncovin	
Fluorouracil	
Methotrexate	
Thiotepa	
Bisantrene	
Novantrone	
Thioguanine	
Procarabazine	
Cytarabine	
<u>ANTI-BACTERIALS</u>	
Aminoglycosides	
Streptomycin	
Neomycin	

TABLE 3-continued

Exemplary Pharmaceutical Agents for Conjugation

Kanamycin	
Amikacin	
Gentamicin	
Tobramycin	
Streptomycin B	
Spectinomycin	
Ampicillin	
Sulfanilamide	
Polymyxin	
Chloramphenicol	
Turbostatin	
Phenstatins	
Hydroxyphenstatin	
Spongistatin 5	
Spongistatin 7	
Halistatin 1	
Halistatin 2	
Halistatin 3	
Modified Bryostatins	
Halocomstatins	
Pyrrolobenzimidazoles (PBI)	
Cibrostatin 6	
Doxaliform	
Anthracyclines analogues	
Cemadotin analogue (CemCH2-SH)	
Pseudomonas toxin A (PE38) variant	
Pseudomonas toxin A (ZZ-PE38) variant	
ZJ-101	
OSW-1	
4-Nitrobenzoyloxycarbonyl Derivatives of	
O6-Benzylguanine	
Topoisomerase inhibitors	
Hemasterlin	
Cephalotaxine	
Homoharringtonine	
Pyrrolobenzodiazepine dimers (PBDs)	
Functionalized pyrrolobenzodiazepenes	
Calicheamicins	
Podophyllotoxins	
Taxanes	
Vinca alkaloids	
<u>CONJUGATABLE DETECTION REAGENTS</u>	
Fluorescein and derivatives thereof	
Fluorescein isothiocyanate (FITC)	
<u>RADIOPHARMACEUTICALS</u>	
¹²⁵ I	
¹³¹ I	
⁸⁹ Zr	
¹¹¹ In	
¹²³ I	
¹³¹ I	
⁹⁹ mTc	
²⁰¹ Tl	
¹³³ Xe	
¹¹ C	
⁶² Cu	
¹⁸ F	
⁶⁸ Ga	
¹³ N	
¹⁵ O	
³⁸ K	
⁸² Rb	
⁹⁹ mTc (Technetium)	
<u>HEAVY METALS</u>	
Barium	
Gold	
Platinum	
<u>ANTI-MYCOPLASMALS</u>	
Tylosine	
Spectinomycin	

[0246] Those of ordinary skill in the art will recognize that a large variety of possible moieties can be coupled to the resultant antibodies of the disclosure. (See, for example, "Conjugate Vaccines", Contributions to Microbiology and Immunology, J. M. Cruse and R. E. Lewis, Jr (eds), Carger Press, New York, (1989), the entire contents of which are incorporated herein by reference).

[0247] Coupling may be accomplished by any chemical reaction that will bind the two molecules so long as the antibody and the other moiety retain their respective activities. This linkage can include many chemical mechanisms, for instance covalent binding, affinity binding, intercalation, coordinate binding and complexation. In some embodiments, the binding is, however, covalent binding. Covalent binding can be achieved either by direct condensation of existing side chains or by the incorporation of external bridging molecules. Many bivalent or polyvalent linking agents are useful in coupling protein molecules, such as the antibodies of the present disclosure, to other molecules. For example, representative coupling agents can include organic compounds such as thioesters, carbodiimides, succinimide esters, diisocyanates, glutaraldehyde, diazobenzenes and hexamethylene diamines. This listing is not intended to be exhaustive of the various classes of coupling agents known in the art but, rather, is exemplary of the more common coupling agents. (See Killen and Lindstrom, *Jour. Immun.* 133:1335-2549 (1984); Jansen et al., *Immunological Reviews* 62:185-216 (1982); and Vitetta et al., *Science* 238:1098 (1987).

[0248] In some embodiments, in addition to the compositions and methods provided herein, the conjugated activatable antibody can also be modified for site-specific conjugation through modified amino acid sequences inserted or otherwise included in the activatable antibody sequence. These modified amino acid sequences are designed to allow for controlled placement and/or dosage of the conjugated agent within a conjugated activatable antibody. For example, the activatable antibody can be engineered to include cysteine substitutions at positions on light and heavy chains that provide reactive thiol groups and do not negatively impact protein folding and assembly, nor alter antigen binding. In some embodiments, the activatable antibody can be engineered to include or otherwise introduce one or more non-natural amino acid residues within the activatable antibody to provide suitable sites for conjugation. In some embodiments, the activatable antibody can be engineered to include or otherwise introduce enzymatically activatable peptide sequences within the activatable antibody sequence.

[0249] Suitable linkers are described in the literature. (See, for example, Ramakrishnan, S. et al., *Cancer Res.* 44:201-208 (1984) describing use of MBS (M-maleimidobenzoyl-N-hydroxysuccinimide ester). See also, U.S. Pat. No. 5,030,719, describing use of halogenated acetyl hydrazide derivative coupled to an antibody by way of an oligopeptide linker. In some embodiments, suitable linkers include: (i) EDC (1-ethyl-3-(3-dimethylamino-propyl) carbodiimide hydrochloride; (ii) SMPT (4-succinimidylloxycarbonyl-alpha-methyl-alpha-(2-pridyl-dithio)-toluene (Pierce Chem. Co., Cat. (21558G); (iii) SPDP (succinimidyl-6-[3-(2-pridyl)dithio]propionamido]hexanoate (Pierce Chem. Co., Cat #21651G); (iv) Sulfo-LC-SPDP (sulfosuccinimidyl 6-[3-(2-pridyl)dithio]-propianamide]hexanoate (Pierce Chem. Co. Cat. #2165-G); and (v) sulfo-NHS (N-hydroxysulfo-succinimide: Pierce Chem. Co., Cat. #24510) conjugated to EDC. Addi-

tional linkers include, but are not limited to, SMCC, sulfo-SMCC, SPDB, or sulfo-SPDB.

[0250] The linkers described above contain components that have different attributes, thus leading to conjugates with differing physio-chemical properties. For example, sulfo-NHS esters of alkyl carboxylates are more stable than sulfo-NHS esters of aromatic carboxylates. NHS-ester containing linkers are less soluble than sulfo-NHS esters. Further, the linker SMPT contains a sterically hindered disulfide bond, and can form conjugates with increased stability. Disulfide linkages, are in general, less stable than other linkages because the disulfide linkage is cleaved in vitro, resulting in less conjugate available. Sulfo-NHS, in particular, can enhance the stability of carbodiimide couplings. Carbodiimide couplings (such as EDC) when used in conjunction with sulfo-NHS, forms esters that are more resistant to hydrolysis than the carbodiimide coupling reaction alone.

[0251] In some embodiments, the linkers are cleavable. In some embodiments, the linkers are non-cleavable. In some embodiments, two or more linkers are present. The two or more linkers are all the same, i.e., cleavable or non-cleavable, or the two or more linkers are different, i.e., at least one cleavable and at least one non-cleavable.

[0252] The present disclosure utilizes several methods for attaching agents to ABs: (a) attachment to the carbohydrate moieties of the AB, or (b) attachment to sulphydryl groups of the AB, or (c) attachment to amino groups of the AB, or (d) attachment to carboxylate groups of the AB. According to the disclosure, ABs may be covalently attached to an agent through an intermediate linker having at least two reactive groups, one to react with AB and one to react with the agent. The linker, which may include any compatible organic compound, can be chosen such that the reaction with AB (or agent) does not adversely affect AB reactivity and selectivity. Furthermore, the attachment of linker to agent might not destroy the activity of the agent. Suitable linkers for reaction with oxidized antibodies or oxidized antibody fragments include those containing an amine selected from the group consisting of primary amine, secondary amine, hydrazine, hydrazide, hydroxylamine, phenylhydrazine, semicarbazide and thiosemicarbazide groups. Such reactive functional groups may exist as part of the structure of the linker, or may be introduced by suitable chemical modification of linkers not containing such groups.

[0253] According to the present disclosure, suitable linkers for attachment to reduced ABs include those having certain reactive groups capable of reaction with a sulphydryl group of a reduced antibody or fragment. Such reactive groups include, but are not limited to: reactive haloalkyl groups (including, for example, haloacetyl groups), p-mercuribenzoate groups and groups capable of Michael-type addition reactions (including, for example, maleimides and groups of the type described by Mitra and Lawton, 1979, *J. Amer. Chem. Soc.* 101: 3097-3110).

[0254] According to the present disclosure, suitable linkers for attachment to neither oxidized nor reduced Abs include those having certain functional groups capable of reaction with the primary amino groups present in unmodified lysine residues in the Ab. Such reactive groups include, but are not limited to, NHS carboxylic or carbonic esters, sulfo-NHS carboxylic or carbonic esters, 4-nitrophenyl carboxylic or carbonic esters, pentafluorophenyl carboxylic or carbonic esters, acyl imidazoles, isocyanates, and isothiocyanates.

[0255] According to the present disclosure, suitable linkers for attachment to neither oxidized nor reduced Abs include those having certain functional groups capable of reaction with the carboxylic acid groups present in aspartate or glutamate residues in the Ab, which have been activated with suitable reagents. Suitable activating reagents include EDC, with or without added NHS or sulfo-NHS, and other dehydrating agents utilized for carboxamide formation. In these instances, the functional groups present in the suitable linkers would include primary and secondary amines, hydrazines, hydroxylamines, and hydrazides.

[0256] The agent may be attached to the linker before or after the linker is attached to the AB. In certain applications it may be desirable to first produce an AB-linker intermediate in which the linker is free of an associated agent. Depending upon the particular application, a specific agent may then be covalently attached to the linker. In some embodiments, the AB is first attached to the MM, CM and associated linkers and then attached to the linker for conjugation purposes.

[0257] Branched Linkers:

[0258] In specific embodiments, branched linkers that have multiple sites for attachment of agents are utilized. For multiple site linkers, a single covalent attachment to an AB would result in an AB-linker intermediate capable of binding an agent at a number of sites. The sites may be aldehyde or sulphydryl groups or any chemical site to which agents can be attached.

[0259] In some embodiments, higher specific activity (or higher ratio of agents to AB) can be achieved by attachment of a single site linker at a plurality of sites on the AB. This

plurality of sites may be introduced into the AB by either of two methods. First, one may generate multiple aldehyde groups and/or sulphydryl groups in the same AB. Second, one may attach to an aldehyde or sulphydryl of the AB a "branched linker" having multiple functional sites for subsequent attachment to linkers. The functional sites of the branched linker or multiple site linker may be aldehyde or sulphydryl groups, or may be any chemical site to which linkers may be attached. Still higher specific activities may be obtained by combining these two approaches, that is, attaching multiple site linkers at several sites on the AB.

[0260] Cleavable Linkers:

[0261] Peptide linkers that are susceptible to cleavage by enzymes of the complement system, such as but not limited to urokinase, tissue plasminogen activator, trypsin, plasmin, or another enzyme having proteolytic activity may be used in one embodiment of the present disclosure. According to one method of the present disclosure, an agent is attached via a linker susceptible to cleavage by complement. The antibody is selected from a class that can activate complement. The antibody-agent conjugate, thus, activates the complement cascade and releases the agent at the target site. According to another method of the present disclosure, an agent is attached via a linker susceptible to cleavage by enzymes having a proteolytic activity such as a urokinase, a tissue plasminogen activator, plasmin, or trypsin. These cleavable linkers are useful in conjugated activatable antibodies that include an extracellular toxin, e.g., by way of non-limiting example, any of the extracellular toxins shown in Table 3.

[0262] Non-limiting examples of cleavable linker sequences are provided in Table 4.

TABLE 4

Exemplary Linker Sequences for Conjugation	
Types of Cleavable Sequences	Amino Acid Sequence
<u>Plasmin cleavable sequences</u>	
Pro-urokinase	PRFKIIGG (SEQ ID NO: 127) PRFRIIGG (SEQ ID NO: 128)
TGF β	SSRHRRALD (SEQ ID NO: 129)
Plasminogen	RKSSIIIRMRDVVL (SEQ ID NO: 130)
Staphylokinase	SSSFDFKGKYKKGDDA (SEQ ID NO: 131) SSSFDFKGKYKRGDDA (SEQ ID NO: 132)
Factor Xa cleavable sequences	IEGR (SEQ ID NO: 133) IDGR (SEQ ID NO: 134) GGSIDGR (SEQ ID NO: 135)
<u>MMP cleavable sequences</u>	
Gelatinase A	PLGLWA (SEQ ID NO: 136)
<u>Collagenase cleavable sequences</u>	
Calf skin collagen (α_1 (I) chain)	GPQGIAGQ (SEQ ID NO: 137)
Calf skin collagen (α_2 (I) chain)	GPQGLLGA (SEQ ID NO: 138)
Bovine cartilage collagen (α_1 (II) chain)	GIAGQ (SEQ ID NO: 139)
Human liver collagen (α_1 (III) chain)	GPLGIAGI (SEQ ID NO: 140)
Human α_2 M	GPEGLRVG (SEQ ID NO: 141)
Human PZP	YGAGLGVV (SEQ ID NO: 142) AGLGVVER (SEQ ID NO: 143) AGLGISST (SEQ ID NO: 144)

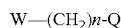
TABLE 4-continued

Exemplary Linker Sequences for Conjugation	
Types of Cleavable Sequences	Amino Acid Sequence
Rat α_1 M	EPQALAMS (SEQ ID NO: 145) QALAMSAI (SEQ ID NO: 146)
Rat α_2 M	AYAYHLVLSQ (SEQ ID NO: 147) MDAFLLESS (SEQ ID NO: 148)
Rat α_1 I ₃ (2J)	ESLPVVAV (SEQ ID NO: 149)
Rat α_1 I ₃ (27J)	SAPAVESE (SEQ ID NO: 150)
Human fibroblast collagenase (autolytic cleavages)	DVAQFVLT (SEQ ID NO: 151) VAQFVLTE (SEQ ID NO: 152) AQFVLTEG (SEQ ID NO: 153) PVQPIGPQ (SEQ ID NO: 154)

[0263] In addition, agents may be attached via disulfide bonds (for example, the disulfide bonds on a cysteine molecule) to the AB. Since many tumors naturally release high levels of glutathione (a reducing agent) this can reduce the disulfide bonds with subsequent release of the agent at the site of delivery. In certain specific embodiments, the reducing agent that would modify a CM would also modify the linker of the conjugated activatable antibody.

[0264] Spacers and Cleavable Elements:

[0265] In some embodiments, it may be necessary to construct the linker in such a way as to optimize the spacing between the agent and the AB of the activatable antibody. This may be accomplished by use of a linker of the general structure:



wherein

W is either —NH—CH₂— or —CH₂—;

Q is an amino acid, peptide; and

n is an integer from 0 to 20.

[0266] In some embodiments, the linker may comprise a spacer element and a cleavable element. The spacer element serves to position the cleavable element away from the core of the AB such that the cleavable element is more accessible to the enzyme responsible for cleavage. Certain of the branched linkers described above may serve as spacer elements.

[0267] Throughout this discussion, it should be understood that the attachment of linker to agent (or of spacer element to cleavable element, or cleavable element to agent) need not be particular mode of attachment or reaction. Any reaction providing a product of suitable stability and biological compatibility is acceptable.

[0268] Serum Complement and Selection of Linkers:

[0269] According to one method of the present disclosure, when release of an agent is desired, an AB that is an antibody of a class that can activate complement is used. The resulting conjugate retains both the ability to bind antigen and activate the complement cascade. Thus, according to this embodiment of the present disclosure, an agent is joined to one end of the cleavable linker or cleavable element and the other end of the linker group is attached to a specific site on the AB. For example, if the agent has an hydroxy group or an amino group, it may be attached to the carboxy terminus of a peptide, amino acid or other suitably chosen linker via an ester or

amide bond, respectively. For example, such agents may be attached to the linker peptide via a carbodimide reaction. If the agent contains functional groups that would interfere with attachment to the linker, these interfering functional groups can be blocked before attachment and deblocked once the product conjugate or intermediate is made. The opposite or amino terminus of the linker is then used either directly or after further modification for binding to an AB that is capable of activating complement.

[0270] Linkers (or spacer elements of linkers) may be of any desired length, one end of which can be covalently attached to specific sites on the AB of the activatable antibody. The other end of the linker or spacer element may be attached to an amino acid or peptide linker.

[0271] Thus when these conjugates bind to antigen in the presence of complement the amide or ester bond that attaches the agent to the linker will be cleaved, resulting in release of the agent in its active form. These conjugates, when administered to a subject, will accomplish delivery and release of the agent at the target site, and are particularly effective for the in vivo delivery of pharmaceutical agents, antibiotics, anti-metabolites, antiproliferative agents and the like as presented in but not limited to those in Table 3.

[0272] Linkers for Release without Complement Activation:

[0273] In yet another application of targeted delivery, release of the agent without complement activation is desired since activation of the complement cascade will ultimately lyse the target cell. Hence, this approach is useful when delivery and release of the agent should be accomplished without killing the target cell. Such is the goal when delivery of cell mediators such as hormones, enzymes, corticosteroids, neurotransmitters, genes or enzymes to target cells is desired. These conjugates may be prepared by attaching the agent to an AB that is not capable of activating complement via a linker that is mildly susceptible to cleavage by serum proteases. When this conjugate is administered to an individual, antigen-antibody complexes will form quickly whereas cleavage of the agent will occur slowly, thus resulting in release of the compound at the target site.

[0274] Biochemical Cross Linkers:

[0275] In some embodiments, the activatable antibody may be conjugated to one or more therapeutic agents using certain biochemical cross-linkers. Cross-linking reagents form

molecular bridges that tie together functional groups of two different molecules. To link two different proteins in a step-wise manner, hetero-bifunctional cross-linkers can be used that eliminate unwanted homopolymer formation.

[0276] Peptidyl linkers cleavable by lysosomal proteases are also useful, for example, Val-Cit, Val-Ala or other dipeptides. In addition, acid-labile linkers cleavable in the low-pH environment of the lysosome may be used, for example: bis-sialyl ether. Other suitable linkers include cathepsin-labile substrates, particularly those that show optimal function at an acidic pH.

[0277] Exemplary hetero-bifunctional cross-linkers are referenced in Table 5.

TABLE 5

Exemplary Hetero-Bifunctional Cross Linkers HETERO-BIFUNCTIONAL CROSS-LINKERS			
Linker	Reactive Toward	Advantages and Applications	Spacer Arm Length after cross-linking (Angstroms)
SMPT	Primary amines Sulphydryls	Greater stability	11.2 Å
SPDP	Primary amines Sulphydryls	Thiolation Cleavable cross-linking	6.8 Å
LC-SPDP	Primary amines Sulphydryls	Extended spacer arm	15.6 Å
Sulfo-LC-SPDP	Primary amines Sulphydryls	Extender spacer arm Water-soluble	15.6 Å
SMCC	Primary amines Sulphydryls	Stable maleimide reactive group Enzyme-antibody conjugation	11.6 Å
Sulfo-SMCC	Primary amines Sulphydryls	Hapten-carrier protein conjugation Stable maleimide reactive group Water-soluble Enzyme-antibody conjugation	11.6 Å
MBS	Primary amines Sulphydryls	Enzyme-antibody conjugation Hapten-carrier protein conjugation	9.9 Å
Sulfo-MBS	Primary amines Sulphydryls	Water-soluble	9.9 Å
SIAB	Primary amines Sulphydryls	Enzyme-antibody conjugation	10.6 Å
Sulfo-SIAB	Primary amines Sulphydryls	Water-soluble	10.6 Å
SMPB	Primary amines Sulphydryls	Extended spacer arm Enzyme-antibody conjugation	14.5 Å
Sulfo-SMPB	Primary amines Sulphydryls	Extended spacer arm Water-soluble	14.5 Å
EDE/Sulfo-NHS	Primary amines Carboxyl groups	Hapten-Carrier conjugation	0
ABH	Carbohydrates Nonselective	Reacts with sugar groups	11.9 Å

[0278] Non-Cleavable Linkers or Direct Attachment:

[0279] In some embodiments of the disclosure, the conjugate may be designed so that the agent is delivered to the target but not released. This may be accomplished by attaching an agent to an AB either directly or via a non-cleavable linker.

[0280] These non-cleavable linkers may include amino acids, peptides, D-amino acids or other organic compounds that may be modified to include functional groups that can

subsequently be utilized in attachment to ABs by the methods described herein. A-general formula for such an organic linker could be



wherein

W is either —NH—CH₂— or —CH₂—;

Q is an amino acid, peptide; and

n is an integer from 0 to 20.

[0281] Non-Cleavable Conjugates:

[0282] In some embodiments, a compound may be attached to ABs that do not activate complement. When using ABs that are incapable of complement activation, this attachment may be accomplished using linkers that are susceptible to cleavage by activated complement or using linkers that are not susceptible to cleavage by activated complement.

[0283] The antibodies disclosed herein can also be formulated as immunoliposomes. Liposomes containing the antibody are prepared by methods known in the art, such as described in Epstein et al., Proc. Natl. Acad. Sci. USA, 82: 3688 (1985); Hwang et al., Proc. Natl. Acad. Sci. USA, 77: 4030 (1980); and U.S. Pat. Nos. 4,485,045 and 4,544,545. Liposomes with enhanced circulation time are disclosed in U.S. Pat. No. 5,013,556.

[0284] Particularly useful liposomes can be generated by the reverse-phase evaporation method with a lipid composition comprising phosphatidylcholine, cholesterol, and PEG-derivatized phosphatidylethanolamine (PEG-PE). Liposomes are extruded through filters of defined pore size to yield liposomes with the desired diameter. Fab' fragments of the antibody of the present disclosure can be conjugated to the liposomes as described in Martin et al., J. Biol. Chem., 257: 286-288 (1982) via a disulfide-interchange reaction.

DEFINITIONS

[0285] Unless otherwise defined, scientific and technical terms used in connection with the present disclosure shall have the meanings that are commonly understood by those of ordinary skill in the art. The term "a" entity or "an" entity refers to one or more of that entity. For example, a compound refers to one or more compounds. As such, the terms "a", "an", "one or more" and "at least one" can be used interchangeably. Further, unless otherwise required by context, singular terms shall include pluralities and plural terms shall include the singular. Generally, nomenclatures utilized in connection with, and techniques of, cell and tissue culture, molecular biology, and protein and oligo- or polynucleotide chemistry and hybridization described herein are those well-known and commonly used in the art. Standard techniques are used for recombinant DNA, oligonucleotide synthesis, and tissue culture and transformation (e.g., electroporation, lipofection). Enzymatic reactions and purification techniques are performed according to manufacturer's specifications or as commonly accomplished in the art or as described herein. The foregoing techniques and procedures are generally performed according to conventional methods well known in the art and as described in various general and more specific references that are cited and discussed throughout the present specification. See e.g., Sambrook et al. Molecular Cloning: A Laboratory Manual (2d ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y. (1989)). The nomenclatures utilized in connection with, and the laboratory procedures and techniques of, analytical chemistry, synthetic organic chemistry, and medicinal and pharmaceutical chemistry described

herein are those well-known and commonly used in the art. Standard techniques are used for chemical syntheses, chemical analyses, pharmaceutical preparation, formulation, and delivery, and treatment of patients.

[0286] As utilized in accordance with the present disclosure, the following terms, unless otherwise indicated, shall be understood to have the following meanings:

[0287] As used herein, the term "antibody" refers to immunoglobulin molecules and immunologically active portions of immunoglobulin (Ig) molecules, i.e., molecules that contain an antigen binding site that specifically binds (immunoreacts with) an antigen. By "specifically bind" or "immunoreacts with" or "immunospecifically bind" is meant that the antibody reacts with one or more antigenic determinants of the desired antigen and does not react with other polypeptides or binds at much lower affinity ($K_d > 10^{-6}$). Antibodies include, but are not limited to, polyclonal, monoclonal, chimeric, domain antibody, single chain, Fab, and F(ab')₂ fragments, scFvs, and an Fab expression library.

[0288] The basic antibody structural unit is known to comprise a tetramer. Each tetramer is composed of two identical pairs of polypeptide chains, each pair having one "light" (about 25 kDa) and one "heavy" chain (about 50-70 kDa). The amino-terminal portion of each chain includes a variable region of about 100 to 110 or more amino acids primarily responsible for antigen recognition. The carboxy-terminal portion of each chain defines a constant region primarily responsible for effector function. In general, antibody molecules obtained from humans relate to any of the classes IgG, IgM, IgA, IgE and IgD, which differ from one another by the nature of the heavy chain present in the molecule. Certain classes have subclasses as well, such as IgG₁, IgG₂, and others. Furthermore, in humans, the light chain may be a kappa chain or a lambda chain.

[0289] The term "monoclonal antibody" (mAb) or "monoclonal antibody composition", as used herein, refers to a population of antibody molecules that contain only one molecular species of antibody molecule consisting of a unique light chain gene product and a unique heavy chain gene product. In particular, the complementarity determining regions (CDRs) of the monoclonal antibody are identical in all the molecules of the population. MAbs contain an antigen binding site capable of immunoreacting with a particular epitope of the antigen characterized by a unique binding affinity for it.

[0290] The term "antigen-binding site" or "binding portion" refers to the part of the immunoglobulin molecule that participates in antigen binding. The antigen binding site is formed by amino acid residues of the N-terminal variable ("V") regions of the heavy ("H") and light ("L") chains. Three highly divergent stretches within the V regions of the heavy and light chains, referred to as "hypervariable regions," are interposed between more conserved flanking stretches known as "framework regions," or "FRs". Thus, the term "FR" refers to amino acid sequences that are naturally found between, and adjacent to, hypervariable regions in immunoglobulins. In an antibody molecule, the three hypervariable regions of a light chain and the three hypervariable regions of a heavy chain are disposed relative to each other in three dimensional space to form an antigen-binding surface. The antigen-binding surface is complementary to the three-dimensional surface of a bound antigen, and the three hypervariable regions of each of the heavy and light chains are referred to as "complementarity-determining regions," or "CDRs." The assignment of amino

acids to each domain is in accordance with the definitions of Kabat Sequences of Proteins of Immunological Interest (National Institutes of Health, Bethesda, Md. (1987 and 1991)), or Chothia & Lesk J. Mol. Biol. 196:901-917 (1987), Chothia et al. Nature 342:878-883 (1989).

[0291] As used herein, the term "epitope" includes any protein determinant capable of specific binding to an immunoglobulin, an scFv, or a T-cell receptor. The term "epitope" includes any protein determinant capable of specific binding to an immunoglobulin or T-cell receptor. Epitopic determinants usually consist of chemically active surface groupings of molecules such as amino acids or sugar side chains and usually have specific three dimensional structural characteristics, as well as specific charge characteristics. For example, antibodies may be raised against N-terminal or C-terminal peptides of a polypeptide. An antibody is said to specifically bind an antigen when the dissociation constant is $\leq 1 \mu\text{M}$; in some embodiments, $\leq 100 \text{ nM}$ and in some embodiments, $\leq 10 \text{ nM}$.

[0292] As used herein, the terms "specific binding," "immunological binding," and "immunological binding properties" refer to the non-covalent interactions of the type which occur between an immunoglobulin molecule and an antigen for which the immunoglobulin is specific. The strength, or affinity of immunological binding interactions can be expressed in terms of the dissociation constant (K_d) of the interaction, wherein a smaller K_d represents a greater affinity. Immunological binding properties of selected polypeptides can be quantified using methods well known in the art. One such method entails measuring the rates of antigen-binding site/antigen complex formation and dissociation, wherein those rates depend on the concentrations of the complex partners, the affinity of the interaction, and geometric parameters that equally influence the rate in both directions. Thus, both the "on rate constant" (K_{on}) and the "off rate constant" (K_{off}) can be determined by calculation of the concentrations and the actual rates of association and dissociation. (See Nature 361:186-87 (1993)). The ratio of K_{off}/K_{on} enables the cancellation of all parameters not related to affinity, and is equal to the dissociation constant K_d . (See, generally, Davies et al. (1990) Annual Rev Biochem 59:439-473). An antibody of the present disclosure is said to specifically bind to the target, when the equilibrium binding constant (K_d) is $\leq 1 \mu\text{M}$, in some embodiments 100 nM, in some embodiments $\leq 10 \text{ nM}$, and in some embodiments $\leq 100 \text{ pM}$ to about 1 pM, as measured by assays such as radioligand binding assays or similar assays known to those skilled in the art.

[0293] The term "isolated polynucleotide" as used herein shall mean a polynucleotide of genomic, cDNA, or synthetic origin or some combination thereof, which by virtue of its origin the "isolated polynucleotide" (1) is not associated with all or a portion of a polynucleotide in which the "isolated polynucleotide" is found in nature, (2) is operably linked to a polynucleotide which it is not linked to in nature, or (3) does not occur in nature as part of a larger sequence. Polynucleotides in accordance with the disclosure include the nucleic acid molecules encoding the heavy chain immunoglobulin molecules shown herein, and nucleic acid molecules encoding the light chain immunoglobulin molecules shown herein.

[0294] The term "isolated protein" referred to herein means a protein of cDNA, recombinant RNA, or synthetic origin or some combination thereof, which by virtue of its origin, or source of derivation, the "isolated protein" (1) is not associated with proteins found in nature, (2) is free of other proteins

from the same source, e.g., free of murine proteins, (3) is expressed by a cell from a different species, or (4) does not occur in nature.

[0295] The term "polypeptide" is used herein as a generic term to refer to native protein, fragments, or analogs of a polypeptide sequence. Hence, native protein fragments, and analogs are species of the polypeptide genus. Polypeptides in accordance with the disclosure comprise the heavy chain immunoglobulin molecules shown herein, and the light chain immunoglobulin molecules shown herein, as well as antibody molecules formed by combinations comprising the heavy chain immunoglobulin molecules with light chain immunoglobulin molecules, such as kappa light chain immunoglobulin molecules, and vice versa, as well as fragments and analogs thereof.

[0296] The term "naturally-occurring" as used herein as applied to an object refers to the fact that an object can be found in nature. For example, a polypeptide or polynucleotide sequence that is present in an organism (including viruses) that can be isolated from a source in nature and that has not been intentionally modified by man in the laboratory or otherwise is naturally-occurring.

[0297] The term "operably linked" as used herein refers to positions of components so described are in a relationship permitting them to function in their intended manner. A control sequence "operably linked" to a coding sequence is ligated in such a way that expression of the coding sequence is achieved under conditions compatible with the control sequences.

[0298] The term "control sequence" as used herein refers to polynucleotide sequences that are necessary to effect the expression and processing of coding sequences to which they are ligated. The nature of such control sequences differs depending upon the host organism in prokaryotes, such control sequences generally include promoter, ribosomal binding site, and transcription termination sequence in eukaryotes, generally, such control sequences include promoters and transcription termination sequence. The term "control sequences" is intended to include, at a minimum, all components whose presence is essential for expression and processing, and can also include additional components whose presence is advantageous, for example, leader sequences and fusion partner sequences. The term "polynucleotide" as referred to herein means nucleotides of at least 10 bases in length, either ribonucleotides or deoxynucleotides or a modified form of either type of nucleotide. The term includes single and double stranded forms of DNA.

[0299] The term oligonucleotide referred to herein includes naturally occurring, and modified nucleotides linked together by naturally occurring, and non-naturally occurring oligonucleotide linkages. Oligonucleotides are a polynucleotide subset generally comprising a length of 200 bases or fewer. In some embodiments, oligonucleotides are 10 to 60 bases in length and in some embodiments, 12, 13, 14, 15, 16, 17, 18, 19, or 20 to 40 bases in length. Oligonucleotides are usually single stranded, e.g., for probes, although oligonucleotides may be double stranded, e.g., for use in the construction of a gene mutant. Oligonucleotides of the disclosure are either sense or antisense oligonucleotides.

[0300] The term "naturally occurring nucleotides" referred to herein includes deoxyribonucleotides and ribonucleotides. The term "modified nucleotides" referred to herein includes nucleotides with modified or substituted sugar groups and the like. The term "oligonucleotide linkages" referred to herein

includes oligonucleotide linkages such as phosphorothioate, phosphorodithioate, phosphoroselenoate, phosphorodiselenoate, phosphoranoilothioate, phosphoranoilate, phosphoronoimide, and the like. See e.g., LaPlanche et al. *Nucl. Acids Res.* 14:9081 (1986); Stec et al. *J. Am. Chem. Soc.* 106:6077 (1984), Stein et al. *Nucl. Acids Res.* 16:3209 (1988), Zon et al. *Anti Cancer Drug Design* 6:539 (1991); Zon et al. *Oligonucleotides and Analogues: A Practical Approach*, pp. 87-108 (F. Eckstein, Ed., Oxford University Press, Oxford England (1991)); Stec et al. U.S. Pat. No. 5,151,510; Uhlmann and Peyman *Chemical Reviews* 90:543 (1990). An oligonucleotide can include a label for detection, if desired.

[0301] As used herein, the twenty conventional amino acids and their abbreviations follow conventional usage. See *Immunology—A Synthesis* (2nd Edition, E. S. Golub and D. R. Gren, Eds., Sinauer Associates, Sunderland7 Mass. (1991)). Stereoisomers (e.g., D-amino acids) of the twenty conventional amino acids, unnatural amino acids such as α - α -disubstituted amino acids, N-alkyl amino acids, lactic acid, and other unconventional amino acids may also be suitable components for polypeptides of the present disclosure. Examples of unconventional amino acids include: 4 hydroxyproline, γ -carboxyglutamate, ϵ -N,N,N-trimethyllysine, ϵ -N-acetyllysine, O-phosphoserine, N-acetylserine, N-formylmethionine, 3-methylhistidine, 5-hydroxylysine, σ -N-methylarginine, and other similar amino acids and imino acids (e.g., 4-hydroxyproline). In the polypeptide notation used herein, the left-hand direction is the amino terminal direction and the right-hand direction is the carboxy-terminal direction, in accordance with standard usage and convention.

[0302] Similarly, unless specified otherwise, the left-hand end of single-stranded polynucleotide sequences is the 5' end the left-hand direction of double-stranded polynucleotide sequences is referred to as the 5' direction. The direction of 5' to 3' addition of nascent RNA transcripts is referred to as the transcription direction sequence regions on the DNA strand having the same sequence as the RNA and that are 5' to the 5' end of the RNA transcript are referred to as "upstream sequences", sequence regions on the DNA strand having the same sequence as the RNA and that are 3' to the 3' end of the RNA transcript are referred to as "downstream sequences".

[0303] As applied to polypeptides, the term "substantial identity" means that two peptide sequences, when optimally aligned, such as by the programs GAP or BESTFIT using default gap weights, share at least 80 percent sequence identity, in some embodiments, at least 90 percent sequence identity, in some embodiments, at least 95 percent sequence identity, and in some embodiments, at least 99 percent sequence identity.

[0304] In some embodiments, residue positions that are not identical differ by conservative amino acid substitutions.

[0305] As discussed herein, minor variations in the amino acid sequences of antibodies or immunoglobulin molecules are contemplated as being encompassed by the present disclosure, providing that the variations in the amino acid sequence maintain at least 75%, in some embodiments, at least 80%, 90%, 95%, and in some embodiments, 99%. In particular, conservative amino acid replacements are contemplated. Conservative replacements are those that take place within a family of amino acids that are related in their side chains. Genetically encoded amino acids are generally divided into families: (1) acidic amino acids are aspartate, glutamate; (2) basic amino acids are lysine, arginine, histidine; (3) non-polar amino acids are alanine, valine, leucine,

isoleucine, proline, phenylalanine, methionine, tryptophan, and (4) uncharged polar amino acids are glycine, asparagine, glutamine, cysteine, serine, threonine, tyrosine. The hydrophilic amino acids include arginine, asparagine, aspartate, glutamine, glutamate, histidine, lysine, serine, and threonine. The hydrophobic amino acids include alanine, cysteine, isoleucine, leucine, methionine, phenylalanine, proline, tryptophan, tyrosine and valine. Other families of amino acids include (i) serine and threonine, which are the aliphatic-hydroxy family; (ii) asparagine and glutamine, which are the amide containing family; (iii) alanine, valine, leucine and isoleucine, which are the aliphatic family; and (iv) phenylalanine, tryptophan, and tyrosine, which are the aromatic family. For example, it is reasonable to expect that an isolated replacement of a leucine with an isoleucine or valine, an aspartate with a glutamate, a threonine with a serine, or a similar replacement of an amino acid with a structurally related amino acid will not have a major effect on the binding or properties of the resulting molecule, especially if the replacement does not involve an amino acid within a framework site. Whether an amino acid change results in a functional peptide can readily be determined by assaying the specific activity of the polypeptide derivative. Assays are described in detail herein. Fragments or analogs of antibodies or immunoglobulin molecules can be readily prepared by those of ordinary skill in the art. Suitable amino- and carboxy-termini of fragments or analogs occur near boundaries of functional domains. Structural and functional domains can be identified by comparison of the nucleotide and/or amino acid sequence data to public or proprietary sequence databases. In some embodiments, computerized comparison methods are used to identify sequence motifs or predicted protein conformation domains that occur in other proteins of known structure and/or function. Methods to identify protein sequences that fold into a known three-dimensional structure are known. Bowie et al. *Science* 253:164 (1991). Thus, the foregoing examples demonstrate that those of skill in the art can recognize sequence motifs and structural conformations that may be used to define structural and functional domains in accordance with the disclosure.

[0306] Suitable amino acid substitutions are those which: (1) reduce susceptibility to proteolysis, (2) reduce susceptibility to oxidation, (3) alter binding affinity for forming protein complexes, (4) alter binding affinities, and (5) confer or modify other physicochemical or functional properties of such analogs. Analogs can include various mutants of a sequence other than the naturally-occurring peptide sequence. For example, single or multiple amino acid substitutions (for example, conservative amino acid substitutions) may be made in the naturally-occurring sequence (for example, in the portion of the polypeptide outside the domain(s) forming intermolecular contacts. A conservative amino acid substitution should not substantially change the structural characteristics of the parent sequence (e.g., a replacement amino acid should not tend to break a helix that occurs in the parent sequence, or disrupt other types of secondary structure that characterizes the parent sequence). Examples of art-recognized polypeptide secondary and tertiary structures are described in *Proteins, Structures and Molecular Principles* (Creighton, Ed., W. H. Freeman and Company, New York (1984)); *Introduction to Protein Structure* (C. Branden and J. Tooze, eds., Garland Publishing, New York, N.Y. (1991)); and Thornton et al. *Nature* 354:105 (1991).

[0307] The term "polypeptide fragment" as used herein refers to a polypeptide that has an amino terminal and/or carboxy-terminal deletion and/or one or more internal deletion(s), but where the remaining amino acid sequence is identical to the corresponding positions in the naturally-occurring sequence deduced, for example, from a full length cDNA sequence. Fragments typically are at least 5, 6, 8 or 10 amino acids long, in some embodiments, at least 14 amino acids long, in some embodiments, at least 20 amino acids long, usually at least 50 amino acids long, and in some embodiments, at least 70 amino acids long. The term "analog" as used herein refers to polypeptides that are comprised of a segment of at least 25 amino acids that has substantial identity to a portion of a deduced amino acid sequence and that has specific binding to the target, under suitable binding conditions. Typically, polypeptide analogs comprise a conservative amino acid substitution (or addition or deletion) with respect to the naturally-occurring sequence. Analogs typically are at least 20 amino acids long, in some embodiments, at least 50 amino acids long or longer, and can often be as long as a full-length naturally-occurring polypeptide.

[0308] The term "agent" is used herein to denote a chemical compound, a mixture of chemical compounds, a biological macromolecule, or an extract made from biological materials.

[0309] As used herein, the terms "label" or "labeled" refers to incorporation of a detectable marker, e.g., by incorporation of a radiolabeled amino acid or attachment to a polypeptide of biotinyl moieties that can be detected by marked avidin (e.g., streptavidin containing a fluorescent marker or enzymatic activity that can be detected by optical or calorimetric methods). In certain situations, the label or marker can also be therapeutic. Various methods of labeling polypeptides and glycoproteins are known in the art and may be used. Examples of labels for polypeptides include, but are not limited to, the following: radioisotopes or radionuclides (e.g., ³H, ¹⁴C, ¹⁵N, ³⁵S, ⁹⁰Y, ⁹⁹Tc, ¹¹¹In, ¹²⁵I, ¹³¹I), fluorescent labels (e.g., FITC, rhodamine, lanthanide phosphors), enzymatic labels (e.g., horseradish peroxidase, p-galactosidase, luciferase, alkaline phosphatase), chemiluminescent, biotinyl groups, predetermined polypeptide epitopes recognized by a secondary reporter (e.g., leucine zipper pair sequences, binding sites for secondary antibodies, metal binding domains, epitope tags). In some embodiments, labels are attached by spacer arms of various lengths to reduce potential steric hindrance. The term "pharmaceutical agent or drug" as used herein refers to a chemical compound or composition capable of inducing a desired therapeutic effect when properly administered to a patient.

[0310] Other chemistry terms herein are used according to conventional usage in the art, as exemplified by *The McGraw-Hill Dictionary of Chemical Terms* (Parker, S., Ed., McGraw-Hill, San Francisco (1985)).

[0311] As used herein, "substantially pure" means an object species is the predominant species present (i.e., on a molar basis it is more abundant than any other individual species in the composition), and in some embodiments, a substantially purified fraction is a composition wherein the object species comprises at least about 50 percent (on a molar basis) of all macromolecular species present.

[0312] Generally, a substantially pure composition will comprise more than about 80 percent of all macromolecular species present in the composition, in some embodiments, more than about 85%, 90%, 95%, and 99%. In some embodiments, the object species is purified to essential homogeneity

(contaminant species cannot be detected in the composition by conventional detection methods) wherein the composition consists essentially of a single macromolecular species.

[0313] The term patient includes human and veterinary subjects.

[0314] Activatable antibodies of the disclosure specifically bind a given target, e.g., a human target protein. Also included in the disclosure are activatable antibodies that bind to the same epitope as the activatable antibodies described herein.

[0315] Those skilled in the art will recognize that it is possible to determine, without undue experimentation, if a monoclonal antibody (e.g., a murine monoclonal or humanized antibody) has the same specificity as a monoclonal antibody used in the methods described herein by ascertaining whether the former prevents the latter from binding to the target. If the monoclonal antibody being tested competes with the monoclonal antibody of the disclosure, as shown by a decrease in binding by the monoclonal antibody of the disclosure, then the two monoclonal antibodies bind to the same, or a closely related, epitope. A method for determining whether a monoclonal antibody has the specificity of a monoclonal antibody of the disclosure is to pre-incubate the monoclonal antibody of the disclosure with the target and then add the monoclonal antibody being tested to determine if the monoclonal antibody being tested is inhibited in its ability to bind the target. If the monoclonal antibody being tested is inhibited then, in all likelihood, it has the same, or functionally equivalent, epitopic specificity as the monoclonal antibody of the disclosure.

[0316] Multispecific Activatable Antibodies

[0317] The disclosure also provides multispecific activatable antibodies. The multispecific activatable antibodies provided herein are multispecific antibodies that recognize two or more different antigens or epitopes and that include at least one masking moiety (MM) linked to at least one antigen- or epitope-binding domain of the multispecific antibody such that coupling of the MM reduces the ability of the antigen- or epitope-binding domain to bind its target. In some embodiments, the MM is coupled to the antigen- or epitope-binding domain of the multispecific antibody via a cleavable moiety (CM) that functions as a substrate for at least one MMP protease. The activatable multispecific antibodies provided herein are stable in circulation, activated at intended sites of therapy and/or diagnosis but not in normal, i.e., healthy tissue, and, when activated, exhibit binding to a target that is at least comparable to the corresponding, unmodified multispecific antibody.

[0318] In some embodiments, the multispecific activatable antibodies are designed to engage immune effector cells, also referred to herein as immune-effector cell engaging multispecific activatable antibodies. In some embodiments, the multispecific activatable antibodies are designed to engage leukocytes, also referred to herein as leukocyte engaging multispecific activatable antibodies. In some embodiments, the multispecific activatable antibodies are designed to engage T cells, also referred to herein as T-cell engaging multispecific activatable antibodies. In some embodiments, the multispecific activatable antibodies engage a surface antigen on a leukocyte, such as on a T cell, on a natural killer (NK) cell, on a myeloid mononuclear cell, on a macrophage, and/or on another immune effector cell. In some embodiments, the immune effector cell is a leukocyte. In some embodiments, the immune effector cell is a T cell. In some embodiments, the immune effector cell is a NK cell. In some embodiments, the immune effector cell is a myeloid mononuclear cell.

immune effector cell is a mononuclear cell, such as a myeloid mononuclear cell. In some embodiments, the multispecific activatable antibodies are designed to bind or otherwise interact with more than one target and/or more than one epitope, also referred to herein as multi-antigen targeting activatable antibodies. As used herein, the terms "target" and "antigen" are used interchangeably.

[0319] In some embodiments, immune effector cell engaging multispecific activatable antibodies of the disclosure include a targeting antibody or antigen-binding fragment thereof and an immune effector cell engaging antibody or antigen-binding portion thereof, where at least one of the targeting antibody or antigen-binding fragment thereof and/or the immune effector cell engaging antibody or antigen-binding portion thereof is masked. In some embodiments, the immune effector cell engaging antibody or antigen binding fragment thereof includes a first antibody or antigen-binding fragment thereof (AB1) that binds a first, immune effector cell engaging target, where the AB1 is attached to a masking moiety (MM1) such that coupling of the MM1 reduces the ability of the AB1 to bind the first target. In some embodiments, the targeting antibody or antigen-binding fragment thereof includes a second antibody or fragment thereof that includes a second antibody or antigen-binding fragment thereof (AB2) that binds a second target, where the AB2 is attached to a masking moiety (MM2) such that coupling of the MM2 reduces the ability of the AB2 to bind the second target. In some embodiments, the immune effector cell engaging antibody or antigen binding fragment thereof includes a first antibody or antigen-binding fragment thereof (AB1) that binds a first, immune effector cell engaging target, where the AB1 is attached to a masking moiety (MM1) such that coupling of the MM1 reduces the ability of the AB1 to bind the first target, and the targeting antibody or antigen-binding fragment thereof includes a second antibody or fragment thereof that includes a second antibody or antigen-binding fragment thereof (AB2) that binds a second target, where the AB2 is attached to a masking moiety (MM2) such that coupling of the MM2 reduces the ability of the AB2 to bind the second target. In some embodiments, the non-immune effector cell engaging antibody is a cancer targeting antibody. In some embodiments the non-immune cell effector antibody is an IgG. In some embodiments the immune effector cell engaging antibody is a scFv. In some embodiments the targeting antibody (e.g., non-immune cell effector antibody) is an IgG and the immune effector cell engaging antibody is a scFv. In some embodiments, the immune effector cell is a leukocyte. In some embodiments, the immune effector cell is a T cell. In some embodiments, the immune effector cell is a NK cell. In some embodiments, the immune effector cell is a myeloid mononuclear cell.

[0320] In some embodiments, T-cell engaging multispecific activatable antibodies of the disclosure include a targeting antibody or antigen-binding fragment thereof and a T-cell engaging antibody or antigen-binding portion thereof, where at least one of the targeting antibody or antigen-binding fragment thereof and/or the T-cell engaging antibody or antigen binding fragment thereof is masked. In some embodiments, the T-cell engaging antibody or antigen binding fragment thereof includes a first antibody or antigen-binding fragment thereof (AB1) that binds a first, T-cell engaging target, where the AB1 is attached to a masking moiety (MM1) such that coupling of the MM1 reduces the ability of the AB1 to bind the first target. In some embodiments, the targeting antibody or antigen-

binding fragment thereof includes a second antibody or fragment thereof that includes a second antibody or antigen-binding fragment thereof (AB2) that binds a second target, where the AB2 is attached to a masking moiety (MM2) such that coupling of the MM2 reduces the ability of the AB2 to bind the second target. In some embodiments, the T-cell engaging antibody or antigen binding fragment thereof includes a first antibody or antigen-binding fragment thereof (AB1) that binds a first, T-cell engaging target, where the AB1 is attached to a masking moiety (MM1) such that coupling of the MM1 reduces the ability of the AB1 to bind the first target, and the targeting antibody or antigen-binding fragment thereof includes a second antibody or fragment thereof that includes a second antibody or antigen-binding fragment thereof (AB2) that binds a second target, where the AB2 is attached to a masking moiety (MM2) such that coupling of the MM2 reduces the ability of the AB2 to bind the second target.

[0321] In some embodiments, the T-cell engaging multispecific activatable antibodies include a cancer targeting antibody or antigen-binding fragment thereof and a T-cell engaging antibody or antigen-binding portion thereof, where at least one of the cancer targeting antibody or antigen-binding fragment thereof and/or the T-cell engaging antibody or antigen-binding portion thereof is masked. In some embodiments, the T-cell engaging antibody or antigen binding fragment thereof includes a first antibody or antigen-binding fragment thereof (AB1) that binds a first, T-cell engaging target, where the AB1 is attached to a masking moiety (MM1) such that coupling of the MM1 reduces the ability of the AB1 to bind the first target. In some embodiments, the cancer targeting antibody or antigen-binding fragment thereof includes a second antibody or fragment thereof that includes a second antibody or antigen-binding fragment thereof (AB2) that binds a second, cancer-related target, where the AB2 is attached to a masking moiety (MM2) such that coupling of the MM2 reduces the ability of the AB2 to bind the second, cancer-related target. In some embodiments, the T-cell engaging antibody or antigen binding fragment thereof includes a first antibody or antigen-binding fragment thereof (AB1) that binds a first, T-cell engaging target, where the AB1 is attached to a masking moiety (MM1) such that coupling of the MM1 reduces the ability of the AB1 to bind the first target, and the cancer targeting antibody or antigen-binding fragment thereof includes a second antibody or fragment thereof that includes a second antibody or antigen-binding fragment thereof (AB2) that binds a second, cancer-related target, where the AB2 is attached to a masking moiety (MM2) such that coupling of the MM2 reduces the ability of the AB2 to bind the second, cancer-related target.

[0322] In some embodiments, the T-cell engaging multispecific activatable antibodies include a cancer targeting IgG antibody or antigen-binding fragment thereof and a T-cell engaging scFv, where at least one of the cancer targeting IgG antibody or antigen-binding fragment thereof and/or the T-cell engaging antibody or antigen-binding portion thereof is masked. In some embodiments, the T-cell engaging antibody or antigen binding fragment thereof includes a first antibody or antigen-binding fragment thereof (AB1) that binds a first, T-cell engaging target, where the AB1 is attached to a masking moiety (MM1) such that coupling of the MM1 reduces the ability of the AB1 to bind the first target. In some embodiments, the cancer targeting IgG antibody or antigen-binding fragment thereof includes a second antibody or fragment thereof

that includes a second antibody or antigen-binding fragment thereof (AB2) that binds a second, cancer-related target, where the AB2 is attached to a masking moiety (MM2) such that coupling of the MM2 reduces the ability of the AB2 to bind the second, cancer-related target. In some embodiments, the T-cell engaging antibody or antigen binding fragment thereof includes a first antibody or antigen-binding fragment thereof (AB1) that binds a first, T-cell engaging target, where the AB1 is attached to a masking moiety (MM1) such that coupling of the MM1 reduces the ability of the AB1 to bind the first target, and the cancer targeting IgG antibody or antigen-binding fragment thereof includes a second antibody or fragment thereof that includes a second antibody or antigen-binding fragment thereof (AB2) that binds a second, cancer-related target, where the AB2 is attached to a masking moiety (MM2) such that coupling of the MM2 reduces the ability of the AB2 to bind the second, cancer-related target.

[0323] In some embodiments of an immune effector cell engaging multispecific activatable antibody, one antigen is typically an antigen present on the surface of a tumor cell or other cell type associated with disease, such as, but not limited to, any target listed in Table 1, such as, but not limited to, EGFR, erbB2, EpCAM, Jagged, PD-L1, B7H3, or CD71 (transferrin receptor), and another antigen is typically a stimulatory or inhibitory receptor present on the surface of a T-cell, natural killer (NK) cell, myeloid mononuclear cell, macrophage, and/or other immune effector cell, such as, but not limited to, B7-H4, BTLA, CD3, CD4, CD8, CD16a, CD25, CD27, CD28, CD32, CD56, CD137, CTLA-4, GITR, HVEM, ICOS, LAG3, NKG2D, OX40, PD-1, TIGIT, TIM3, or VISTA. In some embodiments, the antigen is a stimulatory receptor present on the surface of a T cell or NK cell; examples of such stimulatory receptors include, but are not limited to, CD3, CD27, CD28, CD137 (also referred to as 4-1BB), GITR, HVEM, ICOS, NKG2D, and OX40. In some embodiments, the antigen is an inhibitory receptor present on the surface of a T-cell; examples of such inhibitory receptors include, but are not limited to, BTLA, CTLA-4, LAG3, PD-1, TIGIT, TIM3, and NK-expressed KIRs. The antibody domain conferring specificity to the T-cell surface antigen may also be substituted by a ligand or ligand domain that binds to a T-cell receptor, a NK-cell receptor, a macrophage receptor, and/or other immune effector cell receptor, such as, but not limited to, B7-1, B7-2, B7H3, PD-L1, PD-L2, or TNFSF9.

[0324] One embodiment of the disclosure is a multispecific activatable antibody that is activatable in a cancer microenvironment and that includes an antibody, for example a IgG or scFv, directed to a tumor target and an agonist antibody, for example an IgG or scFv, directed to a co-stimulatory receptor expressed on the surface of an activated T cell or NK cell, wherein at least one of the cancer target antibody and/or agonist antibody is masked. Examples of co-stimulatory receptors include, but are not limited to, CD27, CD137, GITR, HVEM, NKG2D, and OX40. In this embodiment, the multispecific activatable antibody, once activated by tumor-associated proteases, would effectively crosslink and activate the T cell or NK cell expressed co-stimulatory receptors in a tumor-dependent manner to enhance the activity of T cells that are responding to any tumor antigen via their endogenous T cell antigen or NK-activating receptors. The activation-dependent nature of these T cell or NK cell costimulatory receptors would focus the activity of the activated multispecific activatable antibody to tumor-specific T cells, without

activating all T cells independent of their antigen specificity. In one embodiment, at least the co-stimulatory receptor antibody of the multispecific activatable antibody is masked to prevent activation of auto-reactive T cells that may be present in tissues that also express the antigen recognized by the tumor target-directed antibody in the multispecific activatable antibody, but whose activity is restricted by lack of co-receptor engagement.

[0325] One embodiment of the disclosure is a multispecific activatable antibody that is activatable in a disease characterized by T cell overstimulation, such as, but not limited to, an autoimmune disease or inflammatory disease microenvironment. Such a multispecific activatable antibody includes an antibody, for example a IgG or scFv, directed to a target comprising a surface antigen expressed in a tissue targeted by a T cell in autoimmune or inflammatory disease and an antibody, for example a IgG or scFv, directed to an inhibitory receptor expressed on the surface of a T cell or NK cell, wherein at least one of the disease tissue target antibody and/or T cell inhibitory receptor antibody is masked. Examples of inhibitory receptors include, but are not limited to, BTLA, CTLA-4, LAG3, PD-1, TIGIT, TIM3, and NK-expressed KIRs. Examples of a tissue antigen targeted by T cells in autoimmune disease include, but are not limited to, a surface antigen expressed on myelin or nerve cells in multiple sclerosis or a surface antigen expressed on pancreatic islet cells in Type 1 diabetes. In this embodiment, the multispecific activatable antibody when localized in the tissue under autoimmune attack or inflammation is activated and co-engages the T cell or NK cell inhibitory receptor to suppress the activity of autoreactive T cells responding to any disease tissue-targeted antigens via their endogenous TCR or activating receptors. In one embodiment, at least one or multiple antibodies are masked to prevent suppression of T cell responses in non-disease tissues where the target antigen may also be expressed.

[0326] In some embodiments, the T-cell engaging multispecific activatable antibody includes an anti-CD3 epsilon (CD3 ϵ , also referred to herein as CD3 ϵ and CD3) scFv and a targeting antibody or antigen-binding fragment thereof, where at least one of the anti-CD3 ϵ scFv and/or the targeting antibody or antigen-binding portion thereof is masked. In some embodiments, the CD3 ϵ scFv includes a first antibody or antigen-binding fragment thereof (AB1) that binds CD3 ϵ , where the AB1 is attached to a masking moiety (MM1) such that coupling of the MM1 reduces the ability of the AB1 to bind CD3 ϵ . In some embodiments, the targeting antibody or antigen-binding fragment thereof includes a second antibody or antigen-binding fragment thereof (AB2) that binds a second target, where the AB2 is attached to a masking moiety (MM2) such that coupling of the MM2 reduces the ability of the AB2 to bind the second target. In some embodiments, the CD3 ϵ scFv includes a first antibody or antigen-binding fragment thereof (AB1) that binds CD3 ϵ , where the AB1 is attached to a masking moiety (MM1) such that coupling of the MM1 reduces the ability of the AB1 to bind CD3 ϵ , and the targeting antibody or antigen-binding fragment thereof includes a second antibody or fragment thereof that includes a second antibody or antigen-binding fragment thereof (AB2) that binds a second target, where the AB2 is attached to a masking moiety (MM2) such that coupling of the MM2 reduces the ability of the AB2 to bind the second target.

[0327] In some embodiments, the T-cell engaging multispecific activatable antibody includes an anti-CD3 ϵ scFv and a cancer targeting antibody or antigen-binding fragment thereof, where at least one of the anti-CD3 ϵ scFv and/or the cancer targeting antibody or antigen-binding portion thereof is masked. In some embodiments, the CD3 ϵ scFv includes a first antibody or antigen-binding fragment thereof (AB1) that binds CD3 ϵ , where the AB1 is attached to a masking moiety (MM1) such that coupling of the MM1 reduces the ability of the AB1 to bind CD3 ϵ . In some embodiments, the cancer targeting antibody or antigen-binding fragment thereof includes a second antibody or fragment thereof that includes a second antibody or antigen-binding fragment thereof (AB2) that binds a second, cancer-related target, where the AB2 is attached to a masking moiety (MM2) such that coupling of the MM2 reduces the ability of the AB2 to bind the second, cancer-related target. In some embodiments, the CD3 ϵ scFv includes a first antibody or antigen-binding fragment thereof (AB1) that binds CD3 ϵ , where the AB1 is attached to a masking moiety (MM1) such that coupling of the MM1 reduces the ability of the AB1 to bind CD3 ϵ , and the cancer targeting antibody or antigen-binding fragment thereof includes a second antibody or fragment thereof that includes a second antibody or antigen-binding fragment thereof (AB2) that binds a second, cancer-related target, where the AB2 is attached to a masking moiety (MM2) such that coupling of the MM2 reduces the ability of the AB2 to bind the second, cancer-related target.

[0328] In some embodiments, the T-cell engaging multispecific activatable antibody includes an anti-CD3 ϵ scFv and a cancer targeting IgG antibody or antigen-binding fragment thereof, where at least one of the anti-CD3 ϵ scFv and/or the cancer targeting IgG antibody or antigen-binding portion thereof is masked. In some embodiments, the CD3 ϵ scFv includes a first antibody or antigen-binding fragment thereof (AB1) that binds CD3 ϵ , where the AB1 is attached to a masking moiety (MM1) such that coupling of the MM1 reduces the ability of the AB1 to bind CD3 ϵ . In some embodiments, the cancer targeting IgG antibody or antigen-binding fragment thereof includes a second antibody or fragment thereof that includes a second antibody or antigen-binding fragment thereof (AB2) that binds a second, cancer-related target, where the AB2 is attached to a masking moiety (MM2) such that coupling of the MM2 reduces the ability of the AB2 to bind the second, cancer-related target. In some embodiments, the CD3 ϵ scFv includes a first antibody or antigen-binding fragment thereof (AB1) that binds CD3 ϵ , where the AB1 is attached to a masking moiety (MM1) such that coupling of the MM1 reduces the ability of the AB1 to bind CD3 ϵ , and the cancer targeting antibody IgG or antigen-binding fragment thereof includes a second antibody or fragment thereof that includes a second antibody or antigen-binding fragment thereof (AB2) that binds a second, cancer-related target, where the AB2 is attached to a masking moiety (MM2) such that coupling of the MM2 reduces the ability of the AB2 to bind the second, cancer-related target.

[0329] In some embodiments, the T-cell engaging multispecific activatable antibody includes an anti-CD3 epsilon (CD3 ϵ) scFv that is derived from OKT3, where at least one of the targeting antibody or antigen-binding fragment thereof and/or the OKT3 scFv or OKT3-derived scFv is masked. In some embodiments, the OKT3 scFv or OKT3-derived scFv includes a first antibody or antigen-binding fragment thereof (AB1) that binds CD3 ϵ , where the AB1 is attached to a

that binds a second target, where the AB2 is attached to a masking moiety (MM2) such that coupling of the MM2 reduces the ability of the AB2 to bind the second target.

[0334] In some embodiments, the multi-antigen targeting antibodies and/or multi-antigen targeting activatable antibodies include at least a first antibody or antigen-binding fragment thereof that binds a first target and/or first epitope and a second antibody or antigen-binding fragment thereof that binds a second target and/or a second epitope. In some embodiments, the multi-antigen targeting antibodies and/or multi-antigen targeting activatable antibodies bind two or more different targets. In some embodiments, the multi-antigen targeting antibodies and/or multi-antigen targeting activatable antibodies bind two or more different epitopes on the same target. In some embodiments, the multi-antigen targeting antibodies and/or multi-antigen targeting activatable antibodies bind a combination of two or more different targets and two or more different epitopes on the same target.

[0335] In some embodiments, a multispecific activatable antibody comprising an IgG has the IgG variable domains masked. In some embodiments, a multispecific activatable antibody comprising a scFv has the scFv domains masked. In some embodiments, a multispecific activatable antibody has both IgG variable domains and scFv domains, where at least one of the IgG variable domains is coupled to a masking moiety. In some embodiments, a multispecific activatable antibody has both IgG variable domains and scFv domains, where at least one of the scFv domains is coupled to a masking moiety. In some embodiments, a multispecific activatable antibody has both IgG variable domains and scFv domains, where at least one of the IgG variable domains is coupled to a masking moiety and at least one of the scFv domains is coupled to a masking moiety. In some embodiments, a multispecific activatable antibody has both IgG variable domains and scFv domains, where each of the IgG variable domains and the scFv domains is coupled to its own masking moiety. In some embodiments, one antibody domain of a multispecific activatable antibody has specificity for a target antigen and another antibody domain has specificity for a T-cell surface antigen. In some embodiments, one antibody domain of a multispecific activatable antibody has specificity for a target antigen and another antibody domain has specificity for another target antigen. In some embodiments, one antibody domain of a multispecific activatable antibody has specificity for an epitope of a target antigen and another antibody domain has specificity for another epitope of the target antigen.

[0336] In a multispecific activatable antibody, a scFv can be fused to the carboxyl terminus of the heavy chain of an IgG activatable antibody, to the carboxyl terminus of the light chain of an IgG activatable antibody, or to the carboxyl termini of both the heavy and light chains of an IgG activatable antibody. In a multispecific activatable antibody, a scFv can be fused to the amino terminus of the heavy chain of an IgG activatable antibody, to the amino terminus of the light chain of an IgG activatable antibody, or to the amino termini of both the heavy and light chains of an IgG activatable antibody. In a multispecific activatable antibody, a scFv can be fused to any combination of one or more carboxyl termini and one or more amino termini of an IgG activatable antibody. In some embodiments, a masking moiety (MM) linked to a cleavable moiety (CM) is attached to and masks an antigen binding domain of the IgG. In some embodiments, a masking moiety (MM) linked to a cleavable moiety (CM) is attached to and masks an antigen binding domain of at least one scFv. In some

embodiments, a masking moiety (MM) linked to a cleavable moiety (CM) is attached to and masks an antigen binding domain of an IgG and a masking moiety (MM) linked to a cleavable moiety (CM) is attached to and masks an antigen binding domain of at least one scFv.

[0337] The disclosure provides examples of multispecific activatable antibody structures which include, but are not limited to, the following: $(VL-CL)_2:(VH-CH1-CH2-CH3-L4-VH^*-L3-VL^*-L2-CM-L1-MM)_2$; $(VL-CL)_2:(VH-CH1-CH2-CH3-L4-VL^*-L3-VH^*-L2-CM-L1-MM)_2$; $(MM-L1-CM-L2-VL-CL)_2$; $(VH-CH1-CH2-CH3-L4-VH^*-L3-VL^*)_2$; $(MM-L1-CM-L2-VL-CL)_2:(VH-CH1-CH2-CH3-L4-VL^*-L3-VH^*)_2$; $(VL-CL)_2:(MM-L1-CM-L2-VL^*-L3-VH^*-L4-VH-CH1-CH2-CH3)_2$; $(VL-CL)_2:(MM-L1-CM-L2-VL-CL)_2:(VH^*-L3-VL^*-L4-VH-CH1-CH2-CH3)_2$; $(MM-L1-CM-L2-VL-CL)_2:(VH^*-L3-VL^*-L4-VH-CH1-CH2-CH3)_2$; $(VL-CL-L4-VH^*-L3-VL^*-L2-CM-L1-MM)_2$; $(VH-CH1-CH2-CH3)_2$; $(VL-CL-L4-VL^*-L3-VH^*-L2-CM-L1-MM)_2$; $(VH-CH1-CH2-CH3)_2$; $(MM-L1-CM-L2-VL^*-L3-VH^*-L4-VL-CL)_2$; $(VH-CH1-CH2-CH3)_2$; $(MM-L1-CM-L2-VL-CL)_2:(VH-CH1-CH2-CH3)_2$; $(MM-L1-CM-L2-VH^*-L3-VL^*-L4-VL-CL)_2$; $(VH-CH1-CH2-CH3)_2$; $(VL-CL-L4-VH^*-L3-VL^*-L2-CM-L1-MM)_2$; $(MM-L1-CM-L2-VL^*-L3-VH^*-L4-VH-CH1-CH2-CH3)_2$; $(VL-CL-L4-VH^*-L3-VL^*-L2-CM-L1-MM)_2$; $(MM-L1-CM-L2-VH^*-L3-VL^*-L4-VH-CH1-CH2-CH3)_2$; $(VL-CL-L4-VL^*-L3-VH^*)_2$; $(MM-L1-CM-L2-VL^*-L3-VH^*-L4-VH-CH1-CH2-CH3)_2$; $(VL-CL-L4-VH^*-L3-VL^*)_2$; $(MM-L1-CM-L2-VL^*-L3-VH^*-L4-VH-CH1-CH2-CH3)_2$; $(VL-CL-L4-VL^*-L3-VH^*)_2$; $(MM-L1-CM-L2-VH^*-L3-VL^*-L4-VH-CH1-CH2-CH3)_2$; $(VL-CL-L4-VH^*-L3-VL^*-L4-VH-CH1-CH2-CH3)_2$; $(VL-CL-L4-VL^*-L3-VH^*)_2$; $(MM-L1-CM-L2-VH^*-L3-VL^*-L4-VH-CH1-CH2-CH3)_2$; $(VL-CL-L4-VH^*-L3-VL^*-L2-CM-L1-MM)_2$; $(VH^*-L3-VL^*-L4-VH-CH1-CH2-CH3)_2$; $(VL-CL-L4-VL^*-L3-VH^*-L2-CM-L1-MM)_2$; $(VH^*-L3-VL^*-L4-VH-CH1-CH2-CH3)_2$; or $(VL-CL-L4-VL^*-L3-VH^*-L2-CM-L1-MM)_2$; $(VH^*-L3-VL^*-L4-VH-CH1-CH2-CH3)_2$, wherein: VL and VH represent the light and heavy variable domains of the first specificity, contained in the IgG; VL* and VH* represent the variable domains of the second specificity, contained in the scFv; L1 is a linker peptide connecting the masking moiety (MM) and the cleavable moiety (CM); L2 is a linker peptide connecting the cleavable moiety (CM), and the antibody; L3 is a linker peptide connecting the variable domains of the scFv; L4 is a linker peptide connecting the antibody of the first specificity to the antibody of the second specificity; CL is the light-chain constant domain; and CH1, CH2, CH3 are the heavy chain constant domains. The first and second specificities may be toward any antigen or epitope.

[0338] In some embodiments of a T-cell engaging multi-specific activatable antibody, one antigen is typically an antigen present on the surface of a tumor cell or other cell type associated with disease, such as, but not limited to, any target listed in Table 1, such as, but not limited to, EGFR, erbB2, EpCAM, Jagged, PD-L1, B7H3, or CD71 (transferrin receptor), and another antigen is typically a stimulatory (also referred to herein as activating) or inhibitory receptor present on the surface of a T-cell, natural killer (NK) cell, myeloid mononuclear cell, macrophage, and/or other immune effector

cell, such as, but not limited to, B7-H4, BTLA, CD3, CD4, CD8, CD16a, CD25, CD27, CD28, CD32, CD56, CD137 (also referred to as TNFRSF9), CTLA-4, GITR, HVEM, ICOS, LAG3, NKG2D, OX40, PD-1, TIGIT, TIM3, or VISTA. The antibody domain conferring specificity to the T-cell surface antigen may also be substituted by a ligand or ligand domain that binds to a T-cell receptor, a NK-cell receptor, a macrophage receptor, and/or other immune effector cell receptor, such as, but not limited to, B7-1, B7-2, B7H3, PD-L1, PD-L2, or TNFSF9. In some embodiments of a multi-antigen targeting activatable antibody, one antigen is selected from the group of targets listed in Table 1, and another antigen is selected from the group of targets listed in Table 1.

[0339] In some embodiments, the targeting antibody is an anti-EGFR antibody. In some embodiments, the targeting antibody is C225v5, which is specific for binding to EGFR. In some embodiments, the targeting antibody is C225, which is specific for binding to EGFR. In some embodiments, the targeting antibody is C225v4, which is specific for binding to EGFR. In some embodiments, the targeting antibody is C225v6, which is specific for binding to EGFR. In some embodiments, the targeting antibody is an anti-Jagged antibody. In some embodiments, the targeting antibody is 4D11, which is specific for binding to human and mouse Jagged 1 and Jagged 2. In some embodiments, the targeting antibody is 4D11v2, which is specific for binding to human and mouse Jagged 1 and Jagged 2.

[0340] In some embodiments, the targeting antibody can be in the form an activatable antibody. In some embodiments, the scFv(s) can be in the form of a Pro-scFv (see, e.g., WO 2009/025846, WO 2010/081173).

[0341] In some embodiments, the scFv is specific for binding CD3 ϵ , and is or is derived from an antibody or fragment thereof that binds CD3 ϵ , e.g., CH2527, FN18, H2C, OKT3, 2C11, UCHT1, or V9. In some embodiments, the scFv is specific for binding CTLA-4 (also referred to herein as CTLA and CTLA4).

[0342] In some embodiments, the anti-CTLA-4 scFv includes the amino acid sequence:

[0343] In some embodiments, the anti-CTLA-4 scFv includes the amino acid sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to the amino acid sequence of SEQ ID NO: 510.

[0344] In some embodiments, the anti-CD3 ϵ scFv includes the amino acid sequence:

(SEQ ID NO: 511)
GGGSGGGGSGSGGGSGGGGGGGQVQLQGSAGELARPAGASVCKMSCKASGY
TFTRYTMHWVKORPGOOGLEWIGYINPNSRGYTNYNQFKDKATLTTDKSSS

-continued
TAYMQLSSLTSEDSAVYYCARYDDHYCLDYGQGTTLVSSGGGSGGG
GSGGGGSQIVLTQSPAIMSASPGEKVMTCSASSSVSYMNWYQQKSGTSP
KRWIYDTSKLASGVPAHFRGSGSGTYSLTISGMEEADAATYYCQQWSSN
PFTFGSGTKLEINR

[0345] In some embodiments, the anti-CD3e scFv includes the amino acid sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to the amino acid sequence of SEQ ID NO: 511.

[0346] In some embodiments, the scFv is specific for binding one or more T-cells, one or more NK-cells and/or one or more macrophages. In some embodiments, the scFv is specific for binding a target selected from the group consisting of B7-H4, BTLA, CD3, CD4, CD8, CD16a, CD25, CD27, CD28, CD32, CD56, CD137, CTLA-4, GITR, HVEM, ICOS, LAG3, NKG2D, OX40, PD-1, TIGIT, TIM3, or VISTA.

[0347] In some embodiments, the multispecific activatable antibody also includes an agent conjugated to the AB. In some embodiments, the agent is a therapeutic agent. In some embodiments, the agent is an antineoplastic agent. In some embodiments, the agent is a toxin or fragment thereof. In some embodiments, the agent is conjugated to the multispecific activatable antibody via a linker. In some embodiments, the agent is conjugated to the AB via a cleavable linker. In some embodiments, the agent is conjugated to the AB via a linker that includes at least one MMP-cleavable substrate sequence. In some embodiments, the linker is a non-cleavable linker. In some embodiments, the agent is a microtubule inhibitor. In some embodiments, the agent is a nucleic acid damaging agent, such as a DNA alkylator or DNA intercalator, or other DNA damaging agent. In some embodiments, the linker is a cleavable linker. In some embodiments, the agent is an agent selected from the group listed in Table 4. In some embodiments, the agent is a dolastatin. In some embodiments, the agent is an auristatin or derivative thereof. In some embodiments, the agent is auristatin E or a derivative thereof. In some embodiments, the agent is monomethyl auristatin E (MMAE). In some embodiments, the agent is monomethyl auristatin D (MMAD). In some embodiments, the agent is a maytansinoid or maytansinoid derivative. In some embodiments, the agent is DM1 or DM4. In some embodiments, the agent is a diuocarmycin or derivative thereof. In some embodiments, the agent is a calicheamicin or derivative thereof. In some embodiments, the agent is a pyrrolobenzodiazepine.

[0348] In some embodiments, the multispecific activatable antibody also includes a detectable moiety. In some embodiments, the detectable moiety is a diagnostic agent.

[0349] In some embodiments, the multispecific activatable antibody naturally contains one or more disulfide bonds. In some embodiments, the multispecific activatable antibody can be engineered to include one or more disulfide bonds.

[0350] The disclosure also provides an isolated nucleic acid molecule encoding a multispecific activatable antibody described herein, as well as vectors that include these isolated nucleic acid sequences. The disclosure provides methods of producing a multispecific activatable antibody by culturing a cell under conditions that lead to expression of the activatable antibody, wherein the cell comprises such a nucleic acid molecule. In some embodiments, the cell comprises such a vector.

[0351] The disclosure also provides a method of manufacturing multispecific activatable antibodies of the disclosure by (a) culturing a cell comprising a nucleic acid construct that encodes the multispecific activatable antibody under conditions that lead to expression of the multispecific activatable, and (b) recovering the multispecific activatable antibody.

[0352] The disclosure also provides multispecific activatable antibodies and/or multispecific activatable antibody compositions that include at least a first antibody or antigen-binding fragment thereof (AB1) that specifically binds a first target or first epitope and a second antibody or antigen-binding fragment thereof (AB2) that binds a second target or a second epitope, where at least AB1 is coupled or otherwise attached to a masking moiety (MM1), such that coupling of the MM1 reduces the ability of AB1 to bind its target. In some embodiments, the MM1 is coupled to AB1 via a first cleavable moiety (CM1) sequence that includes a substrate for a protease, for example, a protease that is co-localized with the target of AB1 at a treatment site or a diagnostic site in a subject. The multispecific activatable antibodies provided herein are stable in circulation, activated at intended sites of therapy and/or diagnosis but not in normal, i.e., healthy tissue, and, when activated, exhibit binding to the target of AB1 that is at least comparable to the corresponding, unmodified multispecific antibody.

[0353] In some embodiments, the multispecific activatable antibody comprises a linking peptide between the MM1 and the CM1.

[0354] In some embodiments, the multispecific activatable antibody comprises a linking peptide between the CM1 and the AB1.

[0355] In some embodiments, the activatable antibody comprises a first linking peptide (LP1) and a second linking peptide (LP2), and at least a portion of the multispecific activatable antibody has the structural arrangement from N-terminus to C-terminus as follows in the uncleaved state: MM1-LP1-CM1-LP2-AB1 or AB1-LP2-CM1-LP1-MM1. In some embodiments, the two linking peptides need not be identical to each other.

[0356] In some embodiments, at least one of LP1 or LP2 includes an amino acid sequence selected from the group consisting of (GS)_n, (GGS)_n, (GSGGS)_n (SEQ ID NO: 1) and (GGGS)_n (SEQ ID NO: 2), where n is an integer of at least one. In some embodiments, at least one of LP1 or LP2 includes an amino acid sequence selected from the group consisting of GGSG (SEQ ID NO: 3), GGS GG (SEQ ID NO: 4), GSG SG (SEQ ID NO: 5), GS GGG (SEQ ID NO: 6), GGG SG (SEQ ID NO: 7), and GS SSG (SEQ ID NO: 8).

[0357] In some embodiments, the multispecific activatable antibody includes at least a first antibody or antigen-binding fragment thereof (AB1) that specifically binds a first target or first epitope and a second antibody or antigen-binding fragment thereof (AB2) that specifically binds a second target or second epitope. In some embodiments, each of the AB in the multispecific activatable antibody is independently selected from the group consisting of a monoclonal antibody, domain antibody, single chain, Fab fragment, a F(ab')₂ fragment, a scFv, a scAb, a dAb, a single domain heavy chain antibody, and a single domain light chain antibody. In some embodiments, each of the AB in the multispecific activatable antibody is a rodent (e.g., mouse or rat), chimeric, humanized or fully human monoclonal antibody.

[0358] In some embodiments, each of the AB in the multispecific activatable antibody has an equilibrium dissociation constant of about 100 nM or less for binding to its corresponding target or epitope.

[0359] In some embodiments, MM1 has an equilibrium dissociation constant for binding to its corresponding AB that is greater than the equilibrium dissociation constant of the AB to its corresponding target or epitope.

[0360] In some embodiments, MM1 has an equilibrium dissociation constant for binding to its corresponding AB that is no more than the equilibrium dissociation constant of the AB to its corresponding target or epitope.

[0361] In some embodiments, MM1 does not interfere or compete with its corresponding AB for binding to the corresponding target or epitope when the multispecific activatable antibody is in a cleaved state.

[0362] In some embodiments, MM1 is a polypeptide of about 2 to 40 amino acids in length. In some embodiments, each of the MM in the multispecific activatable antibody is a polypeptide of no more than 40 amino acids in length.

[0363] In some embodiments, MM1 has a polypeptide sequence that is different from that of target of the corresponding AB.

[0364] In some embodiments, MM1 has a polypeptide sequence that is no more than 50% identical to any natural binding partner of the corresponding AB. In some embodiments, MM1 has a polypeptide sequence that is no more than 25% identical to any natural binding partner of the corresponding AB. In some embodiments, MM1 has a polypeptide sequence that is no more than 10% identical to any natural binding partner of the corresponding AB.

[0365] In some embodiments, the coupling of MM1 reduces the ability of the corresponding AB to bind its target or epitope such that the dissociation constant (K_d) of the AB when coupled to the MM1 towards its corresponding target or epitope is at least 20 times greater than the K_d of the AB when not coupled to the MM1 towards its corresponding target or epitope.

[0366] In some embodiments, the coupling of MM1 reduces the ability of the corresponding AB to bind its target or epitope such that the dissociation constant (K_d) of the AB when coupled to the MM1 towards its corresponding target or epitope is at least 40 times greater than the K_d of the AB when not coupled to the MM1 towards its corresponding target or epitope.

[0367] In some embodiments, the coupling of MM1 reduces the ability of the corresponding AB to bind its target or epitope such that the dissociation constant (K_d) of the AB when coupled to the MM1 towards its corresponding target or epitope is at least 100 times greater than the K_d of the AB when not coupled to the MM1 towards its corresponding target or epitope.

[0368] In some embodiments, the coupling of MM1 reduces the ability of the corresponding AB to bind its target or epitope such that the dissociation constant (K_d) of the AB when coupled to the MM1 towards its corresponding target or epitope is at least 1000 times greater than the K_d of the AB when not coupled to the MM1 towards its corresponding target or epitope.

[0369] In some embodiments, the coupling of MM1 reduces the ability of the corresponding AB to bind its target or epitope such that the dissociation constant (K_d) of the AB when coupled to the MM1 towards its corresponding target or

epitope is at least 10,000 times greater than the K_d of the AB when not coupled to the MM1 towards its corresponding target or epitope.

[0370] In some embodiments, MM1 is an amino acid sequence selected from a MM disclosed herein.

[0371] In some embodiments, the multispecific activatable antibody includes at least a second masking moiety (MM2) that inhibits the binding of the AB2 to its target when the multispecific activatable antibody is in an uncleaved state, and a second cleavable moiety (CM2) coupled to the AB2, wherein the CM2 is a polypeptide that functions as a substrate for a second protease. In some embodiments, CM2 is a polypeptide of no more than 15 amino acids long. In some embodiments, the second protease is co-localized with the second target or epitope in a tissue, and wherein the second protease cleaves the CM2 in the multispecific activatable antibody when the multispecific activatable antibody is exposed to the second protease. In some embodiments, the first protease and the second protease are co-localized with the first target or epitope and the second target or epitope in a tissue. In some embodiments, the first protease and the second protease are the same protease. In some embodiments, CM1 and CM2 are different substrates for the same protease. In some embodiments, the protease is selected from the group consisting of those shown in Table 7. In some embodiments, the first protease and the second protease are different proteases. In some embodiments, the first protease and the second protease are different proteases selected from the group consisting of those shown in Table 7.

[0372] In some embodiments, each of the MM in the multispecific activatable antibody, e.g., MM1 and at least MM2, has an equilibrium dissociation constant for binding to its corresponding AB that is greater than the equilibrium dissociation constant of the AB to its corresponding target or epitope.

[0373] In some embodiments, each of the MM in the multispecific activatable antibody has an equilibrium dissociation constant for binding to its corresponding AB that is no more than the equilibrium dissociation constant of the AB to its corresponding target or epitope.

[0374] In some embodiments, each of the MM in the multispecific activatable antibody does not interfere or compete with its corresponding AB for binding to the corresponding target or epitope when the multispecific activatable antibody is in a cleaved state.

[0375] In some embodiments, each of the MM in the multispecific activatable antibody is a polypeptide of about 2 to 40 amino acids in length. In some embodiments, each of the MM in the multispecific activatable antibody is a polypeptide of no more than 40 amino acids in length.

[0376] In some embodiments, each of the MM in the multispecific activatable antibody has a polypeptide sequence that is different from that of target of the corresponding AB.

[0377] In some embodiments, each of the MM in the multispecific activatable antibody has a polypeptide sequence that is no more than 50% identical to any natural binding partner of the corresponding AB. In some embodiments, each of the MM in the multispecific activatable antibody has a polypeptide sequence that is no more than 25% identical to any natural binding partner of the corresponding AB. In some embodiments, each of the MM in the multispecific activatable antibody has a polypeptide sequence that is no more than 10% identical to any natural binding partner of the corresponding AB.

[0378] In some embodiments, the coupling of each of the MM reduces the ability of the corresponding AB to bind its target or epitope such that the dissociation constant (K_d) of the AB when coupled to the MM towards its corresponding target or epitope is at least 20 times greater than the K_d of the AB when not coupled to the MM towards its corresponding target or epitope.

[0379] In some embodiments, the coupling of each of the MM reduces the ability of the corresponding AB to bind its target or epitope such that the dissociation constant (K_d) of the AB when coupled to the MM towards its corresponding target or epitope is at least 40 times greater than the K_d of the AB when not coupled to the MM towards its corresponding target or epitope.

[0380] In some embodiments, the coupling of each of the MM reduces the ability of the corresponding AB to bind its target or epitope such that the dissociation constant (K_d) of the AB when coupled to the MM towards its corresponding target or epitope is at least 100 times greater than the K_d of the AB when not coupled to the MM towards its corresponding target or epitope.

[0381] In some embodiments, the coupling of each of the MM reduces the ability of the corresponding AB to bind its target or epitope such that the dissociation constant (K_d) of the AB when coupled to the MM towards its corresponding target or epitope is at least 1000 times greater than the K_d of the AB when not coupled to the MM towards its corresponding target or epitope.

[0382] In some embodiments, the coupling of each of the MM reduces the ability of the corresponding AB to bind its target or epitope such that the dissociation constant (K_d) of the AB when coupled to the MM towards its corresponding target or epitope is at least 10,000 times greater than the K_d of the AB when not coupled to the MM towards its corresponding target or epitope.

[0383] In some embodiments, each of the MM is an amino acid sequence selected from a MM disclosed herein.

[0384] In some embodiments, at least one of CM1 and/or CM2 is cleaved by at least one MMP protease. In some embodiments, at least one of CM1 and/or CM2 includes an amino acid sequence selected from the group consisting of ISSGLLSS (SEQ ID NO: 14); QNQALRMA (SEQ ID NO: 15); AQNLLGMV (SEQ ID NO: 16); STFPFGMF (SEQ ID NO: 17); PVGYTSSL (SEQ ID NO: 18); DWLYWPGI (SEQ ID NO: 19); MIAPVAYR (SEQ ID NO: 20); RPSPMWAY (SEQ ID NO: 21); WATPRPMR (SEQ ID NO: 22); FRLLD-WQW (SEQ ID NO: 23); LKAAPRWA (SEQ ID NO: 24); GPSHLVLT (SEQ ID NO: 25); LPGGLSPW (SEQ ID NO: 26); MGLFSEAG (SEQ ID NO: 27); SPLPLRVP (SEQ ID NO: 28); RMHRLRSLG (SEQ ID NO: 29); LAAPLGLL (SEQ ID NO: 30); AVGLLAPP (SEQ ID NO: 31); LLAPSHRA (SEQ ID NO: 32); PAGLWLDP (SEQ ID NO: 33); and ISS-GLSS (SEQ ID NO: 159).

[0385] In some embodiments, at least one of CM1 and/or CM2 includes an amino acid sequence selected from the group consisting of SEQ ID NOs: 364-370, 379-393, 402-409, 420-424, 434, 435, 450-452, 457, 470-472, 474, and 483.

[0386] In some embodiments, at least one of CM1 and/or CM2 includes an amino acid sequence selected from the group consisting of SEQ ID NOs: 328, 336-339, and 348-351.

[0387] In some embodiments, the protease that cleaves the first cleavable moiety (CM1) sequence is co-localized with the target of the AB1 in the multispecific activatable antibody

in a tissue, and the protease cleaves the CM1 in the multispecific activatable antibody when the multispecific activatable antibody is exposed to the protease.

[0388] In some embodiments, the multispecific activatable antibody includes more than one cleavable moiety sequence, and the protease that cleaves at least one cleavable moiety sequence is co-localized with the target of at least one of the AB regions in the multispecific activatable antibody in a tissue, and the protease cleaves the CM in the multispecific activatable antibody when the multispecific activatable antibody is exposed to the protease.

[0389] In some embodiments, each CM, e.g., CM1 and at least CM2, is positioned in the multispecific activatable antibody such that in the uncleaved state, binding of the multispecific activatable antibody to a target of one of the AB regions is reduced to occur with an equilibrium dissociation constant that is at least twofold greater than the equilibrium dissociation constant of an unmodified AB binding to its target, and whereas in the cleaved state, the AB binds its target.

[0390] In some embodiments, each CM, e.g., CM1 and at least CM2, is positioned in the multispecific activatable antibody such that in the uncleaved state, binding of the multispecific activatable antibody to a target of one of the AB regions is reduced to occur with an equilibrium dissociation constant that is at least threefold greater than the equilibrium dissociation constant of an unmodified AB binding to its target, and whereas in the cleaved state, the AB binds its target.

[0391] In some embodiments, each CM, e.g., CM1 and at least CM2, is positioned in the multispecific activatable antibody such that in the uncleaved state, binding of the multispecific activatable antibody to a target of one of the AB regions is reduced to occur with an equilibrium dissociation constant that is at least fourfold greater than the equilibrium dissociation constant of an unmodified AB binding to its target, and whereas in the cleaved state, the AB binds its target.

[0392] In some embodiments, each CM, e.g., CM1 and at least CM2, is positioned in the multispecific activatable antibody such that in the uncleaved state, binding of the multispecific activatable antibody to a target of one of the AB regions is reduced to occur with an equilibrium dissociation constant that is at least fivefold greater than the equilibrium dissociation constant of an unmodified AB binding to its target, and whereas in the cleaved state, the AB binds its target.

[0393] In some embodiments, each CM, e.g., CM1 and at least CM2, is positioned in the multispecific activatable antibody such that in the uncleaved state, binding of the multispecific activatable antibody to a target of one of the AB regions is reduced to occur with an equilibrium dissociation constant that is at least tenfold greater than the equilibrium dissociation constant of an unmodified AB binding to its target, and whereas in the cleaved state, the AB binds its target.

[0394] In some embodiments, each CM, e.g., CM1 and at least CM2, is positioned in the multispecific activatable antibody such that in the uncleaved state, binding of the multispecific activatable antibody to a target of one of the AB regions is reduced to occur with an equilibrium dissociation constant that is at least 20-fold greater than the equilibrium

dissociation constant of an unmodified AB binding to its target, and whereas in the cleaved state, the AB binds its target.

[0395] In some embodiments, each CM is positioned in the multispecific activatable antibody such that in the uncleaved state, binding of the multispecific activatable antibody to a target of one of the AB regions is reduced to occur with an equilibrium dissociation constant that is at least 40-fold greater than the equilibrium dissociation constant of an unmodified AB binding to its target, and whereas in the cleaved state, the AB binds its target.

[0396] In some embodiments, each CM is positioned in the multispecific activatable antibody such that in the uncleaved state, binding of the multispecific activatable antibody to a target of one of the AB regions is reduced to occur with an equilibrium dissociation constant that is at least 50-fold greater than the equilibrium dissociation constant of an unmodified AB binding to its target, and whereas in the cleaved state, the AB binds its target.

[0397] In some embodiments, each CM is positioned in the multispecific activatable antibody such that in the uncleaved state, binding of the multispecific activatable antibody to a target of one of the AB regions is reduced to occur with an equilibrium dissociation constant that is at least 100-fold greater than the equilibrium dissociation constant of an unmodified AB binding to its target, and whereas in the cleaved state, the AB binds its target.

[0398] In some embodiments, each CM is positioned in the multispecific activatable antibody such that in the uncleaved state, binding of the multispecific activatable antibody to a target of one of the AB regions is reduced to occur with an equilibrium dissociation constant that is at least 200-fold greater than the equilibrium dissociation constant of an unmodified AB binding to its target, and whereas in the cleaved state, the AB binds its target.

[0399] In some embodiments, each CM in the multispecific activatable antibody is a polypeptide of up to 15 amino acids in length.

[0400] In some embodiments, at least one CM in the multispecific activatable antibody includes an amino acid sequence selected from the group consisting of SEQ ID NOs: 14-33 and 159 and the other CM includes the amino acid sequence LSGRSDNH (SEQ ID NO: 26). In some embodiments, at least one CM includes the amino acid sequence LSGRSDNH (SEQ ID NO: 26). In some embodiments, at least one cleavable moiety is selected for use with a specific protease, for example a protease that is known to be co-localized with at least one target of the multispecific activatable antibody. For example, suitable cleavable moieties for use in the multispecific activatable antibodies of the disclosure are cleaved by at least a protease such as urokinase, legumain, and/or matriptase (also referred to herein as MT-SP1 or MTSP1). In some embodiments, a suitable cleavable moiety includes at least one of the following sequences: TGRGPSWV (SEQ ID NO: 27); SARGPSRW (SEQ ID NO: 28); TARGPSFK (SEQ ID NO: 29); LSGRSDNH (SEQ ID NO: 26); GGWHTGRN (SEQ ID NO: 30); HTGRSGAL (SEQ ID NO: 31); PLTGRSGGG (SEQ ID NO: 32); AARGPAIH (SEQ ID NO: 33); RGPAFNPM (SEQ ID NO: 34); SSRGPAYL (SEQ ID NO: 35); RGPATPIM (SEQ ID NO: 36); RGPA (SEQ ID NO: 37); GGQPSGMWGW (SEQ ID NO: 38); FPRPLGITGL (SEQ ID NO: 39); VHMPLGFLGP (SEQ ID NO: 40); SPLTGRSG (SEQ ID NO: 41); SAGFS-

LPA (SEQ ID NO: 42); LAPLGLQRR (SEQ ID NO: 43); SGGPLGVR (SEQ ID NO: 44); and/or PLGL (SEQ ID NO: 45).

[0401] In some embodiments, one CM is a substrate for at least one MMP protease and the other CM in the multispecific activatable antibody is a substrate for a protease selected from the group consisting of those shown in Table 7. In some embodiments, the protease is selected from the group consisting of uPA, legumain, matriptase, ADAM17, BMP-1, TMPRSS3, TMPRSS4, neutrophil elastase, MMP-7, MMP-9, MMP-12, MMP-13, and MMP-14. In some embodiments, the protease is a cathepsin, such as, but not limited to, cathepsin S. In some embodiments, each CM in the multispecific activatable antibody is a substrate for a protease selected from the group consisting of uPA (urokinase plasminogen activator), legumain and matriptase. In some embodiments, the protease comprises uPA. In some embodiments, the protease comprises legumain. In some embodiments, the protease comprises matriptase. In some embodiments, the protease comprises a matrix metalloproteinase (MMP).

[0402] In some embodiments, at least one CM in the multispecific activatable antibody is a substrate for at least two proteases. In some embodiments, each protease is selected from the group consisting of those shown in Table 7. In some embodiments, at least one CM in the multispecific activatable antibody is a substrate for at least two proteases, wherein one of the proteases is selected from the group consisting of uPA, legumain and matriptase and the other protease is selected from the group consisting of those shown in Table 7. In some embodiments, at least one CM in the multispecific activatable antibody is a substrate for at least two proteases selected from the group consisting of uPA, legumain and matriptase.

[0403] In some embodiments, the multispecific activatable antibody includes at least a first CM (CM1) and a second CM (CM2). In some embodiments, CM1 and CM2 are part of a single cleavable linker that joins an MM to an AB. In some embodiments, CM1 is part of a cleavable linker that joins MM1 to AB1, and CM2 is part of a separate cleavable linker that joins an MM2 to AB2. In some embodiments, a multispecific activatable antibody comprises more than two CMs. In some embodiments, such a multispecific activatable antibody comprises more than two CMs and more than two MMs. In some embodiments, CM1 and CM2 are each polypeptides of no more than 15 amino acids long. In some embodiments, at least one of the first CM and the second CM is a polypeptide that functions as a substrate for a protease selected from the group consisting of those listed in Table 7. In some embodiments, at least one of the first CM and the second CM is a polypeptide that functions as a substrate for a protease selected from the group consisting of uPA, legumain, and matriptase. In some embodiments, the first CM is cleaved by a first cleaving agent selected from the group consisting of uPA, legumain, and matriptase in a target tissue and the second CM is cleaved by a second cleaving agent in a target tissue. In some embodiments, the other protease is selected from the group consisting of those shown in Table 7. In some embodiments, the first cleaving agent and the second cleaving agent are the same protease selected from the group consisting of those listed in Table 7, and the first CM and the second CM are different substrates for the enzyme. In some embodiments, the first cleaving agent and the second cleaving agent are the same protease selected from the group consisting of uPA, legumain, and matriptase, and the first CM and the second CM are different substrates for the enzyme. In some

embodiments, the first cleaving agent and the second cleaving agent are the same protease selected from the group listed in Table 7, and the first CM and the second CM are the same substrate. In some embodiments, the first cleaving agent and the second cleaving agent are different proteases. In some embodiments, the first cleaving agent and the second cleaving agent are different proteases selected from the group consisting of those shown in Table 7. In some embodiments, the first cleaving agent and the second cleaving agent are co-localized in the target tissue. In some embodiments, the first CM and the second CM are cleaved by at least one cleaving agent in the target tissue.

[0404] In some embodiments, the multispecific activatable antibody is exposed to and cleaved by a protease such that, in the activated or cleaved state, the activated multispecific activatable antibody includes a light chain amino acid sequence that includes at least a portion of LP2 and/or CM sequence after the protease has cleaved the CM.

[0405] The disclosure also provides compositions and methods that include a multispecific activatable antibody that includes at least a first antibody or antibody fragment (AB1) that specifically binds a target and a second antibody or antibody fragment (AB2), where at least the first AB in the multispecific activatable antibody is coupled to a masking moiety (MM1) that decreases the ability of AB1 to bind its target. In some embodiments, each AB is coupled to a MM that decreases the ability of its corresponding AB to each target. For example, in bispecific activatable antibody embodiments, AB1 is coupled to a first masking moiety (MM1) that decreases the ability of AB1 to bind its target, and AB2 is coupled to a second masking moiety (MM2) that decreases the ability of AB2 to bind its target. In some embodiments, the multispecific activatable antibody comprises more than two AB regions; in such embodiments, AB1 is coupled to a first masking moiety (MM1) that decreases the ability of AB1 to bind its target, AB2 is coupled to a second masking moiety (MM2) that decreases the ability of AB2 to bind its target, AB3 is coupled to a third masking moiety (MM3) that decreases the ability of AB3 to bind its target, and so on for each AB in the multispecific activatable antibody.

[0406] In some embodiments, the multispecific activatable antibody further includes at least one cleavable moiety (CM) that is a substrate for a protease, where the CM links a MM to an AB. For example, in some embodiments, the multispecific activatable antibody includes at least a first antibody or antibody fragment (AB1) that specifically binds a target and a second antibody or antibody fragment (AB2), where at least the first AB in the multispecific activatable antibody is coupled via a first cleavable moiety (CM1) to a masking moiety (MM1) that decreases the ability of AB1 to bind its target. In some bispecific activatable antibody embodiments, AB1 is coupled via CM1 to MM1, and AB2 is coupled via a second cleavable moiety (CM2) to a second masking moiety (MM2) that decreases the ability of AB2 to bind its target. In some embodiments, the multispecific activatable antibody comprises more than two AB regions; in some of these embodiments, AB1 is coupled via CM1 to MM1, AB2 is coupled via CM2 to MM2, and AB3 is coupled via a third cleavable moiety (CM3) to a third masking moiety (MM3) that decreases the ability of AB3 to bind its target, and so on for each AB in the multispecific activatable antibody.

[0407] Activatable Antibodies Having Non-Binding Steric Moieties or Binding Partners for Non-Binding Steric Moieties

[0408] The disclosure also provides activatable antibodies that include non-binding steric moieties (NB) or binding partners (BP) for non-binding steric moieties, where the BP recruits or otherwise attracts the NB to the activatable antibody. The activatable antibodies provided herein include, for example, an activatable antibody that includes a non-binding steric moiety (NB), a cleavable linker (CL) and antibody or antibody fragment (AB) that binds a target; an activatable antibody that includes a binding partner for a non-binding steric moiety (BP), a CL and an AB; and an activatable antibody that includes a BP to which an NB has been recruited, a CL and an AB that binds the target. Activatable antibodies in which the NB is covalently linked to the CL and AB of the activatable antibody or is associated by interaction with a BP that is covalently linked to the CL and AB of the activatable antibody are referred to herein as "NB-containing activatable antibodies." By activatable or switchable is meant that the activatable antibody exhibits a first level of binding to a target when the activatable antibody is in an inhibited, masked or uncleaved state (i.e., a first conformation), and a second level of binding to the target when the activatable antibody is in an uninhibited, unmasked and/or cleaved state (i.e., a second conformation, i.e., activated antibody), where the second level of target binding is greater than the first level of target binding. The activatable antibody compositions can exhibit increased bioavailability and more favorable biodistribution compared to conventional antibody therapeutics.

[0409] In some embodiments, activatable antibodies provide for reduced toxicity and/or adverse side effects that could otherwise result from binding of the at non-treatment sites and/or non-diagnostic sites if the AB were not masked or otherwise inhibited from binding to such a site.

[0410] In one embodiment, the activatable antibody includes a non-binding steric moiety (NB); a cleavable linker (CL); and an antibody or antibody fragment (AB) that binds specifically to the target, wherein the NB is a polypeptide that does not bind specifically to the AB; the CL is a polypeptide that includes a substrate (S) for an enzyme; the CL is positioned such that in an uncleaved state, the NB interferes with binding of the AB to the target and in a cleaved state, the NB does not interfere with binding of the AB to the target; and the NB does not inhibit cleavage of the CL by the enzyme. As used herein and throughout, the term polypeptide refers to any polypeptide that includes at least two amino acid residues, including larger polypeptides, full-length proteins and fragments thereof, and the term polypeptide is not limited to single-chain polypeptides and can include multi-unit, e.g., multi-chain, polypeptides. In cases where the polypeptide is of a shorter length, for example, less than 50 amino acids total, the terms peptide and polypeptide are used interchangeably herein, and in cases where the polypeptide is of a longer length, e.g., 50 amino acids or greater, the terms polypeptide and protein are used interchangeably herein.

[0411] In one embodiment, the activatable antibody includes a non-binding steric moiety (NB); a cleavable linker (CL); and an antibody or antibody fragment (AB) that binds specifically to the target, wherein (i) the NB includes a polypeptide that does not bind specifically to the AB; (ii) CL is a polypeptide of up to 50 amino acids in length that includes a substrate (S) for an enzyme; (iii) the CL is positioned such that in an uncleaved state, the NB interferes with binding of the AB to the target and in a cleaved state, the NB does not interfere with binding of the AB to the target; and (iv) the NB does not inhibit cleavage of the CL by the enzyme. For

example, the CL has a length of up to 15 amino acids, a length of up to 20 amino acids, a length of up to 25 amino acids, a length of up to 30 amino acids, a length of up to 35 amino acids, a length of up to 40 amino acids, a length of up to 45 amino acids, a length of up to 50 amino acids, a length in the range of 10-50 amino acids, a length in the range of 15-50 amino acids, a length in the range of 20-50 amino acids, a length in the range of 30-50 amino acids, a length in the range of 35-50 amino acids, a length in the range of 40-50 amino acids, a length in the range of 45-50 amino acids, a length in the range of 10-40 amino acids, a length in the range of 15-40 amino acids, a length in the range of 20-40 amino acids, a length in the range of 25-40 amino acids, a length in the range of 30-40 amino acids, a length in the range of 35-40 amino acids, a length in the range of 10-30 amino acids, a length in the range of 15-30 amino acids, a length in the range of 20-30 amino acids, a length in the range of 25-30 amino acids, a length in the range of 10-20 amino acids, or a length in the range of 10-15 amino acids.

[0412] In one embodiment, the activatable antibody includes a non-binding steric moiety (NB); a cleavable linker (CL); and an antibody or antibody fragment (AB) that binds specifically to the target, wherein (i) the NB includes a polypeptide that does not bind specifically to the AB; (ii) the CL is a polypeptide that includes a substrate (S) for an enzyme; (iii) the CL is positioned such that in an uncleaved state, the NB interferes with binding of the AB to the target and in a cleaved state, the NB does not interfere with binding of the AB to the target; (iv) the NB does not inhibit cleavage of the CL by the enzyme; and (v) the activatable antibody has the structural arrangement from N-terminus to C-terminus as follows in the uncleaved state: NB-CL-AB or AB-CL-NB.

[0413] In one embodiment, the activatable antibody includes a non-binding steric moiety (NB); a cleavable linker (CL); and an antibody or antibody fragment (AB) that binds specifically to the target, wherein (i) the NB includes a polypeptide that does not bind specifically to the AB; (ii) the CL is a polypeptide that includes a substrate (S) for an enzyme; (iii) the CL is positioned such that in an uncleaved state, the NB interferes with binding of the AB to the target and in a cleaved state, the NB does not interfere with binding of the AB to the target, and wherein the NB in the uncleaved activatable antibody reduces the ability of the AB to bind the target by at least 50%, for example, by at least 60%, by at least 70%, by at least 75%, by at least 80%, by at least 85%, by at least 90%, by at least 95%, by at least 96%, by at least 97%, by at least 98%, by at least 99%, by at least 100% as compared to the ability of the cleaved AB to bind the target; and (iv) the NB does not inhibit cleavage of the CL by the enzyme. The reduction in the ability of the AB to bind the target is determined, e.g., using an assay as described herein or an in vitro target displacement assay such as, for example, the assay described in PCT Publication Nos. WO 2009/025846 and WO 2010/081173.

[0414] In one embodiment, the activatable antibody includes a binding partner (BP) for a non-binding steric moiety (NB); a cleavable linker (CL); and an antibody or antibody fragment (AB) that binds specifically to the target, wherein the BP is a polypeptide that binds to the NB when exposed thereto; the NB does not bind specifically to the AB; the CL is a polypeptide that includes a substrate (S) for an enzyme; the CL is positioned such that in an uncleaved state in the presence of the NB, the NB interferes with binding of the AB to

the target and in a cleaved state, the NB does not interfere with binding of the AB to the target and the BP does not interfere with binding of the AB to the target; and the NB and the BP do not inhibit cleavage of the CL by the enzyme. In some examples of this embodiment, the BP of the activatable antibody is optionally bound to the NB. In one embodiment, the NB is recruited by the BP of the activatable antibody *in vivo*.

[0415] In some examples of any of these activatable antibody embodiments, the activatable antibody is formulated as a composition. In some of these embodiments, the composition also includes the NB, where the NB is co-formulated with the activatable antibody that includes the BP, the CL, and the AB. In some examples of this embodiment, the BP is selected from the group consisting of an albumin binding peptide, a fibrinogen binding peptide, a fibronectin binding peptide, a hemoglobin binding peptide, a transferrin binding peptide, an immunoglobulin domain binding peptide, and other serum protein binding peptides.

[0416] In some examples of any of these activatable antibody embodiments, the NB is a soluble, globular protein. In some examples of any of these activatable antibody embodiments, the NB is a protein that circulates in the bloodstream. In some examples of any of these activatable antibody embodiments, the NB is selected from the group consisting of albumin, fibrinogen, fibronectin, hemoglobin, transferrin, an immunoglobulin domain, and other serum proteins.

[0417] In some examples of any of these activatable antibody embodiments, the CL is a polypeptide that includes a substrate (S) for a protease. In some examples of any of these activatable antibody embodiments, the protease is co-localized with the in a tissue, and the protease cleaves the CL in the activatable antibody when the activatable antibody is exposed to the protease. In some examples of any of these activatable antibody embodiments, the CL is a polypeptide of up to 50 amino acids in length. In some examples of any of these activatable antibody embodiments, the CL is a polypeptide that includes a substrate (S) having a length of up to 15 amino acids, e.g., 3 amino acids long, 4 amino acids long, 5 amino acids long, 6 amino acids long, 7 amino acids long, 8 amino acids long, 9 amino acids long, 10 amino acids long, 11 amino acids long, 12 amino acids long, 13 amino acids long, 14 amino acids long, or 15 amino acids long.

[0418] In some examples of any of these activatable antibody embodiments, the activatable antibody has the structural arrangement from N-terminus to C-terminus as follows in the uncleaved state: NB-CL-AB, AB-CL-NB, BP-CL-AB or AB-CL-BP. In embodiments where the activatable antibody includes a BP and the activatable antibody is in the presence of the corresponding NB, the activatable antibody has a structural arrangement from N-terminus to C-terminus as follows in the uncleaved state: NB:BP-CM-AB or AB-CM-BP:NB, where “:” represents an interaction, e.g., binding, between the NB and BP.

[0419] In some examples of any of these activatable antibody embodiments, the activatable antibody includes an antibody or antigen-binding fragment thereof that specifically binds a given target and is a monoclonal antibody, domain antibody, single chain, Fab fragment, a $F(ab')_2$ fragment, a scFv, a scab, a dAb, a single domain heavy chain antibody, or a single domain light chain antibody. In some embodiments, such an antibody or immunologically active fragment thereof that binds the target a mouse, other rodent, chimeric, humanized or fully human monoclonal antibody.

[0420] In some examples of any of these activatable antibody embodiments, the activatable antibody includes a combination of a variable heavy chain region comprising an amino acid sequence presented herein and a variable light chain region comprising an amino acid sequence presented herein. In some embodiments, the activatable antibody includes a combination of a variable heavy chain region comprising an amino acid sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to an amino acid sequence presented herein, and a variable light chain region comprising an amino acid sequence that is at least 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or more identical to an amino acid sequence presented herein.

[0421] In some examples of any of these activatable antibody embodiments, the activatable antibody also includes an agent conjugated to the AB. In some embodiments, the agent is a therapeutic agent. In some embodiments, the agent is an antineoplastic agent. In some embodiments, the agent is a toxin or fragment thereof. In some embodiments, the agent is conjugated to the AB via a linker. In some embodiments, the linker is a cleavable linker. In some embodiments, the agent is conjugated to the AB via a noncleavable linker. In some embodiments, the agent is an agent selected from the group listed in Table 3. In some embodiments, the agent is a microtubule inhibitor. In some embodiments, the agent is a nucleic acid damaging agent, such as a DNA alkylator or DNA intercalator, or other DNA damaging agent. In some embodiments, the agent is a dolastatin. In some embodiments, the agent is an auristatin or derivative thereof. In some embodiments, the agent is auristatin E or a derivative thereof. In some embodiments, the agent is monomethyl auristatin E (MMAE). In some embodiments, the agent is monomethyl auristatin D (MMAD). In some embodiments, the agent is a maytansinoid or maytansinoid derivative. In some embodiments, the agent is DM1 or DM4. In some embodiments, the agent is a duocarmycin or derivative thereof. In some embodiments, the agent is a calicheamicin or derivative thereof. In some embodiments, the agent is a pyrrolobenzodiazepine.

[0422] In some examples of any of these activatable antibody embodiments, the activatable antibody also includes a detectable moiety. In some embodiments, the detectable moiety is a diagnostic agent.

[0423] In some examples of any of these activatable antibody embodiments, the activatable antibody also includes a spacer. In some examples of any of these activatable antibody embodiments, the activatable antibody also includes a signal peptide. In some embodiments, the signal peptide is conjugated to the activatable antibody via a spacer. In some examples of any of these activatable antibody embodiments, the spacer is joined directly to the MM of the activatable antibody.

[0424] In some embodiments, the serum half-life of the activatable antibody is longer than that of the corresponding antibody; e.g., the pK of the activatable antibody is longer than that of the corresponding antibody. In some embodiments, the serum half-life of the activatable antibody is similar to that of the corresponding antibody. In some embodiments, the serum half-life of the activatable antibody is at least 15 days when administered to an organism. In some embodiments, the serum half-life of the activatable antibody is at least 12 days when administered to an organism. In some embodiments, the serum half-life of the activatable antibody is at least 11 days when administered to an organism. In some

embodiments, the serum half-life of the activatable antibody is at least 10 days when administered to an organism. In some embodiments, the serum half-life of the activatable antibody is at least 9 days when administered to an organism. In some embodiments, the serum half-life of the activatable antibody is at least 8 days when administered to an organism. In some embodiments, the serum half-life of the activatable antibody is at least 7 days when administered to an organism. In some embodiments, the serum half-life of the activatable antibody is at least 6 days when administered to an organism. In some examples of any of these activatable antibody embodiments, the serum half-life of the activatable antibody is at least 5 days when administered to an organism. In some embodiments, the serum half-life of the activatable antibody is at least 4 days when administered to an organism. In some embodiments, the serum half-life of the activatable antibody is at least 3 days when administered to an organism. In some embodiments, the serum half-life of the activatable antibody is at least 2 days when administered to an organism. In some embodiments, the serum half-life of the activatable antibody is at least 24 hours when administered to an organism. In some embodiments, the serum half-life of the activatable antibody is at least 20 hours when administered to an organism. In some embodiments, the serum half-life of the activatable antibody is at least 18 hours when administered to an organism. In some embodiments, the serum half-life of the activatable antibody is at least 16 hours when administered to an organism. In some embodiments, the serum half-life of the activatable antibody is at least 14 hours when administered to an organism. In some embodiments, the serum half-life of the activatable antibody is at least 12 hours when administered to an organism. In some embodiments, the serum half-life of the activatable antibody is at least 10 hours when administered to an organism. In some embodiments, the serum half-life of the activatable antibody is at least 8 hours when administered to an organism. In some embodiments, the serum half-life of the activatable antibody is at least 6 hours when administered to an organism. In some embodiments, the serum half-life of the activatable antibody is at least 4 hours when administered to an organism. In some embodiments, the serum half-life of the activatable antibody is at least 3 hours when administered to an organism.

[0425] The disclosure also provides an isolated nucleic acid molecule encoding any of these activatable antibodies, as well as vectors that include these isolated nucleic acid sequences. The disclosure provides methods of producing an activatable antibody by culturing a cell under conditions that lead to expression of the activatable antibody, wherein the cell comprises such a nucleic acid sequence. In some embodiments, the cell comprises such a vector.

[0426] The dissociation constant (K_d) of the NB-containing activatable antibody toward the target is greater than the K_d of the AB towards the target when it is not associated with the NB or NB:BP. The dissociation constant (K_d) of the NB-containing activatable antibody toward the target is greater than the K_d of the parental AB towards the target. For example, the K_d of the NB-containing activatable antibody toward the target is at least 5, 10, 25, 50, 100, 250, 500, 1,000, 2,500, 5,000, 10,000, 50,000, 100,000, 500,000, 1,000,000, 5,000,000, 10,000,000, 50,000,000 or greater, or between 5-10, 10-100, 10-1,000, 10-10,000, 10-100,000, 10-1,000, 000, 10-10,000,000, 100-1,000, 100-10,000, 100-100,000, 100-1,000,000, 100-10,000,000, 1,000-10,000, 1,000-100,000, 1,000-1,000,000, 1000-10,000,000, 10,000-100,000, 10,000-1,000,000, 10,000-10,000, 000, 100,000-1,000,000, or 100,000-10,000,000 times lower than the binding affinity of the AB when it is not associated with the NB or NB:BP or lower than the binding affinity of the parental AB towards the target.

10,000-1,000,000, 10,000-10,000,000, 100,000-1,000,000, or 100,000-10,000,000 times greater than the K_d of the AB when it is not associated with the NB or NB:BP or the K_d of the parental AB towards the target. Conversely, the binding affinity of the NB-containing activatable antibody towards the target is lower than the binding affinity of the AB when it is not associated with the NB or NB:BP or lower than the binding affinity of the parental AB towards the target. For example, the binding affinity of the NB-containing activatable antibody toward the target is at least 5, 10, 25, 50, 100, 250, 500, 1,000, 2,500, 5,000, 10,000, 50,000, 100,000, 500, 000, 1,000,000, 5,000,000, 10,000,000, 50,000,000 or greater, or between 5-10, 10-100, 10-1,000, 10-10,000, 10-100,000, 10-1,000,000, 10-10,000,000, 100-1,000, 100-10,000, 100-100,000, 100-1,000,000, 100-10,000,000, 1,000-10,000, 1,000-100,000, 1,000-1,000,000, 1000-10,000, 10,000-100,000, 10,000-1,000,000, 10,000-10,000, 000, 100,000-1,000,000, or 100,000-10,000,000 times lower than the binding affinity of the AB when it is not associated with the NB or NB:BP or lower than the binding affinity of the parental AB towards the target.

[0427] When the NB-containing activatable antibody is in the presence of the target, specific binding of the AB to the target is reduced or inhibited, as compared to the specific binding of the AB when it is not associated with the NB or NB:BP. When the NB-containing activatable antibody is in the presence of the target, specific binding of the AB to the target is reduced or inhibited, as compared to the specific binding of the parental AB to the target. When compared to the binding of the AB not associated with an NB or NB:BP or the binding of the parental AB to the target, the ability of the NB-containing activatable antibody to bind the target is reduced, for example, by at least 50%, 60%, 70%, 80%, 90%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or even 100% for at least 2, 4, 6, 8, 12, 28, 24, 30, 36, 48, 60, 72, 84, or 96 hours, or 5, 10, 15, 30, 45, 60, 90, 120, 150, or 180 days, or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months or longer when measured in vitro and/or in vivo.

[0428] When the NB-containing activatable antibody is in the presence of the target but not in the presence of a modifying agent (for example a protease or other enzyme), specific binding of the AB to the target is reduced or inhibited, as compared to the specific binding of the AB when it is not associated with the NB or NB:BP. When the NB-containing activatable antibody is in the presence of the target but not in the presence of a modifying agent (for example a protease, other enzyme, reduction agent, or light), specific binding of the AB to the target is reduced or inhibited, as compared to the specific binding of the parental AB to the target. When compared to the binding of the AB not associated with an NB or NB:BP or the binding of the parental AB to the target, the ability of the NB-containing activatable antibody to bind the target is reduced, for example, by at least 50%, 60%, 70%, 80%, 90%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, or even 100% for at least 2, 4, 6, 8, 12, 28, 24, 30, 36, 48, 60, 72, 84, or 96 hours, or 5, 10, 15, 30, 45, 60, 90, 120, 150, or 180 days, or 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 months or longer when measured in vitro and/or in vivo.

[0429] In some examples of any of these activatable antibody embodiments, the activatable antibody includes an agent conjugated to the AB to produce an activatable antibody conjugate. In some embodiments of the activatable antibody conjugate, the agent is a therapeutic agent. In some embodiments, the agent is a diagnostic agent. In some embodiments,

the agent is a detectable marker. In some embodiments of the activatable antibody conjugate, the agent is an antineoplastic agent. In some embodiments of the activatable antibody conjugate, the agent is a toxin or fragment thereof. In some embodiments of the activatable antibody conjugate, the agent is conjugated to the AB via a linker. In some embodiments of the activatable antibody conjugate, the linker is a cleavable linker. In some embodiments, the agent is conjugated to the AB via a noncleavable linker. In some embodiments, the agent is a microtubule inhibitor. In some embodiments, the agent is a nucleic acid damaging agent, such as a DNA alkylator or DNA intercalator, or other DNA damaging agent. In some embodiments, the agent is an agent selected from the group listed in Table 3. In some embodiments, the agent is a dolastatin. In some embodiments, the agent is an auristatin or derivative thereof. In some embodiments, the agent is auristatin E or a derivative thereof. In some embodiments, the agent is monomethyl auristatin E (MMAE). In some embodiments, the agent is monomethyl auristatin D (MMAD). In some embodiments, the agent is a maytansinoid or maytansinoid derivative. In some embodiments, the agent is DM1 or DM4. In some embodiments, the agent is a duocarmycin or derivative thereof. In some embodiments, the agent is a calicheamicin or derivative thereof. In some embodiments, the agent is a pyrrolobenzodiazepine.

[0430] In some examples of any of these activatable antibody embodiments, the activatable antibodies are dual-target binding activatable antibodies. Such dual target binding activatable antibodies contain two Abs that may bind the same or different targets. In specific embodiments, dual-targeting activatable antibodies contain bispecific antibodies or antibody fragments.

[0431] Dual target binding activatable antibodies are designed so as to have a CL cleavable by a cleaving agent that is co-localized in a target tissue with one or both of the targets capable of binding to the ABs of the activatable antibodies. Dual target binding activatable antibodies with more than one AB to the same or different targets can be designed so as to have more than one CL, wherein the first CL is cleavable by a cleaving agent in a first target tissue and wherein the second CL is cleavable by a cleaving agent in a second target tissue, with one or more of the targets binding to the ABs of the activatable antibodies. In one embodiment, the first and second target tissues are spatially separated, for example, at different sites in the organism. In one embodiment, the first and second target tissues are the same tissue temporally separated, for example the same tissue at two different points in time, for example the first time point is when the tissue is an early stage tumor, and the second time point is when the tissue is a late stage tumor.

[0432] The disclosure also provides nucleic acid molecules encoding the activatable antibodies described herein. The disclosure also provides vectors that include these nucleic acids. The activatable antibodies described herein are produced by culturing a cell under conditions that lead to expression of the activatable antibody, wherein the cell includes these nucleic acid molecules or vectors.

[0433] The disclosure also provides methods of manufacturing activatable antibodies. In one embodiment, the method includes the steps of (a) culturing a cell that includes a nucleic acid construct that encodes the activatable antibody under conditions that lead to expression of the activatable antibody, wherein the activatable antibody includes (i) a non-binding steric moiety (NB); (ii) a cleavable linker (CL); and (iii) an

antibody or an antigen binding fragment thereof (AB) that specifically binds a target, wherein (1) the NB does not bind specifically to the AB; (2) the CL is a polypeptide that includes a substrate (S) for an enzyme; (3) the CL is positioned such that in an uncleaved state, the NB interferes with binding of the AB to the target and in a cleaved state, the NB does not interfere with binding of the AB to the target; and (4) the NB does not inhibit cleavage of the CL by the enzyme; and (b) recovering the activatable antibody.

[0434] In some embodiments, the method includes the steps of (a) culturing a cell that includes a nucleic acid construct that encodes the activatable antibody under conditions that lead to expression of the activatable antibody, wherein the activatable antibody includes (i) a binding partner (BP) for a non-binding steric moiety (NB); (ii) a cleavable linker (CL); and (iii) an antibody or an antigen binding fragment thereof (AB) that specifically binds a target, wherein (1) the NB does not bind specifically to the AB; (2) the CL is a polypeptide that includes a substrate (S) for an enzyme; (3) the CL is positioned such that in an uncleaved state in the presence of the NB, the NB interferes with binding of the AB to the target and in a cleaved state, the NB does not interfere with binding of the AB to the target and the BP does not interfere with binding of the AB to the target; and (4) the NB and the BP do not inhibit cleavage of the CL by the enzyme; and (b) recovering the activatable antibody. In some examples of this embodiment, the BP of the activatable antibody is bound to the NB.

[0435] Use of Activatable Antibodies and Conjugated Activatable Antibodies

[0436] It will be appreciated that administration of therapeutic entities in accordance with the disclosure will be administered with suitable carriers, excipients, and other agents that are incorporated into formulations to provide improved transfer, delivery, tolerance, and the like. A multitude of appropriate formulations can be found in the formulary known to all pharmaceutical chemists: Remington's Pharmaceutical Sciences (15th ed, Mack Publishing Company, Easton, Pa. (1975)), particularly Chapter 87 by Blaug, Seymour, therein. These formulations include, for example, powders, pastes, ointments, jellies, waxes, oils, lipids, lipid (cationic or anionic) containing vesicles (such as LipofectinTM), DNA conjugates, anhydrous absorption pastes, oil-in-water and water-in-oil emulsions, emulsions carbowax (polyethylene glycols of various molecular weights), semi-solid gels, and semi-solid mixtures containing carbowax. Any of the foregoing mixtures may be appropriate in treatments and therapies in accordance with the present disclosure, provided that the active ingredient in the formulation is not inactivated by the formulation and the formulation is physiologically compatible and tolerable with the route of administration. See also Baldrick P. "Pharmaceutical excipient development: the need for preclinical guidance." *Regul. Toxicol Pharmacol.* 32(2):210-8 (2000), Wang W. "Lyophilization and development of solid protein pharmaceuticals." *Int. J. Pharm.* 203(1-2):1-60 (2000), Charman W N "Lipids, lipophilic drugs, and oral drug delivery-some emerging concepts." *J Pharm Sci.* 89(8):967-78 (2000), Powell et al. "Compendium of excipients for parenteral formulations" *PDA J Pharm Sci Technol.* 52:238-311 (1998) and the citations therein for additional information related to formulations, excipients and carriers well known to pharmaceutical chemists.

[0437] Therapeutic formulations of the disclosure, which include a conjugated antibody, an activatable antibody and/or

a conjugated activatable antibody, are used to prevent, treat or otherwise ameliorate a disease or disorder associated with aberrant target expression and/or activity. For example, therapeutic formulations of the disclosure, which include a conjugated antibody, an activatable antibody and/or a conjugated activatable antibody, are used to treat or otherwise ameliorate inflammation, an inflammatory disorder, an autoimmune disease and/or a cancer or other neoplastic condition. In some embodiments, the cancer is a solid tumor or a hematologic malignancy where the target is expressed. In some embodiments, the cancer is a solid tumor where the target is expressed. In some embodiments, the cancer is a hematologic malignancy where the target is expressed. In some embodiments, the target is expressed on parenchyma (e.g., in cancer, the portion of an organ or tissue that often carries out function (s) of the organ or tissue). In some embodiments, the target is expressed on a cell, tissue, or organ. In some embodiments, the target is expressed on stroma (i.e., the connective supportive framework of a cell, tissue, or organ). In some embodiments, the target is expressed on an osteoblast. In some embodiments, the target is expressed on the endothelium (vasculature). In some embodiments, the target is expressed on a cancer stem cell. In some embodiments, the agent to which the activatable antibody is conjugated is a microtubule inhibitor. In some embodiments, the agent to which the activatable antibody is conjugated is a nucleic acid damaging agent.

[0438] Efficaciousness of prevention, amelioration or treatment is determined in association with any known method for diagnosing or treating the disease or disorder associated with target expression and/or activity, such as, for example, aberrant target expression and/or activity. Prolonging the survival of a subject or otherwise delaying the progression of the disease or disorder associated with target expression and/or activity, e.g., aberrant target expression and/or activity, in a subject indicates that the conjugated antibody, activatable antibody and/or conjugated activatable antibody confers a clinical benefit.

[0439] A conjugated antibody, an activatable antibody and/or a conjugated activatable antibody can be administered in the form of pharmaceutical compositions. Principles and considerations involved in preparing such compositions, as well as guidance in the choice of components are provided, for example, in Remington: The Science And Practice Of Pharmacy 19th ed. (Alfonso R. Gennaro, et al., editors) Mack Pub. Co., Easton, Pa.: 1995; Drug Absorption Enhancement: Concepts, Possibilities, Limitations, And Trends, Harwood Academic Publishers, Langhorne, Pa., 1994; and Peptide And Protein Drug Delivery (Advances In Parenteral Sciences, Vol. 4), 1991, M. Dekker, New York.

[0440] In some embodiments where antibody fragments are used, the smallest fragment that specifically binds to the binding domain of the target protein is selected. For example, based upon the variable-region sequences of an antibody, peptide molecules can be designed that retain the ability to bind the target protein sequence. Such peptides can be synthesized chemically and/or produced by recombinant DNA technology. (See, e.g., Marasco et al., Proc. Natl. Acad. Sci. USA, 90: 7889-7893 (1993)). The formulation can also contain more than one active compounds as necessary for the particular indication being treated, for example, in some embodiments, those with complementary activities that do not adversely affect each other. In some embodiments, or in addition, the composition can comprise an agent that

enhances its function, such as, for example, a cytotoxic agent, cytokine, chemotherapeutic agent, or growth-inhibitory agent. Such molecules are suitably present in combination in amounts that are effective for the purpose intended.

[0441] The active ingredients can also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacrylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles, and nanocapsules) or in macroemulsions.

[0442] The formulations to be used for in vivo administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes.

[0443] Sustained-release preparations can be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the form of shaped articles, e.g., films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides (U.S. Pat. No. 3,773,919), copolymers of L-glutamic acid and γ ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOTTM (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid. While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for over 100 days, certain hydrogels release proteins for shorter time periods.

[0444] In some embodiments, the conjugated antibody, activatable antibody and/or conjugated activatable antibody contains a detectable label. An intact antibody, or a fragment thereof (e.g., Fab, scFv, or F(ab)₂) is used. The term "labeled", with regard to the probe or antibody, is intended to encompass direct labeling of the probe or antibody by coupling (i.e., physically linking) a detectable substance to the probe or antibody, as well as indirect labeling of the probe or antibody by reactivity with another reagent that is directly labeled. Examples of indirect labeling include detection of a primary antibody using a fluorescently-labeled secondary antibody and end-labeling of a DNA probe with biotin such that it can be detected with fluorescently-labeled streptavidin. The term "biological sample" is intended to include tissues, cells and biological fluids isolated from a subject, as well as tissues, cells and fluids present within a subject. Included within the usage of the term "biological sample", therefore, is blood and a fraction or component of blood including blood serum, blood plasma, or lymph. That is, the detection method of the disclosure can be used to detect an analyte mRNA, protein, or genomic DNA in a biological sample in vitro as well as in vivo. For example, in vitro techniques for detection of an analyte mRNA include Northern hybridizations and in situ hybridizations. In vitro techniques for detection of an analyte protein include enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations, immunochemical staining, and immunofluorescence. In vitro techniques for detection of an analyte genomic DNA include Southern hybridizations. Procedures for conducting immunoassays are described, for example in "ELISA: Theory and Practice: Methods in Molecular Biology", Vol. 42, J. R. Crowther (Ed.) Human Press, Totowa, N.J., 1995; "Immunoassays: Theory and Practice", Vol. 1, J. R. Crowther (Ed.) 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noassay", E. Diamandis and T. Christopoulos, Academic Press, Inc., San Diego, Calif., 1996; and "Practice and Theory of Enzyme Immunoassays", P. Tijssen, Elsevier Science Publishers, Amsterdam, 1985. Furthermore, in vivo techniques for detection of an analyte protein include introducing into a subject a labeled anti-analyte protein antibody. For example, the antibody can be labeled with a radioactive marker whose presence and location in a subject can be detected by standard imaging techniques.

[0445] The conjugated antibodies, activatable antibodies and/or conjugated activatable antibodies of the disclosure are also useful in a variety of diagnostic and prophylactic formulations. In one embodiment, a conjugated antibody, an activatable antibody and/or a conjugated activatable antibody is administered to patients that are at risk of developing one or more of the aforementioned disorders. A patient's or organ's predisposition to one or more of the aforementioned disorders can be determined using genotypic, serological or biochemical markers.

[0446] In some embodiments, a conjugated antibody, an activatable antibody and/or a conjugated activatable antibody is administered to human individuals diagnosed with a clinical indication associated with one or more of the aforementioned disorders. Upon diagnosis, a conjugated antibody, an activatable antibody and/or a conjugated activatable antibody is administered to mitigate or reverse the effects of the clinical indication.

[0447] A conjugated antibody, an activatable antibody and/or a conjugated activatable antibody of the disclosure is also useful in the detection of a target in patient samples and accordingly are useful as diagnostics. For example, the antibodies and/or activatable antibodies, and conjugated versions thereof, of the disclosure are used in in vitro assays, e.g., ELISA, to detect target levels in a patient sample.

[0448] In one embodiment, a conjugated antibody, an activatable antibody and/or a conjugated activatable antibody of the disclosure is immobilized on a solid support (e.g., the well(s) of a microtiter plate). The immobilized conjugated antibody, activatable antibody and/or conjugated activatable antibody serves as a capture antibody for any target that may be present in a test sample. Prior to contacting the immobilized antibody with a patient sample, the solid support is rinsed and treated with a blocking agent such as milk protein or albumin to prevent nonspecific adsorption of the analyte.

[0449] Subsequently the wells are treated with a test sample suspected of containing the antigen, or with a solution containing a standard amount of the antigen. Such a sample is, e.g., a serum sample from a subject suspected of having levels of circulating antigen considered to be diagnostic of a pathology. After rinsing away the test sample or standard, the solid support is treated with a second antibody that is detectably labeled. The labeled second antibody serves as a detecting antibody. The level of detectable label is measured, and the concentration of target antigen in the test sample is determined by comparison with a standard curve developed from the standard samples.

[0450] It will be appreciated that based on the results obtained using the antibodies of the disclosure, and conjugated versions thereof, in an in vitro diagnostic assay, it is possible to stage a disease in a subject based on expression levels of the target antigen. For a given disease, samples of blood are taken from subjects diagnosed as being at various stages in the progression of the disease, and/or at various points in the therapeutic treatment of the disease. Using a

population of samples that provides statistically significant results for each stage of progression or therapy, a range of concentrations of the antigen that may be considered characteristic of each stage is designated.

[0451] A conjugated antibody, an activatable antibody and/or a conjugated activatable antibody can also be used in diagnostic and/or imaging methods. In some embodiments, such methods are in vitro methods. In some embodiments, such methods are in vivo methods. In some embodiments, such methods are in situ methods. In some embodiments, such methods are ex vivo methods. For example, activatable antibodies having an enzymatically cleavable CM can be used to detect the presence or absence of an enzyme that is capable of cleaving the CM. Such activatable antibodies can be used in diagnostics, which can include in vivo detection (e.g., qualitative or quantitative) of enzyme activity (or, in some embodiments, an environment of increased reduction potential such as that which can provide for reduction of a disulfide bond) through measured accumulation of activated antibodies (i.e., antibodies resulting from cleavage of an activatable antibody) in a given cell or tissue of a given host organism. Such accumulation of activated antibodies indicates not only that the tissue expresses enzymatic activity (or an increased reduction potential depending on the nature of the CM) but also that the tissue expresses target to which the activated antibody binds.

[0452] For example, the CM can be selected to be substrate for a matrix metalloprotease (MMP) found at the site of a tumor, at the site of a viral or bacterial infection at a biologically confined site (e.g., such as in an abscess, in an organ, and the like), and the like. The AB can be one that binds a target antigen. Using methods as disclosed herein, or when appropriate, methods familiar to one skilled in the art, a detectable label (e.g., a fluorescent label or radioactive label or radiotracer) can be conjugated to an AB or other region of an antibody and/or activatable antibody. Suitable detectable labels are discussed in the context of the above screening methods and additional specific examples are provided below. Using an AB specific to a protein or peptide of the disease state, along with an MMP whose activity is elevated in the disease tissue of interest, activatable antibodies will exhibit an increased rate of binding to disease tissue relative to tissues where the CM specific enzyme is not present at a detectable level or is present at a lower level than in disease tissue or is inactive (e.g., in zymogen form or in complex with an inhibitor). Since small proteins and peptides are rapidly cleared from the blood by the renal filtration system, and because the enzyme specific for the CM is not present at a detectable level (or is present at lower levels in non-disease tissues or is present in inactive conformation), accumulation of activated antibodies in the disease tissue is enhanced relative to non-disease tissues.

[0453] In another example, activatable antibodies can be used to detect the presence or absence of a cleaving agent in a sample. For example, where the activatable antibodies contain a CM susceptible to cleavage by an enzyme, the activatable antibodies can be used to detect (either qualitatively or quantitatively) the presence of an enzyme in the sample. In another example, where the activatable antibodies contain a CM susceptible to cleavage by a reducing agent, the activatable antibodies can be used to detect (either qualitatively or quantitatively) the presence of reducing conditions in a sample. To facilitate analysis in these methods, the activatable antibodies can be detectably labeled, and can be bound to a support (e.g.,

a solid support, such as a slide or bead). The detectable label can be positioned on a portion of the activatable antibody that is not released following cleavage, for example, the detectable label can be a quenched fluorescent label or other label that is not detectable until cleavage has occurred. The assay can be conducted by, for example, contacting the immobilized, detectably labeled activatable antibodies with a sample suspected of containing an enzyme and/or reducing agent for a time sufficient for cleavage to occur, then washing to remove excess sample and contaminants. The presence or absence of the cleaving agent (e.g., enzyme or reducing agent) in the sample is then assessed by a change in detectable signal of the activatable antibodies prior to contacting with the sample e.g., the presence of and/or an increase in detectable signal due to cleavage of the activatable antibody by the cleaving agent in the sample.

[0454] Such detection methods can be adapted to also provide for detection of the presence or absence of a target that is capable of binding the AB of the activatable antibodies when cleaved. Thus, the assays can be adapted to assess the presence or absence of a cleaving agent and the presence or absence of a target of interest. The presence or absence of the cleaving agent can be detected by the presence of and/or an increase in detectable label of the activatable antibodies as described above, and the presence or absence of the target can be detected by detection of a target-AB complex e.g., by use of a detectably labeled anti-target antibody.

[0455] Activatable antibodies are also useful in *in situ* imaging for the validation of activatable antibody activation, e.g., by protease cleavage, and binding to a particular target. *In situ* imaging is a technique that enables localization of proteolytic activity and target in biological samples such as cell cultures or tissue sections. Using this technique, it is possible to confirm both binding to a given target and proteolytic activity based on the presence of a detectable label (e.g., a fluorescent label).

[0456] These techniques are useful with any frozen cells or tissue derived from a disease site (e.g. tumor tissue) or healthy tissues. These techniques are also useful with fresh cell or tissue samples.

[0457] In these techniques, an activatable antibody is labeled with a detectable label. The detectable label may be a fluorescent dye, (e.g. a fluorophore, Fluorescein Isothiocyanate (FITC), Rhodamine Isothiocyanate (TRITC), an Alexa Fluor® label), a near infrared (NIR) dye (e.g., Qdot® nanocrystals), a colloidal metal, a hapten, a radioactive marker, biotin and an amplification reagent such as streptavidin, or an enzyme (e.g. horseradish peroxidase or alkaline phosphatase).

[0458] Detection of the label in a sample that has been incubated with the labeled, activatable antibody indicates that the sample contains the target and contains a matrix metallo-protease (MMP) that is specific for the CM of the activatable antibody. In some embodiments, the presence of the MMP can be confirmed using broad spectrum protease inhibitors such as those described herein, and/or by using an agent that is specific for the protease, for example, an antibody such as A11, which is specific for the protease matriptase (MT-SP1) and inhibits the proteolytic activity of matriptase; see e.g., International Publication Number WO 2010/129609, published 11 Nov. 2010. The same approach of using broad spectrum protease inhibitors such as those described herein, and/or by using a more selective inhibitory agent can be used to identify a MMP specific for the CM of the activatable

antibody. In some embodiments, the presence of the target can be confirmed using an agent that is specific for the target, e.g., another antibody, or the detectable label can be competed with unlabeled target. In some embodiments, unlabeled activatable antibody could be used, with detection by a labeled secondary antibody or more complex detection system.

[0459] Similar techniques are also useful for *in vivo* imaging where detection of the fluorescent signal in a subject, e.g., a mammal, including a human, indicates that the disease site contains the target and contains a MMP that is specific for the CM of the activatable antibody.

[0460] These techniques are also useful in kits and/or as reagents for the detection, identification or characterization of protease activity in a variety of cells, tissues, and organisms based on the protease-specific CM in the activatable antibody.

[0461] The disclosure provides methods of using the antibodies and/or activatable antibodies in a variety of diagnostic and/or prophylactic indications. For example, the disclosure provides methods of detecting presence or absence of a cleaving agent and a target of interest in a subject or a sample by (i) contacting a subject or sample with an activatable antibody, wherein the activatable antibody comprises a masking moiety (MM), a cleavable moiety (CM) that is cleaved by the cleaving agent, and an antigen binding domain or fragment thereof (AB) that specifically binds the target of interest, wherein the activatable antibody in an uncleaved, non-activated state comprises a structural arrangement from N-terminus to C-terminus as follows: MM-CM-AB or AB-CM-MM; (a) wherein the MM is a peptide that inhibits binding of the AB to the target, and wherein the MM does not have an amino acid sequence of a naturally occurring binding partner of the AB and is not a modified form of a natural binding partner of the AB; and (b) wherein, in an uncleaved, non-activated state, the MM interferes with specific binding of the AB to the target, and in a cleaved, activated state the MM does not interfere or compete with specific binding of the AB to the target; and (ii) measuring a level of activated activatable antibody in the subject or sample, wherein a detectable level of activated activatable antibody in the subject or sample indicates that the cleaving agent and the target are present in the subject or sample and wherein no detectable level of activated activatable antibody in the subject or sample indicates that the cleaving agent, the target or both the cleaving agent and the target are absent and/or not sufficiently present in the subject or sample. In some embodiments, the activatable antibody is an activatable antibody to which a therapeutic agent is conjugated. In some embodiments, the activatable antibody is not conjugated to an agent. In some embodiments, the activatable antibody comprises a detectable label. In some embodiments, the detectable label is positioned on the AB. In some embodiments, measuring the level of activatable antibody in the subject or sample is accomplished using a secondary reagent that specifically binds to the activated antibody, wherein the reagent comprises a detectable label. In some embodiments, the secondary reagent is an antibody comprising a detectable label.

[0462] The disclosure also provides methods of detecting presence or absence of a cleaving agent in a subject or a sample by (i) contacting a subject or sample with an activatable antibody in the presence of a target of interest, e.g., the target, wherein the activatable antibody comprises a masking moiety (MM), a cleavable moiety (CM) that is cleaved by the cleaving agent, and an antigen binding domain or fragment thereof (AB) that specifically binds the target of interest,

wherein the activatable antibody in an uncleaved, non-activated state comprises a structural arrangement from N-terminus to C-terminus as follows: MM-CM-AB or AB-CM-MM; (a) wherein the MM is a peptide that inhibits binding of the AB to the target, and wherein the MM does not have an amino acid sequence of a naturally occurring binding partner of the AB and is not a modified form of a natural binding partner of the AB; and (b) wherein, in an uncleaved, non-activated state, the MM interferes with specific binding of the AB to the target, and in a cleaved, activated state the MM does not interfere or compete with specific binding of the AB to the target; and (ii) measuring a level of activated activatable antibody in the subject or sample, wherein a detectable level of activated activatable antibody in the subject or sample indicates that the cleaving agent is present in the subject or sample and wherein no detectable level of activated activatable antibody in the subject or sample indicates that the cleaving agent is absent and/or not sufficiently present in the subject or sample. In some embodiments, the activatable antibody is an activatable antibody to which a therapeutic agent is conjugated. In some embodiments, the activatable antibody is not conjugated to an agent. In some embodiments, the activatable antibody comprises a detectable label. In some embodiments, the detectable label is positioned on the AB. In some embodiments, measuring the level of activatable antibody in the subject or sample is accomplished using a secondary reagent that specifically binds to the activated antibody, wherein the reagent comprises a detectable label. In some embodiments, the secondary reagent is an antibody comprising a detectable label.

[0463] The disclosure also provides kits for use in methods of detecting presence or absence of a cleaving agent and the target in a subject or a sample, where the kits include at least an activatable antibody comprises a masking moiety (MM), a cleavable moiety (CM) that is cleaved by the cleaving agent, and an antigen binding domain or fragment thereof (AB) that specifically binds the target of interest, wherein the activatable antibody in an uncleaved, non-activated state comprises a structural arrangement from N-terminus to C-terminus as follows: MM-CM-AB or AB-CM-MM; (a) wherein the MM is a peptide that inhibits binding of the AB to the target, and wherein the MM does not have an amino acid sequence of a naturally occurring binding partner of the AB and is not a modified form of a natural binding partner of the AB; and (b) wherein, in an uncleaved, non-activated state, the MM interferes with specific binding of the AB to the target, and in a cleaved, activated state the MM does not interfere or compete with specific binding of the AB to the target; and (ii) measuring a level of activated activatable antibody in the subject or sample, wherein a detectable level of activated activatable antibody in the subject or sample indicates that the cleaving agent is present in the subject or sample and wherein no detectable level of activated activatable antibody in the subject or sample indicates that the cleaving agent is absent and/or not sufficiently present in the subject or sample. In some embodiments, the activatable antibody is an activatable antibody to which a therapeutic agent is conjugated. In some embodiments, the activatable antibody is not conjugated to an agent. In some embodiments, the activatable antibody comprises a detectable label. In some embodiments, the detectable label is positioned on the AB. In some embodiments, measuring the level of activatable antibody in the subject or sample is accomplished using a secondary reagent that specifically binds to the activated antibody, wherein the reagent

comprises a detectable label. In some embodiments, the secondary reagent is an antibody comprising a detectable label.

[0464] The disclosure also provides methods of detecting presence or absence of a cleaving agent in a subject or a sample by (i) contacting a subject or sample with an activatable antibody, wherein the activatable antibody comprises a masking moiety (MM), a cleavable moiety (CM) that is cleaved by the cleaving agent, an antigen binding domain (AB) that specifically binds the target, and a detectable label, wherein the activatable antibody in an uncleaved, non-activated state comprises a structural arrangement from N-terminus to C-terminus as follows: MM-CM-AB or AB-CM-MM; wherein the MM is a peptide that inhibits binding of the AB to the target, and wherein the MM does not have an amino acid sequence of a naturally occurring binding partner of the AB and is not a modified form of a natural binding partner of the AB; wherein, in an uncleaved, non-activated state, the MM interferes with specific binding of the AB to the target, and in a cleaved, activated state the MM does not interfere or compete with specific binding of the AB to the target; and wherein the detectable label is positioned on a portion of the activatable antibody that is released following cleavage of the CM; and (ii) measuring a level of detectable label in the subject or sample, wherein a detectable level of the detectable label in the subject or sample indicates that the cleaving agent is absent and/or not sufficiently present in the subject or sample and wherein no detectable level of the detectable label in the subject or sample indicates that the cleaving agent is present in the subject or sample. In some embodiments, the activatable antibody is an activatable antibody to which a therapeutic agent is conjugated. In some embodiments, the activatable antibody is not conjugated to an agent. In some embodiments, the activatable antibody comprises a detectable label. In some embodiments, the detectable label is positioned on the AB. In some embodiments, measuring the level of activatable antibody in the subject or sample is accomplished using a secondary reagent that specifically binds to the activated antibody, wherein the reagent comprises a detectable label. In some embodiments, the secondary reagent is an antibody comprising a detectable label.

[0465] The disclosure also provides kits for use in methods of detecting presence or absence of a cleaving agent and the target in a subject or a sample, where the kits include at least an activatable antibody and/or conjugated activatable antibody (e.g., an activatable antibody to which a therapeutic agent is conjugated) described herein for use in contacting a subject or biological sample and means for detecting the level of activated activatable antibody and/or conjugated activatable antibody in the subject or biological sample, wherein a detectable level of activated activatable antibody in the subject or biological sample indicates that the cleaving agent and the target are present in the subject or biological sample and wherein no detectable level of activated activatable antibody in the subject or biological sample indicates that the cleaving agent and the target or both the cleaving agent and the target are absent and/or not sufficiently present in the subject or biological sample, such that the target binding and/or protease cleavage of the activatable antibody cannot be detected in the subject or biological sample.

[0466] The disclosure also provides methods of detecting presence or absence of a cleaving agent in a subject or a sample by (i) contacting a subject or biological sample with an activatable antibody in the presence of the target, and (ii) measuring a level of activated activatable antibody in the

subject or biological sample, wherein a detectable level of activated activatable antibody in the subject or biological sample indicates that the cleaving agent is present in the subject or biological sample and wherein no detectable level of activated activatable antibody in the subject or biological sample indicates that the cleaving agent is absent and/or not sufficiently present in the subject or biological sample at a detectable level, such that protease cleavage of the activatable antibody cannot be detected in the subject or biological sample. Such an activatable antibody includes a masking moiety (MM), a cleavable moiety (CM) that is cleaved by the cleaving agent, and an antigen binding domain or fragment thereof (AB) that specifically binds the target, wherein the activatable antibody in an uncleaved (i.e., non-activated) state comprises a structural arrangement from N-terminus to C-terminus as follows: MM-CM-AB or AB-CM-MM; (a) wherein the MM is a peptide that inhibits binding of the AB to the target, and wherein the MM does not have an amino acid sequence of a naturally occurring binding partner of the AB; and (b) wherein the MM of the activatable antibody in an uncleaved state interferes with specific binding of the AB to the target, and wherein the MM of an activatable antibody in a cleaved (i.e., activated) state does not interfere or compete with specific binding of the AB to the target. In some embodiments, the activatable antibody is an activatable antibody to which a therapeutic agent is conjugated. In some embodiments, the activatable antibody is not conjugated to an agent. In some embodiments, the detectable label is attached to the masking moiety. In some embodiments, the detectable label is attached to the cleavable moiety N-terminal to the protease cleavage site. In some embodiments, a single antigen binding site of the AB is masked. In some embodiments wherein an antibody of the disclosure has at least two antigen binding sites, at least one antigen binding site is masked and at least one antigen binding site is not masked. In some embodiments, all antigen binding sites are masked. In some embodiments, the measuring step includes use of a secondary reagent comprising a detectable label.

[0467] The disclosure also provides kits for use in methods of detecting presence or absence of a cleaving agent and the target in a subject or a sample, where the kits include at least an activatable antibody and/or conjugated activatable antibody described herein for use in contacting a subject or biological sample with an activatable antibody in the presence of the target, and measuring a level of activated activatable antibody in the subject or biological sample, wherein a detectable level of activated activatable antibody in the subject or biological sample indicates that the cleaving agent is present in the subject or biological sample and wherein no detectable level of activated activatable antibody in the subject or biological sample indicates that the cleaving agent is absent and/or not sufficiently present in the subject or biological sample at a detectable level, such that protease cleavage of the activatable antibody cannot be detected in the subject or biological sample. Such an activatable antibody includes a masking moiety (MM), a cleavable moiety (CM) that is cleaved by the cleaving agent, and an antigen binding domain or fragment thereof (AB) that specifically binds the target, wherein the activatable antibody in an uncleaved (i.e., non-activated) state comprises a structural arrangement from N-terminus to C-terminus as follows: MM-CM-AB or AB-CM-MM; (a) wherein the MM is a peptide that inhibits binding of the AB to the target, and wherein the MM does not have an amino acid sequence of a naturally occurring binding partner of the AB;

and (b) wherein the MM of the activatable antibody in an uncleaved state interferes with specific binding of the AB to the target, and wherein the MM of an activatable antibody in a cleaved (i.e., activated) state does not interfere or compete with specific binding of the AB to the target. In some embodiments, the activatable antibody is an activatable antibody to which a therapeutic agent is conjugated. In some embodiments, the activatable antibody is not conjugated to an agent. In some embodiments, the detectable label is attached to the masking moiety. In some embodiments, the detectable label is attached to the cleavable moiety N-terminal to the protease cleavage site. In some embodiments, a single antigen binding site of the AB is masked. In some embodiments wherein an antibody of the disclosure has at least two antigen binding sites, at least one antigen binding site is masked and at least one antigen binding site is not masked. In some embodiments, all antigen binding sites are masked. In some embodiments, the measuring step includes use of a secondary reagent comprising a detectable label.

[0468] The disclosure also provides kits for use in methods of detecting presence or absence of a cleaving agent in a subject or a sample, where the kits include at least an activatable antibody and/or conjugated activatable antibody described herein for use in contacting a subject or biological sample and means for detecting the level of activated activatable antibody and/or conjugated activatable antibody in the subject or biological sample, wherein the activatable antibody includes a detectable label that is positioned on a portion of the activatable antibody that is released following cleavage of the CM, wherein a detectable level of activated activatable antibody in the subject or biological sample indicates that the cleaving agent is absent and/or not sufficiently present in the subject or biological sample such that the target binding and/or protease cleavage of the activatable antibody cannot be detected in the subject or biological sample, and wherein no detectable level of activated activatable antibody in the subject or biological sample indicates that the cleaving agent is present in the subject or biological sample at a detectable level.

[0469] The disclosure provides methods of detecting presence or absence of a cleaving agent and the target in a subject or a sample by (i) contacting a subject or biological sample with an activatable antibody, wherein the activatable antibody includes a detectable label that is positioned on a portion of the activatable antibody that is released following cleavage of the CM and (ii) measuring a level of activated activatable antibody in the subject or biological sample, wherein a detectable level of activated activatable antibody in the subject or biological sample indicates that the cleaving agent, the target or both the cleaving agent and the target are absent and/or not sufficiently present in the subject or biological sample, such that the target binding and/or protease cleavage of the activatable antibody cannot be detected in the subject or biological sample, and wherein a reduced detectable level of activated activatable antibody in the subject or biological sample indicates that the cleaving agent and the target are present in the subject or biological sample. A reduced level of detectable label is, for example, a reduction of about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95% and/or about 100%. Such an activatable antibody includes a masking moiety (MM), a cleavable moiety (CM) that is cleaved by the cleaving agent, and an

antigen binding domain or fragment thereof (AB) that specifically binds the target, wherein the activatable antibody in an uncleaved (i.e., non-activated) state comprises a structural arrangement from N-terminus to C-terminus as follows: MM-CM-AB or AB-CM-MM; (a) wherein the MM is a peptide that inhibits binding of the AB to the target, and wherein the MM does not have an amino acid sequence of a naturally occurring binding partner of the AB; and (b) wherein the MM of the activatable antibody in an uncleaved state interferes with specific binding of the AB to the target, and wherein the MM of an activatable antibody in a cleaved (i.e., activated) state does not interfere or compete with specific binding of the AB to the target. In some embodiments, the activatable antibody is an activatable antibody to which a therapeutic agent is conjugated. In some embodiments, the activatable antibody is not conjugated to an agent. In some embodiments, the activatable antibody comprises a detectable label. In some embodiments, the detectable label is positioned on the AB. In some embodiments, measuring the level of activatable antibody in the subject or sample is accomplished using a secondary reagent that specifically binds to the activated antibody, wherein the reagent comprises a detectable label. In some embodiments, the secondary reagent is an antibody comprising a detectable label.

[0470] The disclosure also provides kits for use in methods of detecting presence or absence of a cleaving agent and the target in a subject or a sample, where the kits include at least an activatable antibody and/or conjugated activatable antibody described herein for use in contacting a subject or biological sample and means for detecting the level of activated activatable antibody and/or conjugated activatable antibody in the subject or biological sample, wherein a detectable level of activated activatable antibody in the subject or biological sample indicates that the cleaving agent, the target or both the cleaving agent and the target are absent and/or not sufficiently present in the subject or biological sample, such that the target binding and/or protease cleavage of the activatable antibody cannot be detected in the subject or biological sample, and wherein a reduced detectable level of activated activatable antibody in the subject or biological sample indicates that the cleaving agent and the target are present in the subject or biological sample. A reduced level of detectable label is, for example, a reduction of about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95% and/or about 100%.

[0471] The disclosure also provides methods of detecting presence or absence of a cleaving agent in a subject or a sample by (i) contacting a subject or biological sample with an activatable antibody, wherein the activatable antibody includes a detectable label that is positioned on a portion of the activatable antibody that is released following cleavage of the CM; and (ii) measuring a level of detectable label in the subject or biological sample, wherein a detectable level of the detectable label in the subject or biological sample indicates that the cleaving agent is absent and/or not sufficiently present in the subject or biological sample at a detectable level, such that protease cleavage of the activatable antibody cannot be detected in the subject or biological sample, and wherein a reduced detectable level of the detectable label in the subject or biological sample indicates that the cleaving agent is present in the subject or biological sample. A reduced level of detectable label is, for example, a reduction of about

5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95% and/or about 100%. Such an activatable antibody includes a masking moiety (MM), a cleavable moiety (CM) that is cleaved by the cleaving agent, and an antigen binding domain or fragment thereof (AB) that specifically binds the target, wherein the activatable antibody in an uncleaved (i.e., non-activated) state comprises a structural arrangement from N-terminus to C-terminus as follows: MM-CM-AB or AB-CM-MM; (a) wherein the MM is a peptide that inhibits binding of the AB to the target, and wherein the MM does not have an amino acid sequence of a naturally occurring binding partner of the AB; and (b) wherein the MM of the activatable antibody in an uncleaved state interferes with specific binding of the AB to the target, and wherein the MM of an activatable antibody in a cleaved (i.e., activated) state does not interfere or compete with specific binding of the AB to the target. In some embodiments, the activatable antibody is an activatable antibody to which a therapeutic agent is conjugated. In some embodiments, the activatable antibody is not conjugated to an agent. In some embodiments, the activatable antibody comprises a detectable label. In some embodiments, the detectable label is positioned on the AB. In some embodiments, measuring the level of activatable antibody in the subject or sample is accomplished using a secondary reagent that specifically binds to the activated antibody, wherein the reagent comprises a detectable label. In some embodiments, the secondary reagent is an antibody comprising a detectable label.

[0472] The disclosure also provides kits for use in methods of detecting presence or absence of a cleaving agent of interest in a subject or a sample, where the kits include at least an activatable antibody and/or conjugated activatable antibody described herein for use in contacting a subject or biological sample and means for detecting the level of activated activatable antibody and/or conjugated activatable antibody in the subject or biological sample, wherein the activatable antibody includes a detectable label that is positioned on a portion of the activatable antibody that is released following cleavage of the CM, wherein a detectable level of the detectable label in the subject or biological sample indicates that the cleaving agent, the target, or both the cleaving agent and the target are absent and/or not sufficiently present in the subject or biological sample, such that the target binding and/or protease cleavage of the activatable antibody cannot be detected in the subject or biological sample, and wherein a reduced detectable level of the detectable label in the subject or biological sample indicates that the cleaving agent and the target are present in the subject or biological sample. A reduced level of detectable label is, for example, a reduction of about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95% and/or about 100%.

[0473] In some embodiments of these methods and kits, the activatable antibody includes a detectable label. In some embodiments of these methods and kits, the detectable label includes an imaging agent, a contrasting agent, an enzyme, a fluorescent label, a chromophore, a dye, one or more metal ions, or a ligand-based label. In some embodiments of these methods and kits, the imaging agent comprises a radioisotope. In some embodiments of these methods and kits, the radioisotope is indium or technetium. In some embodiments

of these methods and kits, the contrasting agent comprises iodine, gadolinium or iron oxide. In some embodiments of these methods and kits, the enzyme comprises horseradish peroxidase, alkaline phosphatase, or β -galactosidase. In some embodiments of these methods and kits, the fluorescent label comprises yellow fluorescent protein (YFP), cyan fluorescent protein (CFP), green fluorescent protein (GFP), modified red fluorescent protein (mRFP), red fluorescent protein tdimer2 (RFP tdimer2), HCRED, or a europium derivative. In some embodiments of these methods and kits, the luminescent label comprises an N-methylacrydium derivative. In some embodiments of these methods, the label comprises an Alexa Fluor® label, such as Alex Fluor® 680 or Alexa Fluor® 750. In some embodiments of these methods and kits, the ligand-based label comprises biotin, avidin, streptavidin or one or more haptens.

[0474] In some embodiments of these methods and kits, the subject is a mammal. In some embodiments of these methods and kits, the subject is a human. In some embodiments, the subject is a non-human mammal, such as a non-human primate, companion animal (e.g., cat, dog, horse), farm animal, work animal, or zoo animal. In some embodiments, the subject is a rodent.

[0475] In some embodiments of these methods, the method is an in vivo method. In some embodiments of these methods, the method is an in situ method. In some embodiments of these methods, the method is an ex vivo method. In some embodiments of these methods, the method is an in vitro method.

[0476] In some embodiments, in situ imaging and/or in vivo imaging are useful in methods to identify which patients to treat. For example, in in situ imaging, the activatable antibodies are used to screen patient samples to identify those patients having the appropriate protease(s) and target(s) at the appropriate location, e.g., at a tumor site.

[0477] In some embodiments, in situ imaging is used to identify or otherwise refine a patient population suitable for treatment with an activatable antibody of the disclosure. For example, patients that test positive for both the target (e.g., the target) and a protease that cleaves the substrate in the cleavable moiety (CM) of the activatable antibody being tested (e.g., accumulate activated antibodies at the disease site) are identified as suitable candidates for treatment with such an activatable antibody comprising such a CM. Likewise, patients that test negative for either or both of the target (e.g., the target) and the protease that cleaves the substrate in the CM in the activatable antibody being tested using these methods might be identified as suitable candidates for another form of therapy. In some embodiments, such patients that test negative with respect to a first activatable antibody can be tested with other activatable antibodies comprising different CMs until a suitable activatable antibody for treatment is identified (e.g., an activatable antibody comprising a CM that is cleaved by the patient at the site of disease). In some embodiments, the patient is then administered a therapeutically effective amount of the conjugated activatable antibody for which the patient tested positive.

[0478] In some embodiments, in vivo imaging is used to identify or otherwise refine a patient population suitable for treatment with an activatable antibody of the disclosure. For example, patients that test positive for both the target (e.g., the target) and a protease that cleaves the substrate in the cleavable moiety (CM) of the activatable antibody being tested (e.g., accumulate activated antibodies at the disease site) are

identified as suitable candidates for treatment with such an activatable antibody comprising such a CM. Likewise, patients that test negative might be identified as suitable candidates for another form of therapy. In some embodiments, such patients that test negative with respect to a first activatable antibody can be tested with other activatable antibodies comprising different CMs until a suitable activatable antibody for treatment is identified (e.g., an activatable antibody comprising a CM that is cleaved by the patient at the site of disease). In some embodiments, the patient is then administered a therapeutically effective amount of the conjugated activatable antibody for which the patient tested positive.

[0479] In some embodiments of the methods and kits, the method or kit is used to identify or otherwise refine a patient population suitable for treatment with an activatable antibody of the disclosure. For example, patients that test positive for both the target (e.g., the target) and a protease that cleaves the substrate in the cleavable moiety (CM) of the activatable antibody being tested in these methods are identified as suitable candidates for treatment with such an activatable antibody comprising such a CM. Likewise, patients that test negative for both of the targets (e.g., the target) and the protease that cleaves the substrate in the CM in the activatable antibody being tested using these methods might be identified as suitable candidates for another form of therapy. In some embodiments, such patients can be tested with other activatable antibodies until a suitable activatable antibody for treatment is identified (e.g., an activatable antibody comprising a CM that is cleaved by the patient at the site of disease). In some embodiments, patients that test negative for either of the target (e.g., the target) are identified as suitable candidates for treatment with such an activatable antibody comprising such a CM. In some embodiments, patients that test negative for either of the target (e.g., the target) are identified as not being suitable candidates for treatment with such an activatable antibody comprising such a CM. In some embodiments, such patients can be tested with other activatable antibodies until a suitable activatable antibody for treatment is identified (e.g., an activatable antibody comprising a CM that is cleaved by the patient at the site of disease). In some embodiments, the activatable antibody is an activatable antibody to which a therapeutic agent is conjugated. In some embodiments, the activatable antibody is not conjugated to an agent. In some embodiments, the activatable antibody comprises a detectable label. In some embodiments, the detectable label is positioned on the AB. In some embodiments, measuring the level of activatable antibody in the subject or sample is accomplished using a secondary reagent that specifically binds to the activated antibody, wherein the reagent comprises a detectable label. In some embodiments, the secondary reagent is an antibody comprising a detectable label.

[0480] In some embodiments, a method or kit is used to identify or otherwise refine a patient population suitable for treatment with an anti-the target activatable antibody and/or conjugated activatable antibody (e.g., activatable antibody to which a therapeutic agent is conjugated) of the disclosure, followed by treatment by administering that activatable antibody and/or conjugated activatable antibody to a subject in need thereof. For example, patients that test positive for both the targets (e.g., the target) and a protease that cleaves the substrate in the cleavable moiety (CM) of the activatable antibody and/or conjugated activatable antibody being tested in these methods are identified as suitable candidates for treatment with such antibody and/or such a conjugated acti-

vatable antibody comprising such a CM, and the patient is then administered a therapeutically effective amount of the activatable antibody and/or conjugated activatable antibody that was tested. Likewise, patients that test negative for either or both of the target (e.g., the target) and the protease that cleaves the substrate in the CM in the activatable antibody being tested using these methods might be identified as suitable candidates for another form of therapy. In some embodiments, such patients can be tested with other antibody and/or conjugated activatable antibody until a suitable antibody and/or conjugated activatable antibody for treatment is identified (e.g., an activatable antibody and/or conjugated activatable antibody comprising a CM that is cleaved by the patient at the site of disease). In some embodiments, the patient is then administered a therapeutically effective amount of the activatable antibody and/or conjugated for which the patient tested positive.

[0481] In some embodiments of these methods and kits, the MM is a peptide having a length from about 4 to 40 amino acids. In some embodiments of these methods and kits, the activatable antibody comprises a linker peptide, wherein the linker peptide is positioned between the MM and the CM. In some embodiments of these methods and kits, the activatable antibody comprises a linker peptide, where the linker peptide is positioned between the AB and the CM. In some embodiments of these methods and kits, the activatable antibody comprises a first linker peptide (L1) and a second linker peptide (L2), wherein the first linker peptide is positioned between the MM and the CM and the second linker peptide is positioned between the AB and the CM. In some embodiments of these methods and kits, each of L1 and L2 is a peptide of about 1 to 20 amino acids in length, and wherein each of L1 and L2 need not be the same linker. In some embodiments of these methods and kits, one or both of L1 and L2 comprises a glycine-serine polymer. In some embodiments of these methods and kits, at least one of L1 and L2 comprises an amino acid sequence selected from the group consisting of (GS)_n, (GSGGS)_n (SEQ ID NO: 1) and (GGGS)_n (SEQ ID NO: 2), where n is an integer of at least one. In some embodiments of these methods and kits, at least one of L1 and L2 comprises an amino acid sequence having the formula (GGS)_n, where n is an integer of at least one. In some embodiments of these methods and kits, at least one of L1 and L2 comprises an amino acid sequence selected from the group consisting of Gly-Gly-Ser-Gly (SEQ ID NO: 3), Gly-Gly-Ser-Gly-Gly (SEQ ID NO: 4), Gly-Ser-Gly-Ser-Gly (SEQ ID NO: 5), Gly-Ser-Gly-Gly-Gly (SEQ ID NO: 6), Gly-Gly-Gly-Ser-Gly (SEQ ID NO: 7), and Gly-Ser-Ser-Ser-Gly (SEQ ID NO: 8).

[0482] In some embodiments of these methods and kits, the AB comprises an antibody or antibody fragment sequence selected from the cross-reactive antibody sequences presented herein. In some embodiments of these methods and kits, the AB comprises a Fab fragment, a scFv or a single chain antibody (scAb).

[0483] In some embodiments of these methods and kits, the cleaving agent is a protease that is co-localized in the subject or sample with the target and the CM is a polypeptide that functions as a substrate for the protease, wherein the protease cleaves the CM in the activatable antibody when the activatable antibody is exposed to the protease. In some embodiments of these methods and kits, the CM is a polypeptide of up to 15 amino acids in length. In some embodiments of these methods and kits, the CM is coupled to the N-terminus of the

AB. In some embodiments of these methods and kits, the CM is coupled to the C-terminus of the AB. In some embodiments of these methods and kits, the CM is coupled to the N-terminus of a VL chain of the AB.

[0484] The activatable antibodies and/or conjugated activatable antibodies of the disclosure are used in diagnostic and prophylactic formulations. In one embodiment, an activatable antibody is administered to patients that are at risk of developing one or more of the aforementioned inflammation, inflammatory disorders, cancer or other disorders.

[0485] A patient's or organ's predisposition to one or more of the aforementioned disorders can be determined using genotypic, serological or biochemical markers.

[0486] In some embodiments, an activatable antibody and/or conjugated activatable antibodies is administered to human individuals diagnosed with a clinical indication associated with one or more of the aforementioned disorders. Upon diagnosis, an activatable antibody and/or conjugated activatable antibodies is administered to mitigate or reverse the effects of the clinical indication.

[0487] Activatable antibodies and/or conjugated activatable antibodies of the disclosure are also useful in the detection of the target in patient samples and accordingly are useful as diagnostics. For example, the activatable antibodies and/or conjugated activatable antibodies of the disclosure are used in in vitro assays, e.g., ELISA, to detect target levels in a patient sample.

[0488] In one embodiment, an activatable antibody of the disclosure is immobilized on a solid support (e.g., the well(s) of a microtiter plate). The immobilized activatable antibody serves as a capture antibody for any target that may be present in a test sample. Prior to contacting the immobilized antibody with a patient sample, the solid support is rinsed and treated with a blocking agent such as milk protein or albumin to prevent nonspecific adsorption of the analyte.

[0489] Subsequently the wells are treated with a test sample suspected of containing the antigen, or with a solution containing a standard amount of the antigen. Such a sample is, e.g., a serum sample from a subject suspected of having levels of circulating antigen considered to be diagnostic of a pathology. After rinsing away the test sample or standard, the solid support is treated with a second antibody that is detectably labeled. The labeled second antibody serves as a detecting antibody. The level of detectable label is measured, and the concentration of target antigen in the test sample is determined by comparison with a standard curve developed from the standard samples.

[0490] It will be appreciated that based on the results obtained using the antibodies of the disclosure in an in vitro diagnostic assay, it is possible to stage a disease in a subject based on expression levels of the Target antigen. For a given disease, samples of blood are taken from subjects diagnosed as being at various stages in the progression of the disease, and/or at various points in the therapeutic treatment of the disease. Using a population of samples that provides statistically significant results for each stage of progression or therapy, a range of concentrations of the antigen that may be considered characteristic of each stage is designated.

[0491] Activatable antibodies and/or conjugated activatable antibodies can also be used in diagnostic and/or imaging methods. In some embodiments, such methods are in vitro methods. In some embodiments, such methods are in vivo methods. In some embodiments, such methods are in situ methods. In some embodiments, such methods are ex vivo

methods. For example, activatable antibodies having an enzymatically cleavable CM can be used to detect the presence or absence of an enzyme that is capable of cleaving the CM. Such activatable antibodies can be used in diagnostics, which can include in vivo detection (e.g., qualitative or quantitative) of enzyme activity (or, in some embodiments, an environment of increased reduction potential such as that which can provide for reduction of a disulfide bond) through measured accumulation of activated antibodies (i.e., antibodies resulting from cleavage of an activatable antibody) in a given cell or tissue of a given host organism. Such accumulation of activated antibodies indicates not only that the tissue expresses enzymatic activity (or an increased reduction potential depending on the nature of the CM) but also that the tissue expresses target to which the activated antibody binds.

[0492] For example, the CM can be selected to be a protease substrate for a protease found at the site of a tumor, at the site of a viral or bacterial infection at a biologically confined site (e.g., such as in an abscess, in an organ, and the like), and the like. The AB can be one that binds a target antigen. Using methods familiar to one skilled in the art, a detectable label (e.g., a fluorescent label or radioactive label or radiotracer) can be conjugated to an AB or other region of an activatable antibody. Suitable detectable labels are discussed in the context of the above screening methods and additional specific examples are provided below. Using an AB specific to a protein or peptide of the disease state, along with a protease whose activity is elevated in the disease tissue of interest, activatable antibodies will exhibit an increased rate of binding to disease tissue relative to tissues where the CM specific enzyme is not present at a detectable level or is present at a lower level than in disease tissue or is inactive (e.g., in zymogen form or in complex with an inhibitor). Since small proteins and peptides are rapidly cleared from the blood by the renal filtration system, and because the enzyme specific for the CM is not present at a detectable level (or is present at lower levels in non-disease tissues or is present in inactive conformation), accumulation of activated antibodies in the disease tissue is enhanced relative to non-disease tissues.

[0493] In another example, activatable antibodies can be used to detect the presence or absence of a cleaving agent in a sample. For example, where the activatable antibodies contain a CM susceptible to cleavage by an enzyme, the activatable antibodies can be used to detect (either qualitatively or quantitatively) the presence of an enzyme in the sample. In another example, where the activatable antibodies contain a CM susceptible to cleavage by reducing agent, the activatable antibodies can be used to detect (either qualitatively or quantitatively) the presence of reducing conditions in a sample. To facilitate analysis in these methods, the activatable antibodies can be detectably labeled, and can be bound to a support (e.g., a solid support, such as a slide or bead). The detectable label can be positioned on a portion of the activatable antibody that is not released following cleavage, for example, the detectable label can be a quenched fluorescent label or other label that is not detectable until cleavage has occurred. The assay can be conducted by, for example, contacting the immobilized, detectably labeled activatable antibodies with a sample suspected of containing an enzyme and/or reducing agent for a time sufficient for cleavage to occur, then washing to remove excess sample and contaminants. The presence or absence of the cleaving agent (e.g., enzyme or reducing agent) in the sample is then assessed by a change in detectable signal of the activatable antibodies prior to contacting with

the sample e.g., the presence of and/or an increase in detectable signal due to cleavage of the activatable antibody by the cleaving agent in the sample.

[0494] Such detection methods can be adapted to also provide for detection of the presence or absence of a target that is capable of binding the AB of the activatable antibodies when cleaved. Thus, the assays can be adapted to assess the presence or absence of a cleaving agent and the presence or absence of a target of interest. The presence or absence of the cleaving agent can be detected by the presence of and/or an increase in detectable label of the activatable antibodies as described above, and the presence or absence of the target can be detected by detection of a target-AB complex e.g., by use of a detectably labeled anti-target antibody.

[0495] Activatable antibodies are also useful in in situ imaging for the validation of activatable antibody activation, e.g., by protease cleavage, and binding to a particular target. In situ imaging is a technique that enables localization of proteolytic activity and target in biological samples such as cell cultures or tissue sections. Using this technique, it is possible to confirm both binding to a given target and proteolytic activity based on the presence of a detectable label (e.g., a fluorescent label).

[0496] These techniques are useful with any frozen cells or tissue derived from a disease site (e.g. tumor tissue) or healthy tissues. These techniques are also useful with fresh cell or tissue samples.

[0497] In these techniques, an activatable antibody is labeled with a detectable label. The detectable label may be a fluorescent dye, (e.g. Fluorescein Isothiocyanate (FITC), Rhodamine Isothiocyanate (TRITC), a near infrared (NIR) dye (e.g., Qdot® nanocrystals), a colloidal metal, a hapten, a radioactive marker, biotin and an amplification reagent such as streptavidin, or an enzyme (e.g. horseradish peroxidase or alkaline phosphatase).

[0498] Detection of the label in a sample that has been incubated with the labeled, activatable antibody indicates that the sample contains the target and contains a protease that is specific for the CM of the activatable antibody. In some embodiments, the presence of the protease can be confirmed using broad spectrum protease inhibitors such as those described herein, and/or by using an agent that is specific for the protease, for example, an antibody such as A11, which is specific for the protease matrix metalloproteinase (MT-SP1) and inhibits the proteolytic activity of matrix metalloproteinase; see e.g., International Publication Number WO 2010/129609, published 11 Nov. 2010. The same approach of using broad spectrum protease inhibitors such as those described herein, and/or by using a more selective inhibitory agent can be used to identify a protease or class of proteases specific for the CM of the activatable antibody. In some embodiments, the presence of the target can be confirmed using an agent that is specific for the target, e.g., another antibody, or the detectable label can be competed with unlabeled target. In some embodiments, unlabeled activatable antibody could be used, with detection by a labeled secondary antibody or more complex detection system.

[0499] Similar techniques are also useful for in vivo imaging where detection of the fluorescent signal in a subject, e.g., a mammal, including a human, indicates that the disease site contains the target and contains a protease that is specific for the CM of the activatable antibody.

[0500] These techniques are also useful in kits and/or as reagents for the detection, identification or characterization

of protease activity in a variety of cells, tissues, and organisms based on the protease-specific CM in the activatable antibody.

[0501] In some embodiments, in situ imaging and/or in vivo imaging are useful in methods to identify which patients to treat. For example, in in situ imaging, the activatable antibodies are used to screen patient samples to identify those patients having the appropriate protease(s) and target(s) at the appropriate location, e.g., at a tumor site.

[0502] In some embodiments, in situ imaging is used to identify or otherwise refine a patient population suitable for treatment with an activatable antibody of the disclosure. For example, patients that test positive for both the target and a protease that cleaves the substrate in the cleavable moiety (CM) of the activatable antibody being tested (e.g., accumulate activated antibodies at the disease site) are identified as suitable candidates for treatment with such an activatable antibody comprising such a CM. Likewise, patients that test negative for either or both of the target and the protease that cleaves the substrate in the CM in the activatable antibody being tested using these methods are identified as suitable candidates for another form of therapy (i.e., not suitable for treatment with the activatable antibody being tested). In some embodiments, such patients that test negative with respect to a first activatable antibody can be tested with other activatable antibodies comprising different CMs until a suitable activatable antibody for treatment is identified (e.g., an activatable antibody comprising a CM that is cleaved by the patient at the site of disease).

[0503] In some embodiments, in vivo imaging is used to identify or otherwise refine a patient population suitable for treatment with an activatable antibody of the disclosure. For example, patients that test positive for both the target and a protease that cleaves the substrate in the cleavable moiety (CM) of the activatable antibody being tested (e.g., accumulate activated antibodies at the disease site) are identified as suitable candidates for treatment with such an activatable antibody comprising such a CM. Likewise, patients that test negative are identified as suitable candidates for another form of therapy (i.e., not suitable for treatment with the activatable antibody being tested). In some embodiments, such patients that test negative with respect to a first activatable antibody can be tested with other activatable antibodies comprising different CMs until a suitable activatable antibody for treatment is identified (e.g., an activatable antibody comprising a CM that is cleaved by the patient at the site of disease).

[0504] Pharmaceutical Compositions

[0505] The conjugated antibodies, activatable antibodies and/or conjugated activatable antibodies of the disclosure (also referred to herein as "active compounds"), and derivatives, fragments, analogs and homologs thereof, can be incorporated into pharmaceutical compositions suitable for administration. Such compositions typically comprise the conjugated antibody, activatable antibody and/or conjugated activatable antibody and a pharmaceutically acceptable carrier. As used herein, the term "pharmaceutically acceptable carrier" is intended to include any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents, and the like, compatible with pharmaceutical administration. Suitable carriers are described in the most recent edition of Remington's Pharmaceutical Sciences, a standard reference text in the field, which is incorporated herein by reference. Suitable examples of such carriers or diluents include, but are not limited to, water, saline, ringer's solutions, dextrose solution, and 5% human

serum albumin. Liposomes and non-aqueous vehicles such as fixed oils may also be used. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active compound, use thereof in the compositions is contemplated. Supplementary active compounds can also be incorporated into the compositions.

[0506] A pharmaceutical composition of the disclosure is formulated to be compatible with its intended route of administration. Examples of routes of administration include parenteral, e.g., intravenous, intradermal, subcutaneous, oral (e.g., inhalation), transdermal (i.e., topical), transmucosal, and rectal administration. Solutions or suspensions used for parenteral, intradermal, or subcutaneous application can include the following components: a sterile diluent such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such as benzyl alcohol or methyl parabens; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid (EDTA); buffers such as acetates, citrates or phosphates, and agents for the adjustment of tonicity such as sodium chloride or dextrose. The pH can be adjusted with acids or bases, such as hydrochloric acid or sodium hydroxide. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

[0507] Pharmaceutical compositions suitable for injectable use include sterile aqueous solutions (where water soluble) or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersion. For intravenous administration, suitable carriers include physiological saline, bacteriostatic water, Cremophor EL™ (BASF, Parsippany, N.J.) or phosphate buffered saline (PBS). In all cases, the composition must be sterile and should be fluid to the extent that easy syringeability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol, and the like), and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. Prevention of the action of microorganisms can be achieved by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, ascorbic acid, thimerosal, and the like. In some embodiments, it will be desirable to include isotonic agents, for example, sugars, polyalcohols such as manitol, sorbitol, sodium chloride in the composition. Prolonged absorption of the injectable compositions can be brought about by including in the composition an agent that delays absorption, for example, aluminum monostearate and gelatin.

[0508] Sterile injectable solutions can be prepared by incorporating the active compound in the required amount in an appropriate solvent with one or a combination of ingredients enumerated above, as required, followed by filtered sterilization. Generally, dispersions are prepared by incorporating the active compound into a sterile vehicle that contains a basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, methods of preparation are vacuum drying and freeze-drying that yields a

powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof. [0509] Oral compositions generally include an inert diluent or an edible carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules. Oral compositions can also be prepared using a fluid carrier for use as a mouthwash, wherein the compound in the fluid carrier is applied orally and swished and expectorated or swallowed. Pharmaceutically compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate or Sterotes; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring. [0510] For administration by inhalation, the compounds are delivered in the form of an aerosol spray from pressured container or dispenser that contains a suitable propellant, e.g., a gas such as carbon dioxide, or a nebulizer.

[0511] Systemic administration can also be by transmucosal or transdermal means. For transmucosal or transdermal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art, and include, for example, for transmucosal administration, detergents, bile salts, and fusidic acid derivatives. Transmucosal administration can be accomplished through the use of nasal sprays or suppositories. For transdermal administration, the active compounds are formulated into ointments, salves, gels, or creams as generally known in the art.

[0512] The compounds can also be prepared in the form of suppositories (e.g., with conventional suppository bases such as cocoa butter and other glycerides) or retention enemas for rectal delivery.

[0513] In one embodiment, the active compounds are prepared with carriers that will protect the compound against rapid elimination from the body, such as a controlled release formulation, including implants and microencapsulated delivery systems. Biodegradable, biocompatible polymers can be used, such as ethylene vinyl acetate, polyhydrides,

polyglycolic acid, collagen, polyorthoesters, and polylactic acid. Methods for preparation of such formulations will be apparent to those skilled in the art. The materials can also be obtained commercially from Alza Corporation and Nova Pharmaceuticals, Inc. Liposomal suspensions (including liposomes targeted to infected cells with monoclonal antibodies to viral antigens) can also be used as pharmaceutically acceptable carriers. These can be prepared according to methods known to those skilled in the art, for example, as described in U.S. Pat. No. 4,522,811.

[0514] It is especially advantageous to formulate oral or parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the subject to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the dosage unit forms of the disclosure are dictated by and directly dependent on the unique characteristics of the active compound and the particular therapeutic effect to be achieved, and the limitations inherent in the art of compounding such an active compound for the treatment of individuals.

[0515] The pharmaceutical compositions can be included in a container, pack, or dispenser together with instructions for administration.

[0516] The invention will be further described in the following examples, which do not limit the scope of the invention described in the claims.

EXAMPLES

Example 1

Ability of Synovial Fluid to Activate Quenched Probes Comprising Substrates of the Disclosure

[0517] This Example demonstrates the ability of synovial fluid samples to cleave MMP substrate sequences of the disclosure. In particular, the MMP cleavable sequences were tested in the context of an activatable antibody construct comprising a masking moiety linked to an anti-IL-6R antibody sequence via a linker region that includes the MMP cleavable sequence being evaluated.

[0518] The following MMP-cleavable activatable antibodies were incubated with synovial fluid:

4792¹⁰⁴¹⁹AV1 amino acid

(SEQ ID NO: 115)

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QGQSGQYGSCSWNYVHI FMDCGSSGGSGGGSISSGLSSGGSDIQMTQSPSSLASAVGDRVT
ITCRASQDISSYLNWYQOKPGKAPKLLIYYTSRLHSGVPSRFSGSGSGTDFPTISSLQPEDIA
TYYCQQGNTLPYTFGQGKTVIEKRTVAAPSVFIPPPSDEQLKSGTASVVCCLNNFYPREAKVQW
KVDNALQSGNSQESVTEQDSKDSTYSLSTLTLKADYEKHKVYACEVTHQGLSPVTKSFNRG
EC
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4792¹⁰⁴¹⁹AV1 nucleotide

(SEQ ID NO: 116)

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Caaggccagtcggccagttgggtctgcagttggaaactatgtacacatattcatggatgcgg
gttcgagcggtggcagcggtggctctgtggctcaggattatgtggcttagcgtggcg
ttctgacatcagatgactcgtctcgtccctgtccctctgtggggaccgagtcc
atcacatgcagacggccaggatattttactgttacactgtggatcagcagaagccggaa
aagcacatcagatgttactatcacccaggatcactgtggcgtcccaggatcggttcag
tggctcaggggcggaaaccttcatttaccatctcaagcgtcggccaggatatgtcc
acatactattgtcagcaggccaaactactgccttacactttggccaggggaccaaggatggaa
tcaaaactgtacggctgtgcacccatctgtctatcttccgcctatgtggatcagttgaaatc
tggaaactgcctgtgtgtgcgtgtgaaataacttctatcccaggagggccaaagtacagtgg
aaggatggataacgcctccaatcggttaactccaggagatgtcacaaggcaggcaggcaagg
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-continued

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acagcaccc tacagcctcagcagcaccctgacgctgagcaaaagcagactacgaaaaacacaaaat  
ctacgctcgcaaggtcacccatcagggccctgagctcgcccgatcacaagagcttcaacaggggaa  
gagtgt
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4792⁵⁵⁹AV1 amino acid

(SEQ ID NO: 117)

QGQSGQYGSQCSWNYVHFMDCGSSGGSGGSSQNOALRMAAGGSDIQMTQSPSSLASAVGDRV
ITCRASODISSYLNWYQQKPGKAPKLLIYTTSRLHSGVPSRFSGSGSGTDFFTTISSLQPEDIA
TYCQQGNTLPYTFGQGTKEVIKRTVAAPSVFIFPPSDEQLKSGTASVVCLNNFYPREAKVQW
KVDNALQSGNSQESVTEQDSKDSTYSLSSLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG
EC

4792⁵⁵⁹AV1 nucleotide

(SEQ ID NO: 118)

4792⁶⁰¹ AV1 amino acid

(SEQ. ID. NO.: 119)

SEQ ID NO: 11
QQGSQGYGSQCSWNYVHI FMDCGSSGGSGGGSAQNLLGMVGSSD1QMTOQSPLSSASVGRDVT
ITCRASQD1ISYLNWYQQKPGKAPKLL1IYTSLHSGVPSPRFSGSGSGTDFFTISSLQPEDIA
TXYCQGQNTLPYTFGQGQTKEV1KRTVAAPSPV1FPPSDEQLKSGTASVCLNNNFYPREAKVQW
KVDNALQGSNSQESVTEQDSDKSTDYSTSLSSTLTSKADYEKHKVYACEVTHQGLSSPVTKSFNRC
EC

4792⁶⁰¹AV1 nucleotide

(SFC ID NO. 120)

(SEQ ID NO: 12
Caaggccagtctggccagtatgggtctgcagttggaaactatgtacacatcatggattgcg
gctcgaggggtggcagcggtggctctgggtctcagcacagaatctgttaggtatggtaggggg
ttctgacatccagatgactcagtctcctagtcctctgtcgctctgtgggggaccgagtcacc
atcacatgcagccagccaggatattctgttactctgaaactgttacgcagcagaagcccgaa
aagccactaaatgtgtatctactataccctcagggtgcacttgcgtggccactgtgggg
tggctcaggggagcggaaaccgacttcacttttacatctcaaggctgcaggccagaggatattggc
actactatgttacgggcaataactgcctacacttggccaggggaccacagggtggaaa
tcaaagctacgggtggctgaccatctgtttcatcttcccgccatctgtatggcagttggaaa
tggactgcctgttgtgtgcctgtgaataactctatcccaagagggccaaagtacagtgg
aaagggtggataacccctccaaatcggttaactccaggagatgtcacagagcaggacagcaagg
acacgacactacagccctcagcagcaccctgacgctgaccaagcagactacagaaaacacaaaatg
ctacgcctgcgaagtccccatcaggccctgagctcgccctgcacaaagagcttacacaggggaa
gatgtt

4792³⁴⁵⁷AV1 amino acid

(SEO ID NO.: 131)

(SEQ ID: 12)
QGQSQGYGCSWNYVHFMDCGSSGGSGGSSTFPGMFGGSDIQMTQSPLSSASVGRDTI
ITCRASQDIISSYLNWYQQKPGKAPKLLIYTTSRLHSGVPSPRFSGSGSGTDFFTISSLQPEDIA
TYYCCQQGNTLPYTFGQGTKEVIKRTVAAPSVEFPPSDEQLKSGTASVCLNNFYPREAKVQW
KVDNALQSGNSQESVTBQDSKDDSTYLSLTLKADYEHKHVYACEVTHQGLSSPVTKSFNRC
EC

4793³⁴⁵⁷AV1 nucleotide

(SEQ ID NO: 12
Caaggccagtctggccagtatgggtctgcgacttggaaactatgtacacatattcatggattgcg
gctcgagcggtggcagcggtggctctggggctcaagtagtacattccattcggtatgttccggcg
ttctgacatccagatgactcgtctcttagtccctgtccgcctctgtggggccaggatcacc
atcacatgcagagccaggatattctagttactcgaaactgttatcagcagaagcccgaa
aagcacctaagctgtatctactataccctccaggctgcactctggctgcccaggcggttcag
tggtctcaaggagccggaaacggactctactttttaccatctcaagcgactcgccaggatattgc
acatattatgtccatcgaggcataactgcctacttggccaggggaccaaagggtggaaa
tcaaaacgtacggtggtgcaccatctgttccatcttcccccattgtatgcgactgttggaaaatc
tggaaactgcctctgtgtgtgcctgtcaataactctatcccaaggagggccaaaggatcactgtgg
aagggtggataacgcctccaaatcggttaactccaggaggtgcacagagcaggacagcagg
acagcacttacacgcctcagcagcaccctgacgctgagcaaggcagactacgagaaacacaaggat
ctacgcctcgaaagtccccatcaggccgttagctcgccgtcacaaggatcgttcaacaggggaa
qactgt

-continued

4792³⁴⁵⁸AV1 amino acid

(SEQ ID NO: 123)

QGQSGQYGSWNYVHI FMDCGSSGGGGSPVGYTSSLGGSDIQMTQSPSSLASVGDRVT
 ITCRASQDISSYLNWYQQKPGKAPKLLIYYSRHLHSGVPSRFSGSGSGTDFFTISSLQPEDIA
 TYYCQQGNTLPYTFQGQTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVCLNNFYPREAKVQW
 KVDNALQSGNSQESVTEQDSKDSTYSLSSLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG
 EC

4792³⁴⁵⁸AV1 nucleotide

(SEQ ID NO: 124)

Caaggccagtcggccagttggcctgcagttggaaactatgtacacatattcatggatttcg
 gctcgagcggtggcagcggtggctctgggtggctcacatgtggatatacgagtagtctggccgg
 ttctgacatccagatgactcgtctccatgtccctgtccgcctgtgggggaccgagtcacc
 atcacatgcagggccaggatattttagttacctgtggatatacgagtagtctggccgg
 aaggccatctaactgtgtatccatcttccatgtggatatacgagtagtctggccgg
 tggctcaggggccggaaaccgacttcacttttaccatctcaagcgtcagccaggatatttgc
 acatactattgtcagcaggccaaactgtccctacactttggccaggggaccaggatggaaa
 tcaaacgtacgggtggctgcacccatgttccatcttcccccctgtatgagcagttgaaatc
 tggaaactgtccctgtgtgtggctgtgaataacttctatcccaggagggccaaagtacatgg
 aagggtggataacgcgcctccatcggttaactcccaggaggtgtcagagcaggacagg
 acagcacctacagcgtcagcggccatcttccatgtggatatacgagtagtctggccgg
 ctacgcctgcgaaagtccacccatcgaggccctgtggatctggccgtcacaaggatgttcaacagg
 gagtgt

4792³⁴⁶³AV1 amino acid

(SEQ ID NO: 125)

QGQSGQYGSWNYVHI FMDCGSSGGGGSPVGYTSSLGGSDWLWPGIGGSIDIQMTQSPSSLASVGDRVT
 ITCRASQDISSYLNWYQQKPGKAPKLLIYYSRHLHSGVPSRFSGSGSGTDFFTISSLQPEDIA
 TYYCQQGNTLPYTFQGQTKVEIKRTVAAPSVFIFPPSDEQLKSGTASVCLNNFYPREAKVQW
 KVDNALQSGNSQESVTEQDSKDSTYSLSSLTLSKADYEKHKVYACEVTHQGLSSPVTKSFNRG
 EC

4792³⁴⁶³AV1 nucleotide

(SEQ ID NO: 66)

Caaggccagtcggccagttggcctgcagttggaaactatgtacacatattcatggatttcg
 gctcgagcggtggcagcggtggctctgggtggctcacatgtggatatacgagtagtctggccgg
 ttctgacatccagatgactcgtctccatgtccctgtccgcctgtgggggaccgagtcacc
 atcacatgcagggccaggatattttagttacctgtggatatacgagtagtctggccgg
 aaggccatctaactgtgtatccatcttccatgtggatatacgagtagtctggccgg
 tggctcaggggccggaaaccgacttcacttttaccatctcaagcgtcagccaggatatttgc
 acatactattgtcagcaggccaaactgtccctacactttggccaggggaccaggatggaaa
 tcaaacgtacgggtggctgcacccatgttccatcttcccccctgtatgagcagttgaaatc
 tggaaactgtccctgtgtgtggctgtgaataacttctatcccaggagggccaaagtacatgg
 aagggtggataacgcgcctccatcggttaactcccaggaggtgtcagagcaggacagg
 acagcacctacagcgtcagcggccatcttccatgtggatatacgagtagtctggccgg
 ctacgcctgcgaaagtccacccatcgaggccctgtggatctggccgtcacaaggatgttcaacagg
 gagtgt

[0519] The extent of activatable antibody activation was determined by an ELISA format that measured the ability of the activatable antibody, following incubation in synovial fluid, to bind to human IL6R as compared to the binding of anti-IL6R parental antibody to IL6R. Briefly, Nunc Maxisorp plates were coated overnight at 4° C. with 100 µl/well (microliters/well) of a 500-nug/mL solution of human IL6R (R and D Systems, Cat No. 227-SR/CF) in PBS, pH 7.4. Plates were washed 3 times with PBST (PBS, pH 7.4, 0.05% Tween-20). Wells were then blocked with 200 µl/well, 2% NFDM (non-fat dry milk) in PBST for 2 hours at room temperature. The IL6R-coated plates were washed 3 times with PBST (PBS, pH 7.4, 0.05% Tween-20). A dilution series of each activatable antibody—synovial fluid reaction mixture, as well as a dilution series of the parental anti-IL6R antibody, was added to appropriate wells of the IL6R-coated ELISA plate. The plates were incubated 1 hour at room temperature, and then washed 3 times with PBST (PBS, pH 7.4, 0.05% Tween-20). One hundred µl/well 1:3000 dilution goat-anti-human IgG (Fab specific, Sigma Cat No. A0293) in 2% NFDM-PBST was added, and the plate incubated for 1 hour at room temperature. The plates were washed 6 times with PBST (PBS, pH 7.4, 0.05% Tween-20) and then developed with TMB and 1N HCl.

[0520] Table 6 provides the results of this experiment. The data indicate that anti-IL6R activatable antibodies comprising the substrates in Table 6 are cleaved by at least some synovial fluid samples (SyF) obtained from RA patients.

TABLE 6

Activatable Antibody Activation			
Substrate/ Sequence	Activation in vivo	Activation in SyF	Incidence in SyF
10419 ISSGLSS (SEQ ID NO: 159)	<5%	>30%	3/3
559 QNQALRMA (SEQ ID NO: 15)	<5%	20%	3/3
601 AQNLLLGMV (SEQ ID NO: 16)	<5%	>30%	3/3
3457 STFPFGMF (SEQ ID NO: 17)	10%	>50%	3/3

TABLE 6-continued

Activatable Antibody Activation			
substrate/sequence	Activation in vivo	Activation in SyF	Incidence in SyF
3458 PVGYTSSL (SEQ ID NO: 18)	10%	20%	3/3
3463 DWLYWPGI (SEQ ID NO: 19)	<5%	>30%	3/3

Example 2

Activatable Anti-EGFR Antibody with MMP-Cleavable Substrate to Inhibit Tumor Growth

[0521] This Example demonstrates the ability of an activatable anti-EGFR antibody that contains a masking moiety comprising the amino acid sequence CISPRGCPDG-PYVMY (SEQ ID NO: 160), a cleavage moiety comprising the MMP14 substrate 520 (also referred to herein as MN520) ISSGLLSS (SEQ ID NO: 14), and the heavy chain (SEQ ID NO: 56) and light chain (SEQ ID NO: 59) of the anti-EGFR antibody C225v5, where the entire activatable antibody construct is referred to herein as Pb-MN520, to inhibit tumor growth in the H292 xenograft lung cancer model. The configuration of the light chain of the activatable antibody was masking moiety—MMP substrate—light chain of C225v5. [0522] FIG. 1A is a graph depicting the effects seen in H292 xenograft tumor-bearing mice that were treated using Pb-520 (12.5 mg/kg, solid blue line) and IVIG (12.5 mg/kg, green dashed line) dosed at different times. Data are presented as mean tumor volume±SEM. FIG. 1B is a graph depicting systemic stability of the Pb-520 activatable antibody in H292 tumor bearing mice. Blood samples were taken through retro-orbital bleeds at Day 7 and the circulating stability of substrate 520 was determined by analysis of IgG pull-downs with capillary electrophoresis (GXII; Caliper LifeSciences). Concentrations of cleaved and uncleaved light chain were determined using LabChip GX software (Caliper LifeSciences).

Example 3

Materials and Methods

[0523] Reagents and Strains:

[0524] Streptavidin-conjugated phycoerythrin (SA-PE) (Invitrogen, Life Technologies) was used without modifications. Human MMP9 (Research & Diagnostics Systems, Inc.) was activated following the supplied protocol and used without modifications. Human MMP14 (Research & Diagnostics Systems, Inc.) was activated following the supplied protocol and used without modifications. Human Plasmin (Haemato-logic Technologies Inc.) was used without modifications. Human tPA (Molecular Innovations) was used without modifications. YPet fused to the SH3 domain of Mona (monocytic adaptor protein) was produced at CytomX Therapeutics and used without modifications. MMP14 Buffer HCM (50 mM HEPES (pH 6.8), 10 mM CaCl₂, 0.5 mM MgCl₂), was used. MMP9 Buffer TCNB (50 mM Tris-HCl, 10 mM CaCl₂, 150 mM NaCl, 0.05% (w/v) Brij-35, pH 7.5) was used. Plasmin Buffer (50 mM Tris-Cl pH 7.5, 100 mM NaCl, 0.01%

Tween20 and 1 mM EDTA was used. TBST (50 mM Tris-HCl, 150 mM NaCl, 0.05% Tween20, pH 7.4) was used. *E. coli* MC1061 (Casadaban et al., JMB 138(2):179-207 (1980) was used. All bacterial growth was performed at 37° C. with vigorous shaking in Luria-Bertani broth (LB) supplemented with 34 µg/mL chloramphenicol, unless another antibiotic is specified.

[0525] Substrate Cleavage and Scaffold Stability Analysis:

[0526] For screening and clone analysis, overnight cultures were subcultured by dilution into fresh medium (1:50) and grown for 1.5-2 hours. The subculture was then induced with 0.04% arabinose and incubated with shaking at 37° C. for 45 minutes to 1 hour. To stop further growth cells were incubated on ice for 15 minutes to 1 hour. Cell aliquots were harvested and washed with PBS (pH 7.4). Cells were pelleted by centrifugation, the supernatant removed and the cells resuspended in reaction buffer containing the enzyme; the reaction mixture was incubated at 37° C. static. To stop the reaction, cells were removed and diluted 10-fold in PBS, pelleted by centrifugation, and resuspended in PBS containing either (eCLiPS) SA-PE (20 µg/mL) or YPet-MONA (50 nM). After incubation on ice (30 min), cells were washed with PBS and analyzed using a FACS Aria™ cell sorter.

[0527] For MMP9 protease cleavage assays, cultures were induced for 45 minutes to 1 hour. The reaction buffer for MMP9 was TCNB. Assays for MMP9 hydrolysis were performed after fresh cells were incubated with 5 nM-25 nM MMP9 for 1 hr. Background hydrolysis of the regions flanking the substrate site (using platform eCLiPS3.0-NSUB_SP described in PCT patent application PCT/US13/54378, filed Aug. 9, 2013, which was published as International Publication No. WO 2014/026136 on 13 Feb. 2014, the contents of which are hereby incorporated by reference in their entirety) was measured under each reaction condition to ensure that hydrolysis occurred in the designated substrate region.

[0528] For MMP14 protease cleavage assays, cultures were induced for 45 minutes to 1 hour. The reaction buffer for MMP14 was HCM. Assays for MMP14 hydrolysis were performed after reactions with 3 nM-250 nM MMP14 or 1 hr. Background hydrolysis of the regions flanking the substrate site (using platform eCLiPS3.0-NSUB_SP described herein) was measured under each reaction condition to ensure that hydrolysis occurred in the designated substrate region.

[0529] For human plasmin stability assays, platform eCLiPS3.0-NSUB_SP is used; cultures are induced for 45 minutes to 1 hr. The reaction buffer for plasmin is 50 mM Tris-HCl pH 7.5 supplemented with 100 mM NaCl, 0.01% Tween20 and 1 mM EDTA. Assays for plasmin hydrolysis are performed after reactions with plasmin for 1 hr.

[0530] For human tPA stability assays, platform eCLiPS3.0-NSUB_SP is used; cultures are induced for 45 minutes to 1 hr. The reaction buffer for tPA is TBST. Assays for tPA hydrolysis are performed after reactions with tPA for 1 hr.

[0531] Amino and Carboxy Terminus Labeling Conditions:

[0532] Streptavidin conjugated phycoerythrin (SAPE) was used for labeling streptavidin binding affinity ligand on the N-termini of CPX. Fluorescent protein YPet fused to the SH3 domain of Mona was used for labeling the MONA binding affinity ligand on the C-termini of CPX. For optimum labeling of cells without protease reaction, the cells were incubated for 30 min at 4° C. with SAPE (20 µg/mL) or YPet-MONA (50 nM). For the described example below 30 min incubation was used.

[0533] Kinetic Data Analysis:

[0534] The extent of conversion of cell surface displayed peptide substrates was measured directly, using flow cytometry to measure changes in mean fluorescence of clonal cell populations upon protease treatment. Specifically, for each sample, conversion was determined by flow cytometry analyses using the relationship

$$\text{Conversion} = \frac{FL_- - FL_+}{FL_- - FL_0} \quad [1]$$

where (FL_-) is the fluorescence after incubating without enzyme, (FL_+) is fluorescence after incubation with enzyme, and (FL_0) is fluorescence of unlabeled cells. Given that the expected substrate concentrations that were used are significantly below the expected K_M of the substrate for the target protease, the Michaelis-Menten model simplifies to:

$$\frac{d[S]}{dt} \approx \frac{k_{cat}}{K_M} [S][E] \quad [2]$$

allowing substrate conversion to be expressed as

$$\text{Conversion} = 1 - \exp\left(-\frac{k_{cat}}{K_M} \cdot [E] \cdot t\right) \quad [3]$$

where $[S]$ is the substrate concentration, $[E]$ is enzyme concentration and t is time. To determine the second order rate constant (k_{cat}/K_M), equation [3] was simplified to:

$$\frac{k_{cat}}{K_M} = -\ln(1 - C) / (t * p)$$

where C is product conversion, t is time and p is protease concentration.

[0535] Sequence Data Analysis—Directed Families:

[0536] Substrates were submitted to Ion Torrent™ sequencing (see, e.g., Rothenberg, J M, *Nature* 475, 348-352). Raw Ion Torrent reads were cropped by invariant vector sequences to obtain just the variable peptide insert. Insert sequences were translated, and sequences with stop codons were excluded from further analysis. The frequency of each sequence was obtained by number of times observed out of all viable peptide reads observed. Enrichment of sequences was obtained by comparison of observed frequency of each sequence post selection to the frequency of each sequence pre-selection. Individual sequences were identified and isolated from these data, and sequences were aligned in CLC main lab (CLC Main Workbench 6.6.2, available online). The alignment file was imported to Jalview (see, e.g., Waterhouse, A. M., et al., 2009, *Bioinformatics* 9, 1189-1191), and an average distance tree was assembled using the BLOSUM62 algorithm (S Henikoff S et al., 1992, *Proc Natl Acad Sci USA* 89, 10915-10919). The restricted group of sequences includes members of the cluster closest to the sequence of interest. The extended group of sequences includes the restricted group of sequences plus members of the branch that shares the closest common ancestor (where applicable).

Example 4

Selection and Characterization of Substrate Pools in a Platform Scaffold

[0537] The use of multi-copy substrate display on whole cells enabled selection of populations of substrates cleaved by MMP9. Selections were performed as described in U.S. Pat. No. 7,666,817 B2, issued Feb. 23, 2010, using recombinant human MMP9. Background hydrolysis of the regions flanking the substrate site (using platform eCLiPS3.0-NSUB_SP) was measured under each reaction condition to ensure that hydrolysis occurred in the designated substrate region. Selected pools were tested with MMP9 and MMP14. FIGS. 2A and 2B show cleavage of pool SMP87 by MMP9 at 5 nM in TCNB buffer.

Example 5

Characterization of Substrate Cleavage Kinetics in the Platform Scaffold

[0538] The use of multi-copy substrate display on whole cells enabled simple and direct quantitative characterization of cleavage kinetics. Consequently, flow cytometry was used to rank individual isolated clones on the basis of substrate conversion, and clones were identified by DNA sequencing. In this way, the extent of conversion for each clone could be determined at several different protease concentrations and fit to a Michaelis-Menten model (Kinetic Data Analysis Section). The observed second order rate constant (k_{cat}/K_M) was determined for each substrate versus MMP9. Background hydrolysis of the regions flanking the substrate site (using platform eCLiPS3.0-NSUB_SP), was measured under each reaction condition to ensure that hydrolysis occurred in the designated substrate region. For example, FIGS. 3A and 3B show cleavage of a substrate comprising amino acid sequence VAGRSMRP (SEQ ID NO: 484) by 5 nM MMP9 in TBST.

Example 6

Correlation of Next Generation Sequencing Frequency and Substrate Cleavage Kinetics in the Platform Scaffold

[0539] Final pools of enriched substrates were sequenced using Ion Torrent Next-Generation Sequencing. Raw Ion Torrent reads were cropped by invariant vector sequences to obtain just the variable peptide insert. Insert sequences were translated, and sequences with stop codons were excluded from further analysis. A selection of clones (displaying a range of frequencies) was selected for functional analysis. Selected clones were cleaved with human MMP9, and a k_{cat}/K_M was determined for each. The log of the clone copy number in the pool was then plotted versus the log of the k_{cat}/K_M . FIG. 4 shows the correlation between frequency of particular cleavage moieties (Copy Number) and their abilities to be cleaved by MMP9 ($\text{MMP9 } k_{cat}/K_M \text{ M}^{-1} \text{ s}^{-1}$).

Example 7

Selection and Characterization of Substrate Pools in a Platform Scaffold

[0540] The use of multi-copy substrate display on whole cells enabled selection of populations of substrates cleaved by MMP14. Selections were performed as described in U.S. Pat.

No. 7,666,817 B2, using recombinant human MMP14. Background hydrolysis of the regions flanking the substrate site (using platform eCLiPS3.0-NSUB_SP) was measured under each reaction condition to ensure that hydrolysis occurred in the designated substrate region. Selected pools were tested with MMP9 and MMP14. FIGS. 5A and 5B show cleavage of pool SMP39 by MMP14 at 60 nM in HCM buffer.

Example 8

Characterization of Substrate Cleavage Kinetics in the Platform Scaffold

[0541] The use of multi-copy substrate display on whole cells enabled simple and direct quantitative characterization of cleavage kinetics. Consequently, flow cytometry was used to rank individual isolated clones on the basis of substrate conversion, and clones were identified by DNA sequencing. In this way, the extent of conversion for each clone could be determined at several different protease concentrations and fit to a Michaelis-Menten model (Kinetic Data Analysis Section). The observed second order rate constant (k_{cat}/K_M) was determined for each substrate versus MMP14. Background hydrolysis of the regions flanking the substrate site (using platform eCLiPS3.0-NSUB_SP), was measured under each reaction condition to ensure that hydrolysis occurred in the designated substrate region. For example, FIGS. 6A and 6B show cleavage of a substrate comprising amino acid sequence QNQALRMA (SEQ ID NO: 15) by 30 nM MMP14 in HCM buffer.

Example 9

In Vitro Substrate Activity in Activatable Antibodies

[0542] This Example demonstrates the in vitro activity of substrates of the disclosure when they are incorporated into activatable antibodies.

[0543] Several substrates identified in these studies were inserted into activatable antibodies having the 3954 mask and C225v5 variant of cetuximab, which is described in PCT Publication No. WO 2013/163631, and which is incorporated herein by reference in its entirety.

[0544] The ability of substrates in the resultant activatable antibodies to be cleaved by MMP9 or MMP14 was determined as follows. MMP9 protease digests were performed in TCNB, 50 mM Tris-HCl, 10 mM CaCl₂, 150 mM NaCl, 0.05% (w/v) Brij-35, pH 7.5. MMP14 digests were performed in 50 mM HEPES (pH 6.8), 10 mM CaCl₂, 0.5 mM MgCl₂. Varying concentrations of active site titrated MMP9 or MMP14 were combined with a fixed activatable antibody concentration to maintain a substrate to protease ratio of at least 50. Samples comprising MMP9 substrates were incubated at 37° C. for up to 24 hr. Samples comprising MMP14 substrates were incubated at 37° C. for 4 hr. To stop the reaction, 5 µl of the digest was added to 7 µl of HT Protein Express Sample Buffer (Caliper LifeSciences) containing 20 mM 2-Mercaptoethanol for 10 minutes at 95° C. After heat denaturation, 32 µl of ddH₂O was added and samples analyzed on a LabChip GXII per manufacturer's instructions. The LabChip GXII software was used to quantify light chain peak area. Product conversion was calculated by plugging the light chain peak areas into the following equation: cleaved LC/(cleaved LC+uncleaved LC), LC=light chain. k_{cat}/K_M values were determined with the following equation

$$\frac{k_{cat}}{K_m} = -\ln(1 - C)/(t * p)$$

where C is product conversion, t is time (s), and p is protease concentration (M), which assumes that the substrate concentration is below the K_M and in excess of the protease concentration.

[0545] Resultant activatable antibodies comprising substrates selected for cleavage by MMP14 tested for cleavage by MMP14 had k_{cat}/K_M values ranging from about 400 to 60,000 M⁻¹ s⁻¹ for MMP14. Resultant activatable antibodies comprising substrates selected for cleavage by MMP9 tested for cleavage by MMP9 were cleaved by MMP9.

Example 10

Substrate Stability of Activatable Antibodies In Vivo

[0546] This Example demonstrates the in vivo stability of substrates of the disclosure when they are incorporated into activatable antibodies and injected into mice.

[0547] Three nude mice (Cr1:NU-Foxn1nu) received a single IP dose of each activatable antibody at 12.5 mg/kg on Day 0. Mice were euthanized on day 4 (~96 h post-dose) by CO₂ asphyxiation, and blood was collected immediately as plasma-EDTA and stored at -80° C.

[0548] Activatable antibodies were purified from plasma by anti-human IgG immunoprecipitation using magnetic beads. Eluted activatable antibodies were prepared for analysis by capillary electrophoresis as described in the k_{cat}/K_M section. Briefly, 5 µl of eluted IgG was added to 7 µl Protein Express Sample Buffer with 2-mercaptoethanol. Quantification of circulating stability was identical to quantification of product conversion.

[0549] Of ten activatable antibodies comprising substrates of the disclosure selected for cleavage by MMP14, seven demonstrated less than 20% cleavage in the collected plasma samples. Of seven activatable antibodies comprising substrates of the disclosure selected for cleavage by MMP9, four demonstrated no more than 20% cleavage in the collected plasma samples.

Example 11

Materials and Methods

[0550] Reagents and Strains:

[0551] Human MMP9 (catalog no. 911-MP, Research & Diagnostics Systems, Inc.) was activated following the supplied protocol and used without modifications. Human MMP14 (catalog no. 918-M), Research & Diagnostics Systems, Inc.) was activated following the supplied protocol and used without modifications. Human Plasmin (catalog no. HCPM-0140, Haematologic Technologies Inc.) was used without modifications. Anti-EE monoclonal antibody (Covance, Princeton, N.J.) was labeled with Alexa 647 (Life Sciences) and used with no other modifications (named EE647). *E. coli* MC1061 or MC1061 derived strains (DH10 β) were used for all experiments (Casadaban et al., JMB 138(2):179-207 (1980)). All bacterial growth was performed at 37° C. with vigorous shaking in Luria-Bertani broth (LB) supplemented with 34 µg/mL chloramphenicol (cm), unless another antibiotic is specified.

[0552] Display Platforms:

[0553] Display platforms, each engineered to contain an 8-amino acid substrate of the embodiments, were produced and used as described in International Publication No. WO 2014/026136, published 13 Feb. 2014, the contents of which are hereby incorporated by reference in their entirety. The amino acid sequence of the mature (i.e., without a signal peptide) CYTX-DP-XXXXXXX display platform (SEQ ID NO: 512) is shown in FIG. 7A. XXXXXXXX indicates the location into which each substrate is inserted. The amino acid sequence of CYTX-DP-XXXXXXX display platform also including its signal peptide, i.e., SP-CYTX-DP-XXXXXXX display platform (SEQ ID NO: 513) is shown in FIG. 7B.

CYTX-DP-XXXXXXX Display Platform:

[0554]

(SEQ ID NO: 512)
 GQSGQEYMPMEGGSGQXXXXXXXXXSGGQGGGGSGGGSGGGSGGSAYYGITA
 GPAYRINDWASIYGVVGVGYGSGPGBSYGFSYAGLQFNPMENVALDFSY
 EQSRIRSVDVGTWILSVGYRFGSKSRRATSTVGGYAQSDAQGQMNKMG
 FNLKYRYEEDNSPLGVIGSFTYTGGGGSSGQAAAGHHHHHHHH

SP-CYTX-DP-XXXXXXX Display Platform:

[0555]

(SEQ ID NO: 513)
 MKKIACLSALAAVLAFTAGTSAVQSGQEQYMPMEGGSGQXXXXXXXXXSGG
 QGGGGGGGGGGSGGSAYYGITAGPAYRINDWASIYGVVGVGYGSGPGBGS
 YGFSYAGLQFNPMENVALDFSYEQSRIRSVDVGTWILSVGYRFGSKSRR
 ATSTVGGYAQSDAQGQMNKMGGFNLKYRYEEDNSPLGVIGSFTYTGGSG
 GSSGQAAAGHHHHHHHH

[0556] Substrate Cleavage and Cleavage Kinetics Analysis:

[0557] For clone analysis, overnight cultures were subcultured by dilution into fresh medium (1:40) and grown for 1.5-2 hours. The subculture was then induced with 0.04% arabinose and incubated with shaking at 37° C. for 40 minutes to 1 hour. To stop further growth, cells were then incubated on ice for 15 minutes to 1 hour. Cell aliquots were harvested and washed with PBS (pH 7.4). Cells were pelleted by centrifugation, the supernatant removed and the cells resuspended in reaction buffer containing the enzyme; the reaction mixture was incubated at 37° C. with shaking. To stop the reaction cells were removed and diluted 10-fold in PBS, pelleted by centrifugation, and resuspended in PBS containing EE647 (20 micrograms per ml (also referred to herein as ug/ml or μ g/ml)). After incubation on ice (1 hour), cells were washed with PBS and analyzed using an Accuri C6 cell sorter.

[0558] For MMP9 protease cleavage assays, cultures were induced for 45 minutes. The reaction buffer for MMP9 was 50 mM Tris-HCl, pH 7.4, supplemented with 150 mM NaCl, 10 mM CaCl₂ and 0.05% (w/v) Brij-35. Assays for MMP9 hydrolysis, were performed after cleavage with 5 nM-150 nM MMP9 for 1 hour. Background hydrolysis of the regions flanking the substrate site (using, e.g., CYTX-DP-NSUB, a display platform in which the "Substrate" is non-cleavable

linker GGGSGGGGS) was measured under each reaction condition to ensure that hydrolysis occurred in the designated substrate region.

[0559] For MMP14 protease cleavage assays, cultures were induced for 45 minutes. The reaction buffer for MMP14 was 50 mM HEPES, pH 6.8, supplemented with 10 mM CaCl₂ and 0.5 mM MgCl₂. Assays for MMP14 hydrolysis, were performed after cleavage with 5 nM-150 nM MMP14 for 1 hr. Background hydrolysis of the regions flanking the substrate site (using, e.g., CYTX-DP-NSUB) was measured under each reaction condition to ensure that hydrolysis occurred in the designated substrate region.

[0560] For human plasmin stability assays, cultures were induced for 45 minutes. The reaction buffer for plasmin was 50 mM Tris-HCl pH 7.4, supplemented with 100 mM NaCl, 0.01% Tween20 and 1 mM EDTA. Assays for plasmin hydrolysis were performed after cleavage with 500 pM plasmin for 1 hr. Background hydrolysis of the regions flanking the substrate site (using, e.g., CYTX-DP-NSUB) was measured under each reaction condition to ensure that hydrolysis occurred in the designated substrate region.

[0561] Amino and Carboxyl Terminus Labeling Conditions:

[0562] Alexa-647 conjugated anti-EE antibody (EE647) was used for labeling EE binding affinity ligand on the N-termini of the CYTX-DP display platform. Alexa-647 conjugated anti-His antibody (His647) was used for labeling the 8His binding affinity ligand on the C-termini of the CYTX-DP display platform. For optimum labeling of cells without protease reaction, the cells were incubated for 1 hour at 4° C. with EE647 (20 μ g/mL) or His647 (2 μ g/mL). For the example described below, a 1-hour incubation was used.

[0563] Kinetic Data Analysis:

[0564] The extent of conversion of cell surface displayed peptide substrates was measured directly, using flow cytometry to measure changes in mean fluorescence of clonal cell populations upon protease treatment. Specifically, for each sample, conversion was determined by flow cytometry analyses using the relationship

$$\text{Conversion}_{\text{CLPS}} = \frac{FL_- - FL_+}{FL_- - FL_0} \quad [1]$$

where (FL₋) is the fluorescence after incubating without enzyme, (FL₊) is fluorescence after incubation with enzyme, and (FL₀) is fluorescence of unlabeled cells. Given that the expected substrate concentrations that were used are significantly below the expected K_M of the substrate for the target protease, the Michaelis-Menten model simplifies to

$$\frac{d[S]}{dt} \approx \frac{k_{cat}}{K_M} [S][E] \quad [2]$$

allowing substrate conversion to be expressed as

$$\text{Conversion}_{\text{MM}} = 1 - \exp\left(-\frac{k_{cat}}{K_M} \cdot [E] \cdot t\right) \quad [3]$$

where [S] is the substrate concentration, [E] is enzyme concentration and t is time. To determine the second order rate constant (k_{cat}/K_M), the time dependent conversion for each substrate was fit to equation [3].

Example 12

Characterization of Substrate Cleavability in CYTX-DP Display Platform

[0565] This Example demonstrates the ability of substrates of the embodiments to be cleaved by MMP but not by plasmin.

[0566] The use of multi-copy substrate display on whole cells enabled simple and direct quantitative characterization of cleavage kinetics. Clones encoding substrates were identified by DNA sequencing and subcloned into the CYTX-DP display platform such that the expressed display platform contained the 8-amino acid substrate in place of XXXXXXXX. Individual substrate displaying clones (127 independent substrate-containing display platforms in total) were assessed for cleavage by either MMP9 or MMP14 (target proteases, i.e., the proteases used to select the substrate) and plasmin (off-target protease); turnover was determined by flow cytometry. Thirty-one of the MMP9-selected substrates were selected from the same pool that was the source of substrates comprising amino acid sequences SEQ ID NOS: 17, 18, 19, 20, 21, 22, or 23 (MMP9 substrates from pool). Nine of the MMP9-selected substrates comprise consensus amino acid sequences SEQ ID NOS: 328, 336, 337, 338, 339, 348, 349, 350 or 351 (MMP9 consensus sequences). Thirty-eight of the MMP14-selected substrates were selected from the same pool that was the source of substrates comprising amino acid sequences SEQ ID NOS: 14, 15, 16, 24, 25, 26, 27, 28, 29, 30, or 33 (MMP14 substrates from 1st pool). Ten of the MMP14-selected substrates were selected from the same pool that was the source of substrates comprising amino acid sequences SEQ ID NOS: 31 or 32 (MMP14 substrates from 2nd pool). Thirty-nine of the MMP14-selected substrates were chosen from consensus amino acid sequences SEQ ID NOS: 364-370, 379-393, 402-409, 420-424, 434-435, 450-452, 457, 470-472, 474, or 483 (MMP14 consensus sequences).

[0567] In this way, the extent of cleavage for each clone could be determined and the data aggregated to determine a percent of clones that are cleaved by the target protease and not the off-target protease. Background hydrolysis of the regions flanking the substrate site (using, e.g., CYTX-DP-NSUB) was measured under each reaction condition to ensure that hydrolysis occurred in the designated substrate region. Results are presented in Table 9.

TABLE 9

Summary statistics of substrate cleavability			
Discovery effort	Substrate Group	>20% Cleavage with 50 nM MMP9 or MMP14	<20% Cleavage with 500 pM Plasmin
MMP9-selected Substrates	All MMP9 substrates tested	35% (14 of 40)	85% (34 of 40)
	MMP9 substrates from pool	39% (12 of 31)	84% (26 of 31)
	MMP9 consensus substrates	22% (2 of 9)	89% (8 of 9)
MMP14-selected Substrates	All MMP14 substrates tested	85% (74 of 87)	94% (82 of 87)
	MMP14 substrates from 1 st and 2 nd pools	79% (38 of 48)	94% (45 of 48)
	MMP14 substrates from 1 st pool	79% (30 of 38)	95% (36 of 38)

TABLE 9-continued

Summary statistics of substrate cleavability			
Discovery effort	Substrate Group	>20% Cleavage with 50 nM MMP9 or MMP14	<20% Cleavage with 500 pM Plasmin
Combined MMP9 and MMP14	MMP14 substrates from 2 nd pool	80% (8 of 10)	100% (9 of 10)
	MMP14 consensus substrates	92% (36 of 39)	95% (37 of 39)
	Total	69% (88 of 127)	91% (116 of 127)

[0568] Table 9 depicts (a) the percentage of MMP9-selected substrates tested in the CYTX-DP display platform that exhibited at least 20% cleavage when incubated with 50 nM human MMP9 (catalog no. 911-MP, Research & Diagnostics Systems, Inc., activated following the supplied protocol and used without modifications) for 1 hour at 37° C. in 50 mM Tris-HCl, pH 7.4, supplemented with 150 mM NaCl, 10 mM CaCl₂, and 0.05% (w/v) Brij-35 (>20% Cleavage with 50 nM MMP9); (b) the percentage of MMP14-selected substrates tested in the CYTX-DP display platform that exhibited at least 20% cleavage when incubated with 50 nM human MMP14 (catalog no. 918-MP, Research & Diagnostics Systems, Inc., activated following the supplied protocol and used without modifications) for 1 hour at 37° C. in 50 mM HEPES, pH 6.8, supplemented with 10 mM CaCl₂, and 0.5 mM MgCl₂ (>20% Cleavage with 50 nM MMP14); and (c) the percentage of MMP9-selected or MMP14-selected substrates tested in the CYTX-DP display platform that exhibited less than 20% cleavage when incubated with 500 pM human plasmin (catalog number HCPM-0140, Haematologic Technologies, Inc., used without modifications) for 1 hour at 37° C. in 50 mM Tris-HCl, pH 7.4, supplemented with 100 mM NaCl, 0.01% Tween20 and 1 mM EDTA (<20% cleavage with 500 pM plasmin).

Example 13

Characterization of Substrate Cleavage Kinetics in CYTX-DP Display Platforms

[0569] This Example demonstrates the cleavage kinetics of various substrates.

[0570] The use of multi-copy substrate display on whole cells enabled simple and direct quantitative characterization of cleavage kinetics. Clones were identified by DNA sequencing and subcloned into the CYTX-DP-XXXXXXX display platform as described in the preceding example. Seventy-two individual substrate-displaying clones were assessed for cleavage and a subset were chosen to assess cleavage kinetics by their target protease. The extent of conversion for each clone could be determined at several different protease concentrations and fit to the Michaelis-Menten model described herein. Observed k_{cat}/K_M values were then plotted versus frequency of the clone within the substrate pool and a correlation between frequency and k_{cat}/K_M was seen. Background hydrolysis of the regions flanking the substrate site (using, e.g., CYTX-DP-NSUB) was measured under each reaction condition to ensure that hydrolysis occurred in the designated substrate region. Results are presented in Table 10.

TABLE 10

Summary statistics of substrate kinetics				
	Substrate Group	Target Protease $k_{cat}/K_M > 1 \times 10E2$	Target Protease $k_{cat}/K_M > 1 \times 10E3$	Target Protease $k_{cat}/K_M > 1 \times 10E4$
MMP9 Substrates	All MMP9 substrates tested	100% (16 of 16)	100% (16 of 16)	63% (10 of 16)
	MMP9 substrates from pool	100% (15 of 15)	100% (15 of 15)	67% (10 of 15)
	MMP9 consensus substrates	100% (1 of 1)	100% (1 of 1)	0% (0 of 1)
MMP14 Substrates	All MMP-14 substrates	100% (55 of 55)	98% (54 of 55)	36% (20 of 55)
	MMP14 substrates from 1 st and 2 nd pools	100% (47 of 47)	98% (46 of 47)	36% (17 of 47)
	MMP14 substrates from 1 st pool	100% (38 of 38)	100% (38 of 38)	39% (15 of 38)
	MMP14 substrates from 2 nd pool	100% (9 of 9)	89% (8 of 9)	22% (2 of 9)
	MMP14 consensus substrates	100% (8 of 8)	100% (8 of 8)	38% (3 of 8)
Combined MMP9 and MMP14	Total	100% (71 of 71)	99% (70 of 71)	42% (30 of 71)

Example 14

In Vivo Efficacy and In Situ Activation of Activatable Antibodies Comprising a MMP Substrate

[0571] This Example demonstrates that activatable antibodies comprising MMP substrates of the embodiments are efficacious in vivo. This Example also demonstrates that such activatable antibodies are activatable in an in situ imaging assay, such as that described in International Publication No. WO 2014/107559, published 10 Jul. 2014, the contents of which are hereby incorporated by reference in their entirety. Six activatable antibodies comprising different MMP substrates (one MMP9-selected and five MMP14-selected) of the embodiments were administered at 10 mg/kg or 12.5 mg/kg to H292 xenograft tumor-bearing (lung cancer) mice. All six activatable antibodies also comprised the masking moiety comprising the amino acid sequence CISPRGCPDGPYVMY (SEQ ID NO: 160) and anti-EGFR antibody C225v5 antibody comprising a light chain (SEQ ID NO: 59) and a heavy chain (SEQ ID NO: 56). The configuration of the light chain of the activatable antibody was masking moiety—MMP substrate—light chain of C225v5. All six activatable antibodies demonstrated tumor growth inhibition ranging from 22% to 81% as measured by mean % Δ inhibition. Mean % Δ inhibition is calculated as $(\text{mean}(C) - \text{mean}(C0)) - (\text{mean}(T) - \text{mean}(T0)) / (\text{mean}(C) - \text{mean}(C0)) * 100\%$, wherein T is the current test group value, T0 is the current test group initial value, C is the control group value, and C0 is the control group initial value. The EGFR antibody cetuximab demonstrated 96-98% inhibition in this study.

[0572] The same six activatable antibodies were submitted to in situ imaging assays of H292 tumor tissue, using the

conditions described in the examples of WO 2014/107559. All six activatable antibodies were activated, demonstrating that all six MMP substrates were cleaved and the released antibodies bound to EGFR on the tumor tissue. The staining signals ranged from 15% to 65% of the IHC signal intensity of cetuximab. In general, the percentage of activation of each activatable antibody demonstrated a positive correlation with the efficacy that activatable antibody demonstrated in the H292 mouse model.

[0573] Tissue from ten triple negative breast cancer patients was submitted to in situ imaging using an anti-Jagged activatable antibody (e.g., an anti-Jagged activatable antibody cited in International Publication No. WO 2013/192550, published 27 Dec. 2013, the contents of which are hereby incorporated by reference in their entirety) comprising an MMP 14-selected substrate under the conditions described in the examples of WO 2014/107559. Nine of the ten tissue samples demonstrated activatable antibody activation staining scores ranging from 15% to 100% as compared to the IHC signal intensity of cetuximab: Eight of the ten tissue samples demonstrated activatable antibody activation staining scores ranging from 30% to 100% as compared to the IHC signal intensity of cetuximab.

OTHER EMBODIMENTS

[0574] While the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following.

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His Ala Trp Ser Trp Val Arg Gln Pro Pro Gly Arg Gly Leu Glu Trp
35 40 45

Ile Gly Tyr Ile Ser Tyr Ser Gly Ile Thr Thr Tyr Asn Pro Ser Leu
50 55 60

Lys Ser Arg Val Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Arg Ser Leu Ala Arg Thr Thr Ala Met Asp Tyr Trp Gly Gln Gly
100 105 110

Ser Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
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Arg Thr Pro Glu Val Thr Cys Val Val Asp Val Ser His Glu Asp
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Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
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Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
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Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
 305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
 325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
 340 345 350

Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
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Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
 370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
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Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
 405 410 415

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Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
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Lys

<210> SEQ ID NO 55
 <211> LENGTH: 214
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Av1 Antibody Light Chain

<400> SEQUENCE: 55

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Ser Tyr
 20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45

Tyr Tyr Thr Ser Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80

Glu Asp Ile Ala Thr Tyr Tyr Cys Gln Gln Gly Asn Thr Leu Pro Tyr
 85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
 100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
 115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
 130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
 145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser

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165	170	175
Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr		
180	185	190
Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser		
195	200	205
Phe Asn Arg Gly Glu Cys		
210		
<210> SEQ_ID NO 56		
<211> LENGTH: 449		
<212> TYPE: PRT		
<213> ORGANISM: Artificial Sequence		
<220> FEATURE:		
<223> OTHER INFORMATION: C225v5 Antibody Heavy Chain		
<400> SEQUENCE: 56		
Gln Val Gln Leu Lys Gln Ser Gly Pro Gly Leu Val Gln Pro Ser Gln		
1	5	10
		15
Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Asn Tyr		
20	25	30
Gly Val His Trp Val Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp Leu		
35	40	45
Gly Val Ile Trp Ser Gly Gly Asn Thr Asp Tyr Asn Thr Pro Phe Thr		
50	55	60
Ser Arg Leu Ser Ile Asn Lys Asp Asn Ser Lys Ser Gln Val Phe Phe		
65	70	75
		80
Lys Met Asn Ser Leu Gln Ser Gln Asp Thr Ala Ile Tyr Tyr Cys Ala		
85	90	95
Arg Ala Leu Thr Tyr Tyr Asp Tyr Glu Phe Ala Tyr Trp Gly Gln Gly		
100	105	110
Thr Leu Val Thr Val Ser Ala Ala Ser Thr Lys Gly Pro Ser Val Phe		
115	120	125
Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu		
130	135	140
Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp		
145	150	155
		160
Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu		
165	170	175
Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser		
180	185	190
Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro		
195	200	205
Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys		
210	215	220
Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro		
225	230	235
		240
Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser		
245	250	255
Arg Thr Pro Glu Val Thr Cys Val Val Asp Val Ser His Glu Asp		
260	265	270
Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn		
275	280	285
Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val		

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290	295	300
Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu		
305	310	315
Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys		
325	330	335
Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr		
340	345	350
Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr		
355	360	365
Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu		
370	375	380
Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu		
385	390	395
Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys		
405	410	415
Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu		
420	425	430
Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly		
435	440	445

Lys

<210> SEQ ID NO 57		
<211> LENGTH: 449		
<212> TYPE: PRT		
<213> ORGANISM: Artificial Sequence		
<220> FEATURE:		
<223> OTHER INFORMATION: C225v4 Antibody Heavy Chain		
<400> SEQUENCE: 57		
Gln Val Gln Leu Lys Gln Ser Gly Pro Gly Leu Val Gln Pro Ser Gln		
1	5	10
15		
Ser Leu Ser Ile Thr Cys Thr Val Ser Gly Phe Ser Leu Thr Asn Tyr		
20	25	30
Gly Val His Trp Val Arg Gln Ser Pro Gly Lys Gly Leu Glu Trp Leu		
35	40	45
Gly Val Ile Trp Ser Gly Gly Asn Thr Asp Tyr Asn Thr Pro Phe Thr		
50	55	60
Gly Val Leu Ser Ile Asn Lys Asp Asn Ser Lys Ser Gln Val Phe Phe		
65	70	75
80		
Ser Arg Leu Ser Ile Asn Ser Asn Asp Thr Ala Ile Tyr Tyr Cys Ala		
85	90	95
Lys Met Asn Ser Leu Gln Ser Asn Asp Thr Ala Ile Tyr Tyr Cys Ala		
Arg Ala Leu Thr Tyr Tyr Asp Tyr Glu Phe Ala Tyr Trp Gly Gln Gly		
100	105	110
Thr Leu Val Thr Val Ser Ala Ala Ser Thr Lys Gly Pro Ser Val Phe		
115	120	125
Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu		
130	135	140
Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp		
145	150	155
160		
Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu		
165	170	175
Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser		
180	185	190

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Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
 195 200 205
 Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
 210 215 220
 Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
 225 230 235 240
 Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
 245 250 255
 Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
 260 265 270
 Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
 275 280 285
 Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
 290 295 300
 Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
 305 310 315 320
 Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
 325 330 335
 Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
 340 345 350
 Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
 355 360 365
 Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
 370 375 380
 Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
 385 390 395 400
 Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
 405 410 415
 Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
 420 425 430
 Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
 435 440 445
 Lys

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<210> SEQ ID NO 58
<211> LENGTH: 449
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: C225v6 Antibody Heavy Chain
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<400> SEQUENCE: 58

Gln	Val	Gln	Leu	Lys	Gln	Ser	Gly	Pro	Gly	Leu	Val	Gln	Pro	Ser	Gln
1				5					10					15	
Ser	Leu	Ser	Ile	Thr	Cys	Thr	Val	Ser	Gly	Phe	Ser	Leu	Thr	Asn	Tyr
			20					25					30		
Gly	Val	His	Trp	Val	Arg	Gln	Ser	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Leu
			35					40					45		
Gly	Val	Ile	Trp	Ser	Gly	Gly	Asn	Thr	Asp	Tyr	Asn	Thr	Pro	Phe	Thr
			50					55					60		
Ser	Arg	Leu	Ser	Ile	Asn	Lys	Asp	Asn	Ser	Lys	Ser	Gln	Val	Phe	Phe
					65			70			75			80	

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Lys Met Asn Ser Leu Gln Ser Gln Asp Thr Ala Ile Tyr Tyr Cys Ala
 85 90 95

Arg Ala Leu Thr Tyr Tyr Asp Tyr Glu Phe Ala Tyr Trp Gly Gln Gly
 100 105 110

Thr Leu Val Thr Val Ser Ala Ala Ser Thr Lys Gly Pro Ser Val Phe
 115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
 130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
 145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
 165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
 180 185 190

Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
 195 200 205

Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
 210 215 220

Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
 225 230 235 240

Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
 245 250 255

Arg Thr Pro Glu Val Thr Cys Val Val Val Asp Val Ser His Glu Asp
 260 265 270

Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
 275 280 285

Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Ala Ser Thr Tyr Arg Val
 290 295 300

Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
 305 310 315 320

Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
 325 330 335

Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
 340 345 350

Leu Pro Pro Ser Arg Asp Glu Leu Thr Lys Asn Gln Val Ser Leu Thr
 355 360 365

Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
 370 375 380

Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
 385 390 395 400

Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
 405 410 415

Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
 420 425 430

Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
 435 440 445

Lys

<210> SEQ ID NO 59
 <211> LENGTH: 214
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence

-continued

<220> FEATURE:

<223> OTHER INFORMATION: C225 Antibody Light Chain

<400> SEQUENCE: 59

Gln Ile Leu Leu Thr Gln Ser Pro Val Ile Leu Ser Val Ser Pro Gly
 1 5 10 15

Glu Arg Val Ser Phe Ser Cys Arg Ala Ser Gln Ser Ile Gly Thr Asn
 20 25 30

Ile His Trp Tyr Gln Gln Arg Thr Asn Gly Ser Pro Arg Leu Leu Ile
 35 40 45

Lys Tyr Ala Ser Glu Ser Ile Ser Gly Ile Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Ser Ile Asn Ser Val Glu Ser
 65 70 75 80

Glu Asp Ile Ala Asp Tyr Tyr Cys Gln Gln Asn Asn Asn Trp Pro Thr
 85 90 95

Thr Phe Gly Ala Gly Thr Lys Leu Glu Leu Lys Arg Thr Val Ala Ala
 100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
 115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
 130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
 145 150 155 160

Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
 165 170 175

Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
 180 185 190

Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
 195 200 205

Phe Asn Arg Gly Glu Cys
 210

<210> SEQ ID NO 60

<211> LENGTH: 108

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Variable Light Chain Lc4

<400> SEQUENCE: 60

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
 20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Val Val Ala Pro Leu
 85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg

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100 105

<210> SEQ ID NO 61
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Variable Heavy Chain Hc4

<400> SEQUENCE: 61

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Glu Gln Met Gly Trp Gln Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Asp Ile Gly Gly Arg Ser Ala Phe Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> SEQ ID NO 62
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Variable Light Chain Lc5

<400> SEQUENCE: 62

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Val Val Ala Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> SEQ ID NO 63
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Variable Heavy Chain Hc5

<400> SEQUENCE: 63

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Glu Val Gln Leu Leu Glu Ser Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30
 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Ser Ile Glu Gln Met Gly Trp Gln Thr Tyr Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Lys Ser Pro Pro Tyr His Gly Gln Phe Asp Tyr Trp Gly Gln Gly
 100 105 110
 Thr Leu Val Thr Val Ser Ser
 115

<210> SEQ ID NO 64
 <211> LENGTH: 108
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Variable Light Chain Lc7

 <400> SEQUENCE: 64

 Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15
 Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
 20 25 30
 Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45
 Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80
 Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Val Val Ala Pro Leu
 85 90 95
 Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
 100 105

<210> SEQ ID NO 65
 <211> LENGTH: 119
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Variable Heavy Chain Hc7

 <400> SEQUENCE: 65

 Glu Val Gln Leu Leu Glu Ser Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30
 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Ser Ile Glu Gln Met Gly Trp Gln Thr Tyr Tyr Ala Asp Ser Val

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50	55	60
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Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr	65	70	75	80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys	85	90	95	
Ala Lys Ser Pro Pro Phe Phe Gly Gln Phe Asp Tyr Trp Gly Gln Gly	100	105	110	
Thr Leu Val Thr Val Ser Ser	115			

<210> SEQ ID NO 66

<211> LENGTH: 774

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: 4792 3463 AV1

<400> SEQUENCE: 66

caaggccagt ctggccagta tgggtctgc agtttggact atgtacacat attcatggat	60
tgccggctcga gccgggtggcag cgggtggctct ggtggctcag actggttata ctggcgtgg	120
attggccgtt ctgacatcca gatgactcag tctccttagct ccctgtccgc ctctgtgggg	180
gaccgagtc a ccatcacatg cagagccagc caggatattt ctatgttacct gaactggat	240
cacccagaagc ccggaaaagc acctaagctg ctgatctact atacccatcg gctgactct	300
ggcgtgccc a gtcgggttcag tggctcaggg agcggaaaccg acttcacttt taccatctca	360
agcctgcagc cagaggatata tggccacatac tattgtcagc agggcaatac actgccttac	420
acttttggcc aggggaccaa ggtggaaatc aaacgtacgg tggctgcacc atctgtcttc	480
atcttccgc catctgatga gcagttgaaa tctggaaactg cctctgtgt gtgcctgctg	540
aataacttct atcccagaga ggccaaatgtc cagtgaaagg tggataacgc cctccaaatcg	600
gttaactccc aggagagtgt cacagagcag gacagcaagg acagcaccta cagcctcagc	660
agcaccctga cgctgagcaa agcagactac gagaaacaca aagtctacgc ctgcgaagtc	720
acccatcagg gcctgagtc gcccgtcaca aagagttca acaggggaga gtgt	774

<210> SEQ ID NO 67

<211> LENGTH: 108

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Variable Light Chain Lc8

<400> SEQUENCE: 67

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly	1	5	10	15
---	---	---	----	----

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr	20	25	30
---	----	----	----

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile	35	40	45
---	----	----	----

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly	50	55	60
---	----	----	----

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro	65	70	75	80
---	----	----	----	----

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Val Val Ala Pro Leu		
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85

90

95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
 100 105

<210> SEQ ID NO 68

<211> LENGTH: 119

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Variable Heavy Chain Hc8

<400> SEQUENCE: 68

Glu Val Gln Leu Leu Glu Ser Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ser Ser Ile Glu Gln Met Gly Trp Gln Thr Tyr Tyr Ala Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Lys His Ile Gly Arg Thr Asn Pro Phe Asp Tyr Trp Gly Gln Gly
 100 105 110

Thr Leu Val Thr Val Ser Ser
 115

<210> SEQ ID NO 69

<211> LENGTH: 108

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Variable Light Chain Lc13

<400> SEQUENCE: 69

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
 20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Val Val Ala Pro Leu
 85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
 100 105

<210> SEQ ID NO 70

<211> LENGTH: 116

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

-continued

<223> OTHER INFORMATION: Variable Heavy Chain Hc13

<400> SEQUENCE: 70

Glu Val Gln Leu Leu Glu Ser Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Glu Gln Met Gly Trp Gln Thr Glu Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Ser Ala Ala Ala Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> SEQ ID NO 71

<211> LENGTH: 108

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Variable Light Chain Lc16

<400> SEQUENCE: 71

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Val Val Ala Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> SEQ ID NO 72

<211> LENGTH: 119

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Variable Heavy Chain Hc16

<400> SEQUENCE: 72

Glu Val Gln Leu Leu Glu Ser Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val

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35	40	45
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Ser Ser Ile Glu Gln Met Gly Trp Gln Thr Tyr Tyr Ala Asp Ser Val	50	55	60	
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr	65	70	75	80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys	85	90	95	
Ala Lys Ser Pro Pro Tyr Tyr Gly Gln Phe Asp Tyr Trp Gly Gln Gly	100	105	110	
Thr Leu Val Thr Val Ser Ser	115			

<210> SEQ ID NO 73

<211> LENGTH: 108

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Variable Light Chain Lc19

<400> SEQUENCE: 73

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly	1	5	10	15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr	20	25	30	
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile	35	40	45	
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly	50	55	60	
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro	65	70	75	80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Val Val Ala Pro Leu	85	90	95	
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg	100	105		

<210> SEQ ID NO 74

<211> LENGTH: 119

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Variable Heavy Chain Hc19

<400> SEQUENCE: 74

Glu Val Gln Leu Leu Glu Ser Gly Gly Leu Val Gln Pro Gly Gly	1	5	10	15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr	20	25	30	
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val	35	40	45	
Ser Ser Ile Glu Gln Met Gly Trp Gln Thr Tyr Tyr Ala Asp Ser Val	50	55	60	
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr	65	70	75	80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys	85	90	95	

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Ala Lys Ser Pro Pro Phe Phe Gly Gln Phe Asp Tyr Trp Gly Gln Gly
 100 105 110

Thr Leu Val Thr Val Ser Ser
 115

<210> SEQ ID NO 75
 <211> LENGTH: 108
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Variable Light Chain Lc21

<400> SEQUENCE: 75

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
 20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Val Val Ala Pro Leu
 85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
 100 105

<210> SEQ ID NO 76
 <211> LENGTH: 119
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Variable Heavy Chain Hc21

<400> SEQUENCE: 76

Glu Val Gln Leu Leu Glu Ser Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ser Ser Ile Glu Gln Met Gly Trp Gln Thr Tyr Tyr Ala Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Lys Asp Ile Gly Gly Arg Ser Ala Phe Asp Tyr Trp Gly Gln Gly
 100 105 110

Thr Leu Val Thr Val Ser Ser
 115

<210> SEQ ID NO 77
 <211> LENGTH: 108
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence

-continued

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Val Val Ala Pro Leu
 85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
 100 105

<210> SEQ ID NO 80

<211> LENGTH: 119

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Variable Heavy Chain Hc26

<400> SEQUENCE: 80

Glu Val Gln Leu Leu Glu Ser Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ser Ser Ile Glu Gln Met Gly Trp Gln Thr Tyr Tyr Ala Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Lys Asp Ile Gly Gly Arg Ser Ala Phe Asp Tyr Trp Gly Gln Gly
 100 105 110

Thr Leu Val Thr Val Ser Ser
 115

<210> SEQ ID NO 81

<211> LENGTH: 108

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Variable Light Chain Lc27

<400> SEQUENCE: 81

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
 20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Val Val Ala Pro Leu
 85 90 95

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Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> SEQ ID NO 82
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Variable Heavy Chain Hc27

<400> SEQUENCE: 82

Glu Val Gln Leu Leu Glu Ser Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Glu Gln Met Gly Trp Gln Thr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Ser Pro Pro Phe Tyr Gly Gln Phe Asp Tyr Trp Gly Gln Gly
100 105 110

Thr Leu Val Thr Val Ser Ser
115

<210> SEQ ID NO 83
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Variable Light Chain Lc28

<400> SEQUENCE: 83

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Val Val Ala Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> SEQ ID NO 84
<211> LENGTH: 119
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Variable Heavy Chain Hc28

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<400> SEQUENCE: 84

Glu Val Gln Leu Leu Glu Ser Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30
 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Ser Ile Glu Gln Met Gly Trp Gln Thr Tyr Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Lys Ser Pro Pro Phe Phe Gly Gln Phe Asp Tyr Trp Gly Gln Gly
 100 105 110
 Thr Leu Val Thr Val Ser Ser
 115

<210> SEQ ID NO 85

<211> LENGTH: 108

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Variable Light Chain Lc30

<400> SEQUENCE: 85

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15
 Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
 20 25 30
 Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45
 Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80
 Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Val Val Ala Pro Leu
 85 90 95
 Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
 100 105

<210> SEQ ID NO 86

<211> LENGTH: 115

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Variable Heavy Chain Hc30

<400> SEQUENCE: 86

Glu Val Gln Leu Leu Glu Ser Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30
 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

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Ser Ser Ile Glu Glu Met Gly Trp Gln Thr Leu Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Ala
 85 90 95
 Lys Ser Ala Ala Ala Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val Thr
 100 105 110
 Val Ser Ser
 115

<210> SEQ ID NO 87
 <211> LENGTH: 108
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Variable Light Chain Lc31

 <400> SEQUENCE: 87

 Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15
 Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
 20 25 30
 Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45
 Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60
 Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80
 Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Val Val Ala Pro Leu
 85 90 95
 Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
 100 105

<210> SEQ ID NO 88
 <211> LENGTH: 119
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Variable Heavy Chain Hc31

 <400> SEQUENCE: 88

 Glu Val Gln Leu Leu Glu Ser Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30
 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Ser Ile Glu Gln Met Gly Trp Gln Thr Tyr Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Lys Asp Ile Gly Gly Arg Ser Ala Phe Asp Tyr Trp Gly Gln Gly

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100 105 110

Thr Leu Val Thr Val Ser Ser
115

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<210> SEQ ID NO 89
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Variable Light Chain Lc32
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<400> SEQUENCE: 89

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
1					5					10					15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Val Val Ala Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> SEQ ID NO 90
<211> LENGTH: 116
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Variable Heavy Chain Hc32

<400> SEQUENCE: 90

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Asp Pro Glu Gly Trp Gln Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Ser Ala Ala Ala Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
 100 105 110

Thr Val Ser Ser

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<210> SEQ_ID NO 91
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<223> OTHER INFORMATION: Variable Light Chain Lc37

<400> SEQUENCE: 91

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
1															
															15
Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Ser	Ile	Ser	Ser	Tyr
															30
Leu	Asn	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile
															45
Tyr	Ala	Ala	Ser	Ser	Leu	Gln	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly
															60
Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
															80
Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Ser	Val	Val	Ala	Pro	Leu
															95
Thr	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys	Arg				
															105

<210> SEQ ID NO 92

<211> LENGTH: 119

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Variable Heavy Chain Hc37

<400> SEQUENCE: 92

Glu	Val	Gln	Leu	Leu	Glu	Ser	Gly	Gly	Gly	Leu	Val	Gln	Pro	Gly	Gly
1															
															15
Ser	Leu	Arg	Leu	Ser	Cys	Ala	Ala	Ser	Gly	Phe	Thr	Phe	Ser	Ser	Tyr
															30
Ala	Met	Ser	Trp	Val	Arg	Gln	Ala	Pro	Gly	Lys	Gly	Leu	Glu	Trp	Val
															45
Ser	Ser	Ile	Glu	Gln	Met	Gly	Trp	Gln	Thr	Tyr	Tyr	Ala	Asp	Ser	Val
															60
Lys	Gly	Arg	Phe	Thr	Ile	Ser	Arg	Asp	Asn	Ser	Lys	Asn	Thr	Leu	Tyr
															80
Leu	Gln	Met	Asn	Ser	Leu	Arg	Ala	Glu	Asp	Thr	Ala	Val	Tyr	Tyr	Cys
															95
Ala	Lys	Ser	Pro	Pro	His	Asn	Gly	Gln	Phe	Asp	Tyr	Trp	Gly	Gln	Gly
															110
Thr	Leu	Val	Thr	Val	Ser	Ser									
															115

<210> SEQ ID NO 93

<211> LENGTH: 108

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Variable Light Chain Lc39

<400> SEQUENCE: 93

Asp	Ile	Gln	Met	Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly
1															
															15
Asp	Arg	Val	Thr	Ile	Thr	Cys	Arg	Ala	Ser	Gln	Ser	Ile	Ser	Ser	Tyr
															30
Leu	Asn	Trp	Tyr	Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Leu	Ile

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35	40	45
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Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly	50	55	60	
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro	65	70	75	80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Val Val Ala Pro Leu	85	90	95	
Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg	100	105		

<210> SEQ ID NO 94

<211> LENGTH: 116

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Variable Heavy Chain Hc39

<400> SEQUENCE: 94

Glu Val Gln Leu Leu Glu Ser Gly Gly Leu Val Gln Pro Gly Gly	1	5	10	15
Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr	20	25	30	
Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val	35	40	45	
Ser Ser Ile Glu Gln Met Gly Trp Gln Thr Glu Tyr Ala Asp Ser Val	50	55	60	
Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr	65	70	75	80
Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys	85	90	95	
Ala Lys Ser Ala Ala Ala Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val	100	105	110	
Thr Val Ser Ser				
	115			

<210> SEQ ID NO 95

<211> LENGTH: 108

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Variable Light Chain Lc40

<400> SEQUENCE: 95

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly	1	5	10	15
Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr	20	25	30	
Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile	35	40	45	
Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly	50	55	60	
Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro	65	70	75	80
Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Val Val Ala Pro Leu	85	90	95	

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Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
 100 105

<210> SEQ ID NO 96
 <211> LENGTH: 119
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Heavy Chain Hc40

<400> SEQUENCE: 96

Glu Val Gln Leu Leu Glu Ser Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ser Ser Ile Glu Gln Met Gly Trp Gln Thr Tyr Tyr Ala Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Lys Ser Pro Pro Phe Phe Gly Gln Phe Asp Tyr Trp Gly Gln Gly
 100 105 110

Thr Leu Val Thr Val Ser Ser
 115

<210> SEQ ID NO 97
 <211> LENGTH: 108
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Variable Light Chain Lc47

<400> SEQUENCE: 97

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
 20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Val Val Ala Pro Leu
 85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
 100 105

<210> SEQ ID NO 98
 <211> LENGTH: 116
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Variable Heavy Chain Hc47

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<400> SEQUENCE: 98

Glu Val Gln Leu Leu Glu Ser Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ser Ser Ile Asp Glu Met Gly Trp Gln Thr Glu Tyr Ala Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Lys Ser Ala Ala Ala Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
 100 105 110

Thr Val Ser Ser
 115

<210> SEQ ID NO 99

<211> LENGTH: 108

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Variable 4B2 Light Chain

<400> SEQUENCE: 99

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
 20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Thr Leu Asp Ala Pro Pro
 85 90 95

Gln Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
 100 105

<210> SEQ ID NO 100

<211> LENGTH: 119

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Variable 4B2 Heavy Chain

<400> SEQUENCE: 100

Glu Val Gln Leu Leu Glu Ser Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

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Ser Ser Ile Glu Gln Met Gly Trp Gln Thr Tyr Tyr Ala Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Lys Asp Ile Gly Gly Arg Ser Ala Phe Asp Tyr Trp Gly Gln Gly
 100 105 110

Thr Leu Val Thr Val Ser Ser
 115

<210> SEQ ID NO 101

<211> LENGTH: 108

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Variable 4D11 Light Chain

<400> SEQUENCE: 101

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
 20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Thr Val Val Ala Pro Pro
 85 90 95

Leu Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
 100 105

<210> SEQ ID NO 102

<211> LENGTH: 119

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Variable 4D11 Heavy Chain

<400> SEQUENCE: 102

Glu Val Gln Leu Leu Glu Ser Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ser Ser Ile Asp Pro Glu Gly Arg Gln Thr Tyr Tyr Ala Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Lys Asp Ile Gly Gly Arg Ser Ala Phe Asp Tyr Trp Gly Gln Gly
 100 105 110

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Thr Leu Val Thr Val Ser Ser
115

<210> SEQ ID NO 103
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Variable 4E7 Light Chain

<400> SEQUENCE: 103

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ser Leu Val Ala Pro Leu
85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100 105

<210> SEQ ID NO 104

<211> LENGTH: 116
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Variable 4E7 Heavy Chain

<400> SEQUENCE: 104

Glu Val Gln Leu Leu Glu Ser Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Glu Glu Met Gly Trp Gln Thr Lys Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Ser Ala Ala Ala Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> SEQ ID NO 105

<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Variable 4E11 Light Chain

-continued

<400> SEQUENCE: 105

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1           5           10           15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
20          25          30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35          40          45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50          55          60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65          70          75          80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Leu Asp Ala Pro Leu
85          90          95

Met Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
100         105

```

<210> SEQ ID NO 106

<211> LENGTH: 119

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Variable 4E11 Heavy Chain

<400> SEQUENCE: 106

```

Glu Val Gln Leu Leu Glu Ser Gly Gly Leu Val Gln Pro Gly Gly
1           5           10           15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20          25          30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35          40          45

Ser Ser Ile Glu Pro Met Gly Gln Leu Thr Glu Tyr Ala Asp Ser Val
50          55          60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65          70          75          80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85          90          95

Ala Lys Asp Ile Gly Gly Arg Ser Ala Phe Asp Tyr Trp Gly Gln Gly
100         105         110

Thr Leu Val Thr Val Ser Ser
115

```

<210> SEQ ID NO 107

<211> LENGTH: 108

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: Variable 6B7 Light Chain

<400> SEQUENCE: 107

```

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1           5           10           15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
20          25          30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35          40          45

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-continued

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Leu Val Ala Pro Leu
 85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg
 100 105

<210> SEQ ID NO 108
 <211> LENGTH: 116
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Variable 6B7 Heavy Chain

<400> SEQUENCE: 108

Glu Val Gln Leu Leu Glu Ser Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ser Ser Ile Asp Glu Met Gly Trp Gln Thr Tyr Tyr Ala Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Lys Ser Ala Ala Ala Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
 100 105 110

Thr Val Ser Ser
 115

<210> SEQ ID NO 109
 <211> LENGTH: 108
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: Variable 6F8 Light Chain

<400> SEQUENCE: 109

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
 1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
 20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
 35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
 50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
 65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Ala Leu Val Ala Pro Leu
 85 90 95

Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg

-continued

100 105

<210> SEQ ID NO 110
<211> LENGTH: 116
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Variable 6F8 Heavy Chain
<400> SEQUENCE: 110

Glu Val Gln Leu Leu Glu Ser Gly Gly Gly Leu Val Gln Pro Gly Gly
1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
35 40 45

Ser Ser Ile Asp Glu Met Gly Trp Gln Thr Tyr Tyr Ala Asp Ser Val
50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
85 90 95

Ala Lys Ser Ala Ala Ala Phe Asp Tyr Trp Gly Gln Gly Thr Leu Val
100 105 110

Thr Val Ser Ser
115

<210> SEQ ID NO 111
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 4D11 Light Chain
<400> SEQUENCE: 111

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly
50 55 60

Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Ser Leu Gln Pro
65 70 75 80

Glu Asp Phe Ala Thr Tyr Tyr Cys Gln Gln Thr Val Val Ala Pro Pro
85 90 95

Leu Phe Gly Gln Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala
100 105 110

Pro Ser Val Phe Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly
115 120 125

Thr Ala Ser Val Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala
130 135 140

Lys Val Gln Trp Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln
145 150 155 160

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Glu Ser Val Thr Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser
 165 170 175
 Ser Thr Leu Thr Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr
 180 185 190
 Ala Cys Glu Val Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser
 195 200 205
 Phe Asn Arg Gly Glu Cys
 210

<210> SEQ ID NO 112
 <211> LENGTH: 449
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: 4D11 Heavy Chain

 <400> SEQUENCE: 112

 Glu Val Gln Leu Leu Glu Ser Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15
 Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30
 Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45
 Ser Ser Ile Asp Pro Glu Gly Arg Gln Thr Tyr Tyr Ala Asp Ser Val
 50 55 60
 Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80
 Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95
 Ala Lys Asp Ile Gly Gly Arg Ser Ala Phe Asp Tyr Trp Gly Gln Gly
 100 105 110
 Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
 115 120 125
 Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
 130 135 140
 Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
 145 150 155 160
 Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
 165 170 175
 Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser
 180 185 190
 Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro
 195 200 205
 Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys
 210 215 220
 Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro
 225 230 235 240
 Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser
 245 250 255
 Arg Thr Pro Glu Val Thr Cys Val Val Asp Val Ser His Glu Asp
 260 265 270
 Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn
 275 280 285

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Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val
 290 295 300
 Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu
 305 310 315 320
 Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys
 325 330 335
 Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr
 340 345 350
 Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr
 355 360 365
 Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu
 370 375 380
 Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu
 385 390 395 400
 Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys
 405 410 415
 Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu
 420 425 430
 Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly
 435 440 445
 Lys

<210> SEQ ID NO 113
 <211> LENGTH: 449
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: 4D11v2 Heavy Chain

<400> SEQUENCE: 113

Glu Val His Leu Leu Glu Ser Gly Gly Leu Val Gln Pro Gly Gly
 1 5 10 15

Ser Leu Arg Leu Ser Cys Ala Ala Ser Gly Phe Thr Phe Ser Ser Tyr
 20 25 30

Ala Met Ser Trp Val Arg Gln Ala Pro Gly Lys Gly Leu Glu Trp Val
 35 40 45

Ser Ser Ile Asp Pro Glu Gly Arg Gln Thr Tyr Tyr Ala Asp Ser Val
 50 55 60

Lys Gly Arg Phe Thr Ile Ser Arg Asp Asn Ser Lys Asn Thr Leu Tyr
 65 70 75 80

Leu Gln Met Asn Ser Leu Arg Ala Glu Asp Thr Ala Val Tyr Tyr Cys
 85 90 95

Ala Lys Asp Ile Gly Gly Arg Ser Ala Phe Asp Tyr Trp Gly Gln Gly
 100 105 110

Thr Leu Val Thr Val Ser Ser Ala Ser Thr Lys Gly Pro Ser Val Phe
 115 120 125

Pro Leu Ala Pro Ser Ser Lys Ser Thr Ser Gly Gly Thr Ala Ala Leu
 130 135 140

Gly Cys Leu Val Lys Asp Tyr Phe Pro Glu Pro Val Thr Val Ser Trp
 145 150 155 160

Asn Ser Gly Ala Leu Thr Ser Gly Val His Thr Phe Pro Ala Val Leu
 165 170 175

Gln Ser Ser Gly Leu Tyr Ser Leu Ser Ser Val Val Thr Val Pro Ser

-continued

180	185	190
Ser Ser Leu Gly Thr Gln Thr Tyr Ile Cys Asn Val Asn His Lys Pro		
195	200	205
Ser Asn Thr Lys Val Asp Lys Lys Val Glu Pro Lys Ser Cys Asp Lys		
210	215	220
Thr His Thr Cys Pro Pro Cys Pro Ala Pro Glu Leu Leu Gly Gly Pro		
225	230	235
Ser Val Phe Leu Phe Pro Pro Lys Pro Lys Asp Thr Leu Met Ile Ser		
245	250	255
Arg Thr Pro Glu Val Thr Cys Val Val Asp Val Ser His Glu Asp		
260	265	270
Pro Glu Val Lys Phe Asn Trp Tyr Val Asp Gly Val Glu Val His Asn		
275	280	285
Ala Lys Thr Lys Pro Arg Glu Glu Gln Tyr Asn Ser Thr Tyr Arg Val		
290	295	300
Val Ser Val Leu Thr Val Leu His Gln Asp Trp Leu Asn Gly Lys Glu		
305	310	315
Tyr Lys Cys Lys Val Ser Asn Lys Ala Leu Pro Ala Pro Ile Glu Lys		
325	330	335
Thr Ile Ser Lys Ala Lys Gly Gln Pro Arg Glu Pro Gln Val Tyr Thr		
340	345	350
Leu Pro Pro Ser Arg Glu Glu Met Thr Lys Asn Gln Val Ser Leu Thr		
355	360	365
Cys Leu Val Lys Gly Phe Tyr Pro Ser Asp Ile Ala Val Glu Trp Glu		
370	375	380
Ser Asn Gly Gln Pro Glu Asn Asn Tyr Lys Thr Thr Pro Pro Val Leu		
385	390	395
Asp Ser Asp Gly Ser Phe Phe Leu Tyr Ser Lys Leu Thr Val Asp Lys		
405	410	415
Ser Arg Trp Gln Gln Gly Asn Val Phe Ser Cys Ser Val Met His Glu		
420	425	430
Ala Leu His Asn His Tyr Thr Gln Lys Ser Leu Ser Leu Ser Pro Gly		
435	440	445

Lys

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<210> SEQ_ID NO 114
<211> LENGTH: 214
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER_INFORMATION: 4D11v2 Light Chain
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (182)..(182)
<223> OTHER_INFORMATION: Xaa may be any amino acid

<400> SEQUENCE: 114

Asp Ile Gln Met Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly
1 5 10 15

Asp Arg Val Thr Ile Thr Cys Arg Ala Ser Gln Ser Ile Ser Ser Tyr
20 25 30

Leu Asn Trp Tyr Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile
35 40 45

Tyr Ala Ala Ser Ser Leu Gln Ser Gly Val Pro Ser Arg Phe Ser Gly

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50	55	60													
Ser	Gly	Ser	Gly	Thr	Asp	Phe	Thr	Leu	Thr	Ile	Ser	Ser	Leu	Gln	Pro
65				70			75			80					
Glu	Asp	Phe	Ala	Thr	Tyr	Tyr	Cys	Gln	Gln	Thr	Val	Val	Ala	Pro	Pro
	85				90					95					
Leu	Phe	Gly	Gln	Gly	Thr	Lys	Val	Glu	Ile	Lys	Arg	Thr	Val	Ala	Ala
	100				105				110						
Pro	Ser	Val	Phe	Ile	Phe	Pro	Pro	Ser	Asp	Glu	Gln	Leu	Lys	Ser	Gly
	115				120				125						
Thr	Ala	Ser	Val	Val	Cys	Leu	Leu	Asn	Asn	Phe	Tyr	Pro	Arg	Glu	Ala
	130				135				140						
Lys	Val	Gln	Trp	Lys	Val	Asp	Asn	Ala	Leu	Gln	Ser	Gly	Asn	Ser	Gln
	145				150				155			160			
Glu	Ser	Val	Thr	Glu	Gln	Asp	Ser	Lys	Asp	Ser	Thr	Tyr	Ser	Leu	Ser
	165				170				175						
Ser	Thr	Leu	Thr	Leu	Xaa	Lys	Ala	Asp	Tyr	Glu	Lys	His	Lys	Val	Tyr
	180				185				190						
Ala	Cys	Glu	Val	Thr	His	Gln	Gly	Leu	Ser	Ser	Pro	Val	Thr	Lys	Ser
	195				200				205						
Phe	Asn	Arg	Gly	Glu	Cys										
	210														

<210> SEQ ID NO 115																
<211> LENGTH: 258																
<212> TYPE: PRT																
<213> ORGANISM: Artificial Sequence																
<220> FEATURE:																
<223> OTHER INFORMATION: 4792 10419 AV1																
<400> SEQUENCE: 115																
Gln	Gly	Gln	Ser	Gly	Gln	Tyr	Gly	Ser	Cys	Ser	Trp	Asn	Tyr	Val	His	
1					5				10			15				
Ile	Phe	Met	Asp	Cys	Gly	Ser	Ser	Gly	Gly	Ser	Gly	Gly	Ser	Gly	Gly	
	20				25				30							
Ser	Gly	Ile	Ser	Ser	Gly	Leu	Ser	Ser	Gly	Gly	Ser	Asp	Ile	Gln	Met	
	35				40				45							
Thr	Gln	Ser	Pro	Ser	Ser	Leu	Ser	Ala	Ser	Val	Gly	Asp	Arg	Val	Thr	
	50				55				60							
Ile	Thr	Cys	Arg	Ala	Ser	Gln	Asp	Ile	Ser	Ser	Tyr	Leu	Asn	Trp	Tyr	
	65				70				75			80				
Gln	Gln	Lys	Pro	Gly	Lys	Ala	Pro	Lys	Leu	Ile	Tyr	Tyr	Thr	Ser		
	85				90				95							
Arg	Leu	His	Ser	Gly	Val	Pro	Ser	Arg	Phe	Ser	Gly	Ser	Gly			
	100				105				110							
Thr	Asp	Phe	Thr	Phe	Thr	Ile	Ser	Ser	Leu	Gln	Pro	Glu	Asp	Ile	Ala	
	115				120				125							
Thr	Tyr	Tyr	Cys	Gln	Gln	Gly	Asn	Thr	Leu	Pro	Tyr	Thr	Phe	Gly	Gln	
	130				135				140							
Gly	Thr	Lys	Val	Glu	Ile	Lys	Arg	Thr	Val	Ala	Ala	Pro	Ser	Val	Phe	
	145				150				155			160				
Ile	Phe	Pro	Pro	Ser	Asp	Glu	Gln	Leu	Lys	Ser	Gly	Thr	Ala	Ser	Val	
	165				170				175							
Val	Cys	Leu	Leu	Asn	Asn	Phe	Tyr	Pro	Arg	Glu	Ala	Lys	Val	Gln	Trp	

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180	185	190
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Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr	195	200	205
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Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr	210	215	220
---	-----	-----	-----

Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val	225	230	235	240
---	-----	-----	-----	-----

Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly	245	250	255
---	-----	-----	-----

Glu Cys

<210> SEQ ID NO 116

<211> LENGTH: 774

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: 4792 10419 AV1

<400> SEQUENCE: 116

caaggccagt ctggccagta tgggtctgc agttggact atgtacacat attcatggat	60
tgccggctcga gcgggtggcag cgggtggctct ggtggctcag gtatttagtag tggctttagc	120
agtggcggtt ctgacatcca gatgactcag ttccttagct ccctgtccgc ctctgtgggg	180
gaccgagtc acatcacatc cagagccagc caggatattt ctgttacctt gaactggat	240
cagcagaagc ccggaaaagc acctaagctg ctgtatctact atacctccag gctgactct	300
ggcgtgccc gtcgggttcag tggctcaggg agcggaaaccg acttcacttt taccatctca	360
agcctgcagc cagaggatat tgccacatac tattgtcagc agggcaatac actgcctac	420
actttggcc aggggaccaa ggtggaaatc aaacgtacgg tggctgcacc atctgtttc	480
atcttcccgc catctgatga gcagttgaaa tctggaaactg cctctgtgt gtgcctgctg	540
aataacttct atcccagaga ggc当地aaatc cagtgaaagg tggataacgc cctccaatcg	600
gtaactccc aggagagtgt cacagagcag gacagcaagg acagcaccta cagcctcagc	660
agcacccctga cgctgagcaa agcagactac gagaaacaca aagtctacgc ctgcgaagtc	720
acccatcagg gcctgagtc gcccgtcaca aagagttca acaggggaga gtgt	774

<210> SEQ ID NO 117

<211> LENGTH: 258

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: 4792 559 AV1

<400> SEQUENCE: 117

Gln Gly Gln Ser Gly Gln Tyr Gly Ser Cys Ser Trp Asn Tyr Val His	1	5	10	15
---	---	---	----	----

Ile Phe Met Asp Cys Gly Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly	20	25	30
---	----	----	----

Ser Gln Asn Gln Ala Leu Arg Met Ala Gly Gly Ser Asp Ile Gln Met	35	40	45
---	----	----	----

Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr	50	55	60
---	----	----	----

Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Ser Tyr Leu Asn Trp Tyr	65	70	75	80
---	----	----	----	----

-continued

Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Tyr Thr Ser
85 90 95

Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly
100 105 110

Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro Glu Asp Ile Ala
115 120 125

Thr Tyr Tyr Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gln
130 135 140

Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe
145 150 155 160

Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val
165 170 175

Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp
180 185 190

Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr
195 200 205

Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr
210 215 220

Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val
225 230 235 240

Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly
245 250 255

Glu Cys

<210> SEQ ID NO 118

<211> LENGTH: 774

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: 4792 559 AV1

<400> SEQUENCE: 118

caaggccagt ctggccagta tgggtcctgc agttggaact atgtacacat attcatggat	60
tgcggctcga gcggtggcag cgggtggctct ggtggctcac agaatcaggc attaegtatg	120
gcaggcggtt ctgacatcca gatgactcag tctcctagct ccctgtccgc ctctgtgggg	180
gaccgagtc acatcacatg cagagccagc caggatattt ctgttacct gaactggat	240
cagcagaagc ccggaaaagc acctaagctg ctgatctact atacctccag gctgcactct	300
ggcgtgcca gtcggttcag tggctcaggg agcggAACCG acttcacttt taccatctca	360
agcctgcagc cagaggatat tgcacatac tattgtcagc agggcaatac actgccttac	420
acttttggcc aggggaccaa ggtggaaatc aaacgtacgg tggctgcacc atctgtttc	480
atcttcccgc catctgatga gcagttgaaa tctggaaactg cctctgttgcgtc	540
aataacttct atcccagaga ggccaaagta cagtggaaagg tggataacgc cctccaatcg	600
ggtaactccc aggagagtgt cacagagcag gacagcaagg acagcaccta cagcctcagc	660
agcacccctga cgctgagca agcagactac gagaaacaca aagtctacgc ctgcgaagtc	720
acccatcagg gcctgagtc gcccgtcaca aagagttca acaggggaga gtgt	774

<210> SEQ ID NO 119

<211> LENGTH: 258

<212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: 4792 601 AV1

 <400> SEQUENCE: 119

 Gln Gly Gln Ser Gly Gln Tyr Gly Ser Cys Ser Trp Asn Tyr Val His
 1 5 10 15

 Ile Phe Met Asp Cys Gly Ser Ser Gly Gly Ser Gly Gly
 20 25 30

 Ser Ala Gln Asn Leu Leu Gly Met Val Gly Gly Ser Asp Ile Gln Met
 35 40 45

 Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr
 50 55 60

 Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Ser Tyr Leu Asn Trp Tyr
 65 70 75 80

 Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Tyr Thr Ser
 85 90 95

 Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly
 100 105 110

 Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro Glu Asp Ile Ala
 115 120 125

 Thr Tyr Tyr Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gln
 130 135 140

 Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe
 145 150 155 160

 Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val
 165 170 175

 Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp
 180 185 190

 Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr
 195 200 205

 Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr
 210 215 220

 Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val
 225 230 235 240

 Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly
 245 250 255

 Glu Cys

<210> SEQ ID NO 120
 <211> LENGTH: 774
 <212> TYPE: DNA
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: 4792 601 AV1

 <400> SEQUENCE: 120

 caaggccagt ctggccagta tgggtcctgc agtttggaaact atgtacacat attcatggat 60

 tgccggctcga gcggtggcag cggtggctct ggtggctcag cacagaatct gtttaggtatg 120

 gttaggggtt ctgacatcca gatgactcag tctccttagct ccctgtccgc ctctgtgggg 180

 gaccgagtc a ccatcacatg cagagccagc caggatattt ctatgttacct gaacttggat 240

 cagcagaagc cccgaaaagc acctaagctg ctgtatctact atacacctccag gctgcactct 300

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<210> SEQ ID NO 121

<211> LENGTH: 258

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<219> ORIGIN:

<223> OTHER INFORMATION: 4792 3457 AV1

<400> SEQUENCE: 121

Gln Gly Gln Ser Gly Gln Tyr Gly Ser Cys Ser Trp Asn Tyr Val His
1 5 10 15

Ile Phe Met Asp Cys Gly Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly
20 25 30

Ser Ser Thr Phe Pro Phe Gly Met Phe Gly Gly Ser Asp Ile Gln Met
 35 40 45

Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr
50 55 60

Ile	Thr	Cys	Arg	Ala	Ser	Gln	Asp	Ile	Ser	Ser	Tyr	Leu	Asn	Trp	Tyr
65					70					75					80

Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Tyr Thr Ser
 85 90 95

Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly Ser Gly
100 105 110

Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro Glu Asp Ile Ala
115 120 125

130 135 140
 Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe

Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val

Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp
 180 185 190

Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr
195 200 205

Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr
210 215 220

Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val
225 230 235 240

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<210> SEQ ID NO 122
<211> LENGTH: 774
<212> TYPE: DNA
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 4792 3457 AV1

<400> SEQUENCE: 122

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caaggccagt ctggccagta tgggtcctgc agtttggact atgtacacat attcatggat      60
tgcggctcga cgccgtggcag cgggtggctct ggtggctcaa gtacattcc attcggtatg     120
ttcggcggtt ctgacatcca gatgactca gatgtttttt ccctgtccgc ctctgtgggg     180
gaccgagtca ccatcacatg cagagccagc caggatattt ctgtttttt gaaactggat      240
cagcagaagc ccggaaaagc acctaagctg ctgtttttt atacccatccag gctgcactct     300
ggcgtgccc gtcgggttcag tggctcaggag agcggaaaccg acttcacttt taccatctca     360
agcctgcagc cagaggatat tgccacatac tattgtcagc agggcaatac actgccttac     420
acttttggcc aggggaccaa ggtggaaatc aaacgtacgg tggctgcacc atctgtttc     480
atcttccgc catctgatga gcagttgaaa ttgtttttt cctctgttgt gtgcctgttg     540
aataacttct atccccagaga ggccaaagta cagttttttt tggataacgc cctccaaatcg     600
ggtaactccc aggagagtgt cacagagcag gacagcaagg acagcaccta cagcctcagc     660
agcaccctga cgctgagcaa agcagactac gagaacacaca aagtctacgc ctgcgaagtc     720
acccatcagg gcctgagtc gcccgtcaca aagagttca acaggggaga gtgt      774
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<210> SEQ ID NO 123
<211> LENGTH: 258
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: 4792 3458 AV1

<400> SEQUENCE: 123

```
Gln Gly Gln Ser Gly Gln Tyr Gly Ser Cys Ser Trp Asn Tyr Val His
1           5           10          15

Ile Phe Met Asp Cys Gly Ser Ser Gly Gly Ser Gly Ser Gly Gly
20          25          30

Ser Pro Val Gly Tyr Thr Ser Ser Leu Gly Gly Ser Asp Ile Gln Met
35          40          45

Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr
50          55          60

Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Ser Tyr Leu Asn Trp Tyr
65          70          75          80

Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Tyr Thr Ser
85          90          95

Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly
100         105         110

Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro Glu Asp Ile Ala
115         120         125

Thr Tyr Tyr Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gln
130         135         140

Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe
145         150         155         160
```

-continued

Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val
165 170 175

Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp
180 185 190

Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr
195 200 205

Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr
210 215 220

Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val
225 230 235 240

Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly
245 250 255

Glu Cys

<210> SEQ ID NO 124

<211> LENGTH: 774

<212> TYPE: DNA

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: 4792 3458 AV1

<400> SEQUENCE: 124

caaggccagt ctggccagta tgggtcctgc agtttgaact atgtacacat attcatggat 60
tgcggctcga gcggtggcag cgggtggctct ggtggctcac ctgttggata tacggatgt 120
ctggggcggtt ctgacatcca gatgactcag tctccttagct ccctgtccgc ctctgtgggg 180
gaccgagtc a ccatcacatc cagagccagc caggatattt ctgttacctt gaactggat 240
cagcagaagc ccggaaaagc acctaagctg ctgatctact atacccatcg gctgcactct 300
ggcggtgcca gtcgggttcag tggctcaggc agcggaaacccg acttcacttt taccatctca 360
agcctgcagc cagaggatat tgccacatac tattgtcagc agggcaatac actgcctac 420
acttttggcc aggggaccaa ggtggaaatc aaacgtacgg tggctgcacc atctgtttc 480
atcttcccgcc catctgatga gcagttgaaa tcttggactt cctctgttgt gtgcctgt 540
aataacttct atcccagaga ggccaaagta cagttggagg tggataacgc cctccaaatcg 600
ggtaactccc aggagagtgt cacagagcag gacagcaagg acagcaccta cagcctcagc 660
agcacccctga cgctgagcaa agcagactac gagaaacaca aagtctacgc ctgcgaagtc 720
acccatcagg gcctgagtc gcccgtcaca aagagcttca acaggggaga gtgt 774

<210> SEQ ID NO 125

<211> LENGTH: 258

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: 4792 3463 AV1

<400> SEQUENCE: 125

Gln Gly Gln Ser Gly Gln Tyr Gly Ser Cys Ser Trp Asn Tyr Val His
1 5 10 15

Ile Phe Met Asp Cys Gly Ser Ser Gly Gly Ser Gly Ser Gly Gly
20 25 30

Ser Asp Trp Leu Tyr Trp Pro Gly Ile Gly Gly Ser Asp Ile Gln Met
35 40 45

Thr Gln Ser Pro Ser Ser Leu Ser Ala Ser Val Gly Asp Arg Val Thr

-continued

50	55	60
Ile Thr Cys Arg Ala Ser Gln Asp Ile Ser Ser Tyr Leu Asn Trp Tyr		
65	70	75
Gln Gln Lys Pro Gly Lys Ala Pro Lys Leu Leu Ile Tyr Tyr Thr Ser		
85	90	95
Arg Leu His Ser Gly Val Pro Ser Arg Phe Ser Gly Ser Gly		
100	105	110
Thr Asp Phe Thr Phe Thr Ile Ser Ser Leu Gln Pro Glu Asp Ile Ala		
115	120	125
Thr Tyr Tyr Cys Gln Gln Gly Asn Thr Leu Pro Tyr Thr Phe Gly Gln		
130	135	140
Gly Thr Lys Val Glu Ile Lys Arg Thr Val Ala Ala Pro Ser Val Phe		
145	150	155
Ile Phe Pro Pro Ser Asp Glu Gln Leu Lys Ser Gly Thr Ala Ser Val		
165	170	175
Val Cys Leu Leu Asn Asn Phe Tyr Pro Arg Glu Ala Lys Val Gln Trp		
180	185	190
Lys Val Asp Asn Ala Leu Gln Ser Gly Asn Ser Gln Glu Ser Val Thr		
195	200	205
Glu Gln Asp Ser Lys Asp Ser Thr Tyr Ser Leu Ser Ser Thr Leu Thr		
210	215	220
Leu Ser Lys Ala Asp Tyr Glu Lys His Lys Val Tyr Ala Cys Glu Val		
225	230	235
Thr His Gln Gly Leu Ser Ser Pro Val Thr Lys Ser Phe Asn Arg Gly		
245	250	255
Glu Cys		

<210> SEQ ID NO 126
 <211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 126

Ser Ala Gly Phe Ser Leu Pro Ala
1 5

<210> SEQ ID NO 127
 <211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: cleavable linker sequence

<400> SEQUENCE: 127

Pro Arg Phe Lys Ile Ile Gly Gly
1 5

<210> SEQ ID NO 128
 <211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: cleavable linker sequence

<400> SEQUENCE: 128

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Pro Arg Phe Arg Ile Ile Gly Gly
1 5

<210> SEQ ID NO 129
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable linker sequence

<400> SEQUENCE: 129

Ser Ser Arg His Arg Arg Ala Leu Asp
1 5

<210> SEQ ID NO 130
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable linker sequence

<400> SEQUENCE: 130

Arg Lys Ser Ser Ile Ile Ile Arg Met Arg Asp Val Val Leu
1 5 10

<210> SEQ ID NO 131
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable linker sequence

<400> SEQUENCE: 131

Ser Ser Ser Phe Asp Lys Gly Lys Tyr Lys Lys Gly Asp Asp Ala
1 5 10 15

<210> SEQ ID NO 132
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable linker sequence

<400> SEQUENCE: 132

Ser Ser Ser Phe Asp Lys Gly Lys Tyr Lys Arg Gly Asp Asp Ala
1 5 10 15

<210> SEQ ID NO 133
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable linker sequence

<400> SEQUENCE: 133

Ile Glu Gly Arg
1

<210> SEQ ID NO 134
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable linker sequence

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<400> SEQUENCE: 134

Ile Asp Gly Arg
1

<210> SEQ ID NO 135
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable linker sequence

<400> SEQUENCE: 135

Gly Gly Ser Ile Asp Gly Arg
1 5

<210> SEQ ID NO 136
<211> LENGTH: 6
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable linker sequence

<400> SEQUENCE: 136

Pro Leu Gly Leu Trp Ala
1 5

<210> SEQ ID NO 137
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable linker sequence

<400> SEQUENCE: 137

Gly Pro Gln Gly Ile Ala Gly Gln
1 5

<210> SEQ ID NO 138
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable linker sequence

<400> SEQUENCE: 138

Gly Pro Gln Gly Leu Leu Gly Ala
1 5

<210> SEQ ID NO 139
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable linker sequence

<400> SEQUENCE: 139

Gly Ile Ala Gly Gln
1 5

<210> SEQ ID NO 140
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: cleavable linker sequence

<400> SEQUENCE: 140

Gly Pro Leu Gly Ile Ala Gly Ile
1 5

<210> SEQ ID NO 141

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: cleavable linker sequence

<400> SEQUENCE: 141

Gly Pro Glu Gly Leu Arg Val Gly
1 5

<210> SEQ ID NO 142

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: cleavable linker sequence

<400> SEQUENCE: 142

Tyr Gly Ala Gly Leu Gly Val Val
1 5

<210> SEQ ID NO 143

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: cleavable linker sequence

<400> SEQUENCE: 143

Ala Gly Leu Gly Val Val Glu Arg
1 5

<210> SEQ ID NO 144

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: cleavable linker sequence

<400> SEQUENCE: 144

Ala Gly Leu Gly Ile Ser Ser Thr
1 5

<210> SEQ ID NO 145

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: cleavable linker sequence

<400> SEQUENCE: 145

Glu Pro Gln Ala Leu Ala Met Ser
1 5

<210> SEQ ID NO 146

<211> LENGTH: 8

<212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable linker sequence

<400> SEQUENCE: 146

Gln Ala Leu Ala Met Ser Ala Ile
1 5

<210> SEQ ID NO 147

<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable linker sequence

<400> SEQUENCE: 147

Ala Ala Tyr His Leu Val Ser Gln
1 5

<210> SEQ ID NO 148

<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable linker sequence

<400> SEQUENCE: 148

Met Asp Ala Phe Leu Glu Ser Ser
1 5

<210> SEQ ID NO 149

<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable linker sequence

<400> SEQUENCE: 149

Glu Ser Leu Pro Val Val Ala Val
1 5

<210> SEQ ID NO 150

<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable linker sequence

<400> SEQUENCE: 150

Ser Ala Pro Ala Val Glu Ser Glu
1 5

<210> SEQ ID NO 151

<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable linker sequence

<400> SEQUENCE: 151

Asp Val Ala Gln Phe Val Leu Thr
1 5

<210> SEQ ID NO 152

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<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable linker sequence

<400> SEQUENCE: 152

Val Ala Gln Phe Val Leu Thr Glu
1 5

<210> SEQ ID NO 153
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable linker sequence

<400> SEQUENCE: 153

Ala Gln Phe Val Leu Thr Glu Gly
1 5

<210> SEQ ID NO 154
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable linker sequence

<400> SEQUENCE: 154

Pro Val Gln Pro Ile Gly Pro Gln
1 5

<210> SEQ ID NO 155
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: linking peptide

<400> SEQUENCE: 155

Gly Ser Ser Gly Gly Ser Gly Gly Ser Gly Gly Gly Ser
1 5 10 15

<210> SEQ ID NO 156
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: linking peptide

<400> SEQUENCE: 156

Gly Ser Ser Gly Gly Ser Gly Gly Ser Gly
1 5 10

<210> SEQ ID NO 157
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: linking peptide

<400> SEQUENCE: 157

Gly Ser Ser Gly Gly Ser Gly Gly Ser Gly Ser
1 5 10

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<210> SEQ ID NO 158
<211> LENGTH: 4
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: linking peptide

<400> SEQUENCE: 158

Gly Gly Gly Ser
1

<210> SEQ ID NO 159
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 159

Ile Ser Ser Gly Leu Ser Ser
1 5

<210> SEQ ID NO 160
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 160

Cys Ile Ser Pro Arg Gly Cys Pro Asp Gly Pro Tyr Val Met Tyr
1 5 10 15

<210> SEQ ID NO 161
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: N-terminal AV1 light chain sequence

<400> SEQUENCE: 161

Tyr Gly Ser Cys Ser Trp Asn Tyr Val His Ile Phe Met Asp Cys
1 5 10 15

<210> SEQ ID NO 162
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: N-terminal AV1 light chain sequence

<400> SEQUENCE: 162

Gln Gly Asp Phe Asp Ile Pro Phe Pro Ala His Trp Val Pro Ile Thr
1 5 10 15

<210> SEQ ID NO 163
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: N-terminal AV1 light chain sequence

<400> SEQUENCE: 163

Met Gly Val Pro Ala Gly Cys Val Trp Asn Tyr Ala His Ile Phe Met

-continued

1	5	10	15
Asp Cys			
<210> SEQ ID NO 164			
<211> LENGTH: 21			
<212> TYPE: PRT			
<213> ORGANISM: Artificial Sequence			
<220> FEATURE:			
<223> OTHER INFORMATION: N-terminal AV1 light chain sequence			
<400> SEQUENCE: 164			
Gln Gly Gln Ser Gly Gln Tyr Gly Ser Cys Ser Trp Asn Tyr Val His			
1	5	10	15
Ile Phe Met Asp Cys			
20			
<210> SEQ ID NO 165			
<211> LENGTH: 21			
<212> TYPE: PRT			
<213> ORGANISM: Artificial Sequence			
<220> FEATURE:			
<223> OTHER INFORMATION: N-terminal AV1 light chain sequence			
<400> SEQUENCE: 165			
Gln Gly Gln Ser Gly Gln Gly Asp Phe Asp Ile Pro Phe Pro Ala His			
1	5	10	15
Trp Val Pro Ile Thr			
20			
<210> SEQ ID NO 166			
<211> LENGTH: 24			
<212> TYPE: PRT			
<213> ORGANISM: Artificial Sequence			
<220> FEATURE:			
<223> OTHER INFORMATION: N-terminal AV1 light chain sequence			
<400> SEQUENCE: 166			
Gln Gly Gln Ser Gly Gln Met Gly Val Pro Ala Gly Cys Val Trp Asn			
1	5	10	15
Tyr Ala His Ile Phe Met Asp Cys			
20			
<210> SEQ ID NO 167			
<211> LENGTH: 6			
<212> TYPE: PRT			
<213> ORGANISM: Artificial Sequence			
<220> FEATURE:			
<223> OTHER INFORMATION: masking moiety			
<400> SEQUENCE: 167			
Cys Ile Ser Pro Arg Gly			
1	5		
<210> SEQ ID NO 168			
<211> LENGTH: 8			
<212> TYPE: PRT			
<213> ORGANISM: Artificial Sequence			
<220> FEATURE:			
<223> OTHER INFORMATION: masking moiety			
<400> SEQUENCE: 168			
Cys Ile Ser Pro Arg Gly Cys Gly			

-continued

1 5

<210> SEQ ID NO 169
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 169

Cys Ile Ser Pro Arg Gly Cys Pro Asp Gly Pro Tyr Val Met
1 5 10

<210> SEQ ID NO 170
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 170

Cys Ile Ser Pro Arg Gly Cys Glu Pro Gly Thr Tyr Val Pro Thr
1 5 10 15

<210> SEQ ID NO 171
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 171

Cys Ile Ser Pro Arg Gly Cys Pro Gly Gln Ile Trp His Pro Pro
1 5 10 15

<210> SEQ ID NO 172
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 172

Gly Ser His Cys Leu Ile Pro Ile Asn Met Gly Ala Pro Ser Cys
1 5 10 15

<210> SEQ ID NO 173
<211> LENGTH: 32
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 173

Cys Ile Ser Pro Arg Gly Cys Gly Ser Ser Ala Ser Gln Ser Gly
1 5 10 15

Gln Gly Ser His Cys Leu Ile Pro Ile Asn Met Gly Ala Pro Ser Cys
20 25 30

<210> SEQ ID NO 174
<211> LENGTH: 19
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 174

Cys Asn His His Tyr Phe Tyr Thr Cys Gly Cys Ile Ser Pro Arg Gly
1 5 10 15

Cys Pro Gly

<210> SEQ ID NO 175

<211> LENGTH: 19

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 175

Ala Asp His Val Phe Trp Gly Ser Tyr Gly Cys Ile Ser Pro Arg Gly
1 5 10 15

Cys Pro Gly

<210> SEQ ID NO 176

<211> LENGTH: 19

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 176

Cys His His Val Tyr Trp Gly His Cys Gly Cys Ile Ser Pro Arg Gly
1 5 10 15

Cys Pro Gly

<210> SEQ ID NO 177

<211> LENGTH: 19

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 177

Cys Pro His Phe Thr Thr Ser Cys Gly Cys Ile Ser Pro Arg Gly
1 5 10 15

Cys Pro Gly

<210> SEQ ID NO 178

<211> LENGTH: 19

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 178

Cys Asn His His Tyr His Tyr Cys Gly Cys Ile Ser Pro Arg Gly
1 5 10 15

Cys Pro Gly

<210> SEQ ID NO 179

<211> LENGTH: 19

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: masking moiety

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<400> SEQUENCE: 179

Cys Pro His Val Ser Phe Gly Ser Cys Gly Cys Ile Ser Pro Arg Gly
1 5 10 15

Cys Pro Gly

<210> SEQ ID NO 180

<211> LENGTH: 19

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 180

Cys Pro Tyr Tyr Thr Leu Ser Tyr Cys Gly Cys Ile Ser Pro Arg Gly
1 5 10 15

Cys Pro Gly

<210> SEQ ID NO 181

<211> LENGTH: 19

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 181

Cys Asn His Val Tyr Phe Gly Thr Cys Gly Cys Ile Ser Pro Arg Gly
1 5 10 15

Cys Pro Gly

<210> SEQ ID NO 182

<211> LENGTH: 19

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 182

Cys Asn His Phe Thr Leu Thr Cys Gly Cys Ile Ser Pro Arg Gly
1 5 10 15

Cys Pro Gly

<210> SEQ ID NO 183

<211> LENGTH: 19

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 183

Cys His His Phe Thr Leu Thr Cys Gly Cys Ile Ser Pro Arg Gly
1 5 10 15

Cys Pro Gly

<210> SEQ ID NO 184

<211> LENGTH: 18

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: masking moiety

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<400> SEQUENCE: 184

Tyr Asn Pro Cys Ala Thr Pro Met Cys Cys Ile Ser Pro Arg Gly Cys
1 5 10 15
Pro Gly

<210> SEQ ID NO 185

<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 185

Cys Asn His His Tyr Phe Tyr Thr Cys Gly Cys Ile Ser Pro Arg Gly
1 5 10 15

Cys Gly

<210> SEQ ID NO 186

<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 186

Cys Asn His His Tyr His Tyr Tyr Cys Gly Cys Ile Ser Pro Arg Gly
1 5 10 15

Cys Gly

<210> SEQ ID NO 187

<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 187

Cys Asn His Val Tyr Phe Gly Thr Cys Gly Cys Ile Ser Pro Arg Gly
1 5 10 15

Cys Gly

<210> SEQ ID NO 188

<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 188

Cys His His Val Tyr Trp Gly His Cys Gly Cys Ile Ser Pro Arg Gly
1 5 10 15

Cys Gly

<210> SEQ ID NO 189

<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 189

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Cys Pro His Phe Thr Thr Ser Cys Gly Cys Ile Ser Pro Arg Gly
1 5 10 15

Cys Gly

<210> SEQ ID NO 190
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 190

Cys Asn His Phe Thr Leu Thr Cys Gly Cys Ile Ser Pro Arg Gly
1 5 10 15

Cys Gly

<210> SEQ ID NO 191
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 191

Cys His His Phe Thr Leu Thr Cys Gly Cys Ile Ser Pro Arg Gly
1 5 10 15

Cys Gly

<210> SEQ ID NO 192
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 192

Cys Pro Tyr Tyr Thr Leu Ser Tyr Cys Gly Cys Ile Ser Pro Arg Gly
1 5 10 15

Cys Gly

<210> SEQ ID NO 193
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 193

Cys Pro His Val Ser Phe Gly Ser Cys Gly Cys Ile Ser Pro Arg Gly
1 5 10 15

Cys Gly

<210> SEQ ID NO 194
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 194

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Ala Asp His Val Phe Trp Gly Ser Tyr Gly Cys Ile Ser Pro Arg Gly
1 5 10 15

Cys Gly

<210> SEQ ID NO 195
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 195

Tyr Asn Pro Cys Ala Thr Pro Met Cys Cys Ile Ser Pro Arg Gly Cys
1 5 10 15

Gly

<210> SEQ ID NO 196
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 196

Cys His His Val Tyr Trp Gly His Cys Gly Cys Ile Ser Pro Arg Gly
1 5 10 15

Cys Gly

<210> SEQ ID NO 197
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Asn or Phe
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be His, Val or Phe
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Tyr or Thr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Phe, Trp, Thr or Leu
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Tyr, Gly, Thr or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Thr, Ser, Tyr or His

<400> SEQUENCE: 197

Cys Xaa His Xaa Xaa Xaa Xaa Cys Gly Cys Ile Ser Pro Arg Gly
1 5 10 15

Cys Gly

<210> SEQ ID NO 198

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<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 198

Cys Ile Ser Pro Arg Gly Cys Gly Gln Pro Ile Pro Ser Val Lys
1 5 10 15

<210> SEQ ID NO 199
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 199

Cys Ile Ser Pro Arg Gly Cys Thr Gln Pro Tyr His Val Ser Arg
1 5 10 15

<210> SEQ ID NO 200
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 200

Cys Ile Ser Pro Arg Gly Cys Asn Ala Val Ser Gly Leu Gly Ser
1 5 10 15

<210> SEQ ID NO 201
<211> LENGTH: 26
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 201

Gln Gly Gln Ser Gly Gln Gly Gln Gln Trp Cys Asn Ile Trp Ile
1 5 10 15

Asn Gly Gly Asp Cys Arg Gly Trp Asn Gly
20 25

<210> SEQ ID NO 202
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 202

Pro Trp Cys Met Gln Arg Gln Asp Phe Leu Arg Cys Pro Gln Pro
1 5 10 15

<210> SEQ ID NO 203
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 203

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Gln Leu Gly Leu Pro Ala Tyr Met Cys Thr Phe Glu Cys Leu Arg
1 5 10 15

<210> SEQ ID NO 204
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 204

Cys Asn Leu Trp Val Ser Gly Gly Asp Cys Gly Gly Leu Gln Gly
1 5 10 15

<210> SEQ ID NO 205
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 205

Ser Cys Ser Leu Trp Thr Ser Gly Ser Cys Leu Pro His Ser Pro
1 5 10 15

<210> SEQ ID NO 206
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 206

Tyr Cys Leu Gln Leu Pro His Tyr Met Gln Ala Met Cys Gly Arg
1 5 10 15

<210> SEQ ID NO 207
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 207

Cys Phe Leu Tyr Ser Cys Thr Asp Val Ser Tyr Trp Asn Asn Thr
1 5 10 15

<210> SEQ ID NO 208
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 208

Pro Trp Cys Met Gln Arg Gln Asp Tyr Leu Arg Cys Pro Gln Pro
1 5 10 15

<210> SEQ ID NO 209
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

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<400> SEQUENCE: 209

Cys Asn Leu Trp Ile Ser Gly Gly Asp Cys Arg Gly Leu Ala Gly
1 5 10 15

<210> SEQ ID NO 210

<211> LENGTH: 15

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 210

Cys Asn Leu Trp Val Ser Gly Gly Asp Cys Arg Gly Val Gln Gly
1 5 10 15

<210> SEQ ID NO 211

<211> LENGTH: 15

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 211

Cys Asn Leu Trp Val Ser Gly Gly Asp Cys Arg Gly Leu Arg Gly
1 5 10 15

<210> SEQ ID NO 212

<211> LENGTH: 15

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 212

Cys Asn Leu Trp Ile Ser Gly Gly Asp Cys Arg Gly Leu Pro Gly
1 5 10 15

<210> SEQ ID NO 213

<211> LENGTH: 15

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 213

Cys Asn Leu Trp Val Ser Gly Gly Asp Cys Arg Asp Ala Pro Trp
1 5 10 15

<210> SEQ ID NO 214

<211> LENGTH: 15

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 214

Cys Asn Leu Trp Val Ser Gly Gly Asp Cys Arg Asp Leu Leu Gly
1 5 10 15

<210> SEQ ID NO 215

<211> LENGTH: 15

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

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<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 215

Cys Asn Leu Trp Val Ser Gly Gly Asp Cys Arg Gly Leu Gln Gly
1 5 10 15

<210> SEQ ID NO 216

<211> LENGTH: 15

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 216

Cys Asn Leu Trp Leu His Gly Gly Asp Cys Arg Gly Trp Gln Gly
1 5 10 15

<210> SEQ ID NO 217

<211> LENGTH: 15

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 217

Cys Asn Ile Trp Leu Val Gly Gly Asp Cys Arg Gly Trp Gln Gly
1 5 10 15

<210> SEQ ID NO 218

<211> LENGTH: 15

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 218

Cys Thr Thr Trp Phe Cys Gly Gly Asp Cys Gly Val Met Arg Gly
1 5 10 15

<210> SEQ ID NO 219

<211> LENGTH: 15

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 219

Cys Asn Ile Trp Gly Pro Ser Val Asp Cys Gly Ala Leu Leu Gly
1 5 10 15

<210> SEQ ID NO 220

<211> LENGTH: 15

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 220

Cys Asn Ile Trp Val Asn Gly Gly Asp Cys Arg Ser Phe Glu Gly
1 5 10 15

<210> SEQ ID NO 221

<211> LENGTH: 15

<212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 221

Tyr Cys Leu Asn Leu Pro Arg Tyr Met Gln Asp Met Cys Trp Ala
1 5 10 15

<210> SEQ ID NO 222
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 222

Tyr Cys Leu Ala Leu Pro His Tyr Met Gln Ala Asp Cys Ala Arg
1 5 10 15

<210> SEQ ID NO 223
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 223

Cys Phe Leu Tyr Ser Cys Gly Asp Val Ser Tyr Trp Gly Ser Ala
1 5 10 15

<210> SEQ ID NO 224
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 224

Cys Tyr Leu Tyr Ser Cys Thr Asp Ser Ala Phe Trp Asn Asn Arg
1 5 10 15

<210> SEQ ID NO 225
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 225

Cys Tyr Leu Tyr Ser Cys Asn Asp Val Ser Tyr Trp Ser Asn Thr
1 5 10 15

<210> SEQ ID NO 226
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 226

Cys Phe Leu Tyr Ser Cys Thr Asp Val Ser Tyr Trp

1 5 10

<210> SEQ ID NO 227

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<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 227

Cys Phe Leu Tyr Ser Cys Thr Asp Val Ala Tyr Trp Asn Ser Ala
1 5 10 15

<210> SEQ ID NO 228
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 228

Cys Phe Leu Tyr Ser Cys Thr Asp Val Ser Tyr Trp Gly Asp Thr
1 5 10 15

<210> SEQ ID NO 229
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 229

Cys Phe Leu Tyr Ser Cys Thr Asp Val Ser Tyr Trp Gly Asn Ser
1 5 10 15

<210> SEQ ID NO 230
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 230

Cys Phe Leu Tyr Ser Cys Thr Asp Val Ala Tyr Trp Asn Asn Thr
1 5 10 15

<210> SEQ ID NO 231
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 231

Cys Phe Leu Tyr Ser Cys Gly Asp Val Ser Tyr Trp Gly Asn Pro Gly
1 5 10 15

Leu Ser

<210> SEQ ID NO 232
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 232

Cys Phe Leu Tyr Ser Cys Thr Asp Val Ala Tyr Trp Ser Gly Leu

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1	5	10	15
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<210> SEQ ID NO 233
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 233

Cys Tyr Leu Tyr Ser Cys Thr Asp Gly Ser Tyr Trp Asn Ser Thr
1 5 10 15

<210> SEQ ID NO 234
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 234

Cys Phe Leu Tyr Ser Cys Ser Asp Val Ser Tyr Trp Gly Asn Ile
1 5 10 15

<210> SEQ ID NO 235
<211> LENGTH: 12
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 235

Cys Phe Leu Tyr Ser Cys Thr Asp Val Ala Tyr Trp
1 5 10

<210> SEQ ID NO 236
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 236

Cys Phe Leu Tyr Ser Cys Thr Asp Val Ser Tyr Trp Gly Ser Thr
1 5 10 15

<210> SEQ ID NO 237
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 237

Cys Phe Leu Tyr Ser Cys Thr Asp Val Ala Tyr Trp Gly Asp Thr
1 5 10 15

<210> SEQ ID NO 238
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 238

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Gly Cys Asn Ile Trp Leu Asn Gly Gly Asp Cys Arg Gly Trp Val Asp
1 5 10 15

Pro Leu Gln Gly
20

<210> SEQ ID NO 239
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 239

Gly Cys Asn Ile Trp Leu Val Gly Gly Asp Cys Arg Gly Trp Ile Gly
1 5 10 15

Asp Thr Asn Gly
20

<210> SEQ ID NO 240
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 240

Gly Cys Asn Ile Trp Leu Val Gly Gly Asp Cys Arg Gly Trp Ile Glu
1 5 10 15

Asp Ser Asn Gly
20

<210> SEQ ID NO 241
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 241

Gly Cys Asn Ile Trp Ala Asn Gly Gly Asp Cys Arg Gly Trp Ile Asp
1 5 10 15

Asn Ile Asp Gly
20

<210> SEQ ID NO 242
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 242

Gly Cys Asn Ile Trp Leu Val Gly Gly Asp Cys Arg Gly Trp Leu Gly
1 5 10 15

Glu Ala Val Gly
20

<210> SEQ ID NO 243
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 243

Gly Cys Asn Ile Trp Leu Val Gly Gly Asp Cys Arg Gly Trp Leu Glu
1 5 10 15

Glu Ala Val Gly
20

<210> SEQ ID NO 244
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 244

Gly Gly Pro Ala Leu Cys Asn Ile Trp Leu Asn Gly Gly Asp Cys Arg
1 5 10 15

Gly Trp Ser Gly
20

<210> SEQ ID NO 245
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 245

Gly Ala Pro Val Phe Cys Asn Ile Trp Leu Asn Gly Gly Asp Cys Arg
1 5 10 15

Gly Trp Met Gly
20

<210> SEQ ID NO 246
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 246

Gly Gln Gln Gln Trp Cys Asn Ile Trp Ile Asn Gly Gly Asp Cys Arg
1 5 10 15

Gly Trp Asn Gly
20

<210> SEQ ID NO 247
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 247

Gly Lys Ser Glu Phe Cys Asn Ile Trp Leu Asn Gly Gly Asp Cys Arg
1 5 10 15

Gly Trp Ile Gly
20

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<210> SEQ ID NO 248
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 248

Gly Thr Pro Gly Gly Cys Asn Ile Trp Ala Asn Gly Gly Asp Cys Arg
1 5 10 15

Gly Trp Glu Gly
20

<210> SEQ ID NO 249
<211> LENGTH: 20
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 249

Gly Ala Ser Gln Tyr Cys Asn Leu Trp Ile Asn Gly Gly Asp Cys Arg
1 5 10 15

Gly Trp Arg Gly
20

<210> SEQ ID NO 250
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 250

Gly Cys Asn Ile Trp Leu Val Gly Gly Asp Cys Arg Pro Trp Val Glu
1 5 10 15

Gly Gly

<210> SEQ ID NO 251
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 251

Gly Cys Asn Ile Trp Ala Val Gly Gly Asp Cys Arg Pro Phe Val Asp
1 5 10 15

Gly Gly

<210> SEQ ID NO 252
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 252

Gly Cys Asn Ile Trp Leu Asn Gly Gly Asp Cys Arg Ala Trp Val Asp
1 5 10 15

Thr Gly

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<210> SEQ ID NO 253
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 253

Gly Cys Asn Ile Trp Ile Val Gly Gly Asp Cys Arg Pro Phe Ile Asn
1          5          10          15

Asp Gly

<210> SEQ ID NO 254
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 254

Gly Cys Asn Ile Trp Leu Asn Gly Gly Asp Cys Arg Pro Val Val Phe
1          5          10          15

Gly Gly

<210> SEQ ID NO 255
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 255

Gly Cys Asn Ile Trp Leu Ser Gly Gly Asp Cys Arg Met Phe Met Asn
1          5          10          15

Glu Gly

<210> SEQ ID NO 256
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 256

Gly Cys Asn Ile Trp Val Asn Gly Gly Asp Cys Arg Ser Phe Val Tyr
1          5          10          15

Ser Gly

<210> SEQ ID NO 257
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 257

Gly Cys Asn Ile Trp Leu Asn Gly Gly Asp Cys Arg Gly Trp Glu Ala
1          5          10          15

Ser Gly
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<210> SEQ ID NO 258
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 258

Gly Cys Asn Ile Trp Ala His Gly Gly Asp Cys Arg Gly Phe Ile Glu
1 5 10 15

Pro Gly

<210> SEQ ID NO 259
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 259

Gly Cys Asn Ile Trp Leu Asn Gly Gly Asp Cys Arg Thr Phe Val Ala
1 5 10 15

Ser Gly

<210> SEQ ID NO 260
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 260

Gly Cys Asn Ile Trp Ala His Gly Gly Asp Cys Arg Gly Phe Ile Glu
1 5 10 15

Pro Gly

<210> SEQ ID NO 261
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 261

Gly Phe Leu Glu Asn Cys Asn Ile Trp Leu Asn Gly Gly Asp Cys Arg
1 5 10 15

Thr Gly

<210> SEQ ID NO 262
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 262

Gly Ile Tyr Glu Asn Cys Asn Ile Trp Leu Asn Gly Gly Asp Cys Arg
1 5 10 15

Met Gly

<210> SEQ ID NO 263

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<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 263

Gly Ile Pro Asp Asn Cys Asn Ile Trp Ile Asn Gly Gly Asp Cys Arg
1 5 10 15
Tyr Gly

<210> SEQ ID NO 264
<211> LENGTH: 21
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 264

Gln Gly Gln Ser Gly Gln Tyr Gly Ser Cys Ser Trp Asn Tyr Val His
1 5 10 15
Ile Phe Met Asp Cys
20

<210> SEQ ID NO 265
<211> LENGTH: 21
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 265

Gln Gly Gln Ser Gly Gln Gly Asp Phe Asp Ile Pro Phe Pro Ala His
1 5 10 15
Trp Val Pro Ile Thr
20

<210> SEQ ID NO 266
<211> LENGTH: 24
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 266

Gln Gly Gln Ser Gly Gln Met Gly Val Pro Ala Gly Cys Val Trp Asn
1 5 10 15
Tyr Ala His Ile Phe Met Asp Cys
20

<210> SEQ ID NO 267
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 267

Tyr Arg Ser Cys Asn Trp Asn Tyr Val Ser Ile Phe Leu Asp Cys
1 5 10 15

<210> SEQ ID NO 268

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<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 268

Pro Gly Ala Phe Asp Ile Pro Phe Pro Ala His Trp Val Pro Asn Thr
1 5 10 15

<210> SEQ ID NO 269
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 269

Glu Ser Ser Cys Val Trp Asn Tyr Val His Ile Tyr Met Asp Cys
1 5 10 15

<210> SEQ ID NO 270
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 270

Tyr Pro Gly Cys Lys Trp Asn Tyr Asp Arg Ile Phe Leu Asp Cys
1 5 10 15

<210> SEQ ID NO 271
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 271

Tyr Arg Thr Cys Ser Trp Asn Tyr Val Gly Ile Phe Leu Asp Cys
1 5 10 15

<210> SEQ ID NO 272
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 272

Tyr Gly Ser Cys Ser Trp Asn Tyr Val His Ile Phe Leu Asp Cys
1 5 10 15

<210> SEQ ID NO 273
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 273

Tyr Gly Ser Cys Asn Trp Asn Tyr Val His Ile Phe Leu Asp Cys
1 5 10 15

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<210> SEQ ID NO 274
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 274

Tyr Thr Ser Cys Asn Trp Asn Tyr Val His Ile Phe Met Asp Cys
1           5           10          15

<210> SEQ ID NO 275
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 275

Tyr Pro Gly Cys Lys Trp Asn Tyr Asp Arg Ile Phe Leu Asp Cys
1           5           10          15

<210> SEQ ID NO 276
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 276

Trp Arg Ser Cys Asn Trp Asn Tyr Ala His Ile Phe Leu Asp Cys
1           5           10          15

<210> SEQ ID NO 277
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 277

Trp Ser Asn Cys His Trp Asn Tyr Val His Ile Phe Leu Asp Cys
1           5           10          15

<210> SEQ ID NO 278
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 278

Asp Arg Ser Cys Thr Trp Asn Tyr Val Arg Ile Ser Tyr Asp Cys
1           5           10          15

<210> SEQ ID NO 279
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 279

Ser Gly Ser Cys Lys Trp Asp Tyr Val His Ile Phe Leu Asp Cys
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1	5	10	15
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<210> SEQ ID NO 280
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 280

Ser Arg Ser Cys Ile Trp Asn Tyr Ala His Ile His Leu Asp Cys
1 5 10 15

<210> SEQ ID NO 281
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 281

Ser Met Ser Cys Tyr Trp Gln Tyr Glu Arg Ile Phe Leu Asp Cys
1 5 10 15

<210> SEQ ID NO 282
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 282

Tyr Arg Ser Cys Asn Trp Asn Tyr Val Ser Ile Phe Leu Asp Cys
1 5 10 15

<210> SEQ ID NO 283
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 283

Ser Gly Ser Cys Lys Trp Asp Tyr Val His Ile Phe Leu Asp Cys
1 5 10 15

<210> SEQ ID NO 284
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 284

Tyr Lys Ser Cys His Trp Asp Tyr Val His Ile Phe Leu Asp Cys
1 5 10 15

<210> SEQ ID NO 285
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 285

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Tyr Gly Ser Cys Thr Trp Asn Tyr Val His Ile Phe Met Glu Cys
1 5 10 15

<210> SEQ ID NO 286
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 286

Phe Ser Ser Cys Asn Trp Asn Tyr Val His Ile Phe Leu Asp Cys
1 5 10 15

<210> SEQ ID NO 287
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 287

Trp Arg Ser Cys Asn Trp Asn Tyr Ala His Ile Phe Leu Asp Cys
1 5 10 15

<210> SEQ ID NO 288
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 288

Tyr Gly Ser Cys Gln Trp Asn Tyr Val His Ile Phe Leu Asp Cys
1 5 10 15

<210> SEQ ID NO 289
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 289

Tyr Arg Ser Cys Asn Trp Asn Tyr Val His Ile Phe Leu Asp Cys
1 5 10 15

<210> SEQ ID NO 290
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 290

Asn Met Ser Cys His Trp Asp Tyr Val His Ile Phe Leu Asp Cys
1 5 10 15

<210> SEQ ID NO 291
<211> LENGTH: 15
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

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<400> SEQUENCE: 291

Phe Gly Pro Cys Thr Trp Asn Tyr Ala Arg Ile Ser Trp Asp Cys
1 5 10 15

<210> SEQ ID NO 292

<211> LENGTH: 15

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: masking moiety

<220> FEATURE:

<221> NAME/KEY: misc_feature

<222> LOCATION: (1)..(2)

<223> OTHER INFORMATION: Xaa may be any amino acid

<220> FEATURE:

<221> NAME/KEY: misc_feature

<222> LOCATION: (5)..(5)

<223> OTHER INFORMATION: Xaa may be any amino acid

<220> FEATURE:

<221> NAME/KEY: misc_feature

<222> LOCATION: (7)..(7)

<223> OTHER INFORMATION: Xaa may be any amino acid

<220> FEATURE:

<221> NAME/KEY: misc_feature

<222> LOCATION: (13)..(13)

<223> OTHER INFORMATION: Xaa may be any amino acid

<400> SEQUENCE: 292

Xaa Xaa Ser Cys Xaa Trp Xaa Tyr Val His Ile Phe Xaa Asp Cys
1 5 10 15

<210> SEQ ID NO 293

<211> LENGTH: 18

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 293

Arg Asp Thr Gly Gly Gln Cys Arg Trp Asp Tyr Val His Ile Phe Met
1 5 10 15

Asp Cys

<210> SEQ ID NO 294

<211> LENGTH: 18

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 294

Ala Gly Val Pro Ala Gly Cys Thr Trp Asn Tyr Val His Ile Phe Met
1 5 10 15

Glu Cys

<210> SEQ ID NO 295

<211> LENGTH: 18

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 295

Val Gly Val Pro Asn Gly Cys Val Trp Asn Tyr Ala His Ile Phe Met

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1 5 10 15

Glu Cys

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<210> SEQ ID NO 296
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 296
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Asp Gly Gly Pro Ala Gly Cys Ser Trp Asn Tyr Val His Ile Phe Met
1 5 10 15
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Glu Cys

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<210> SEQ ID NO 297
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 297
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Ala Val Gly Pro Ala Gly Cys Trp Trp Asn Tyr Val His Ile Phe Met
1 5 10 15
```

Glu Cys

```
<210> SEQ ID NO 298
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 298
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Cys Thr Trp Asn Tyr Val His Ile Phe Met Asp Cys Gly Glu Gly Glu
1 5 10 15
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Gly Pro

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<210> SEQ ID NO 299
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 299
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Gly Gly Val Pro Glu Gly Cys Thr Trp Asn Tyr Ala His Ile Phe Met
1 5 10 15
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Glu Cys

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<210> SEQ ID NO 300
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 300
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Ala Glu Val Pro Ala Gly Cys Trp Trp Asn Tyr Val His Ile Phe Met
1 5 10 15
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Glu Cys

<210> SEQ ID NO 301
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 301

Ala Gly Val Pro Ala Gly Cys Thr Trp Asn Tyr Val His Ile Phe Met
1 5 10 15

Glu Cys

<210> SEQ ID NO 302
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 302

Ser Gly Ala Ser Gly Gly Cys Lys Trp Asn Tyr Val His Ile Phe Met
1 5 10 15

Asp Cys

<210> SEQ ID NO 303
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 303

Thr Pro Gly Cys Arg Trp Asn Tyr Val His Ile Phe Met Glu Cys Glu
1 5 10 15

Ala Leu

<210> SEQ ID NO 304
<211> LENGTH: 18
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 304

Val Gly Val Pro Asn Gly Cys Val Trp Asn Tyr Ala His Ile Phe Met
1 5 10 15

Glu Cys

<210> SEQ ID NO 305
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 305

Pro Gly Ala Phe Asp Ile Pro Phe Pro Ala His Trp Val Pro Asn Thr
1 5 10 15

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<210> SEQ ID NO 306
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 306

Arg Gly Ala Cys Asp Ile Pro Phe Pro Ala His Trp Ile Pro Asn Thr
1 5 10 15

<210> SEQ ID NO 307
<211> LENGTH: 16
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be any amino acid

<400> SEQUENCE: 307

Xaa Gly Ala Phe Asp Ile Pro Phe Pro Ala His Trp Val Pro Asn Thr
1 5 10 15

<210> SEQ ID NO 308
<211> LENGTH: 19
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 308

Arg Gly Asp Gly Asn Asp Ser Asp Ile Pro Phe Pro Ala His Trp Val
1 5 10 15

Pro Arg Thr

<210> SEQ ID NO 309
<211> LENGTH: 19
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 309

Ser Gly Val Gly Arg Asp Arg Asp Ile Pro Phe Pro Ala His Trp Val
1 5 10 15

Pro Arg Thr

<210> SEQ ID NO 310
<211> LENGTH: 19
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 310

Trp Ala Gly Gly Asn Asp Cys Asp Ile Pro Phe Pro Ala His Trp Ile
1 5 10 15

Pro Asn Thr

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<210> SEQ ID NO 311
<211> LENGTH: 19
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 311

Trp Gly Asp Gly Met Asp Val Asp Ile Pro Phe Pro Ala His Trp Val
1 5 10 15
Pro Val Thr

<210> SEQ ID NO 312
<211> LENGTH: 19
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 312

Ala Gly Ser Gly Asn Asp Ser Asp Ile Pro Phe Pro Ala His Trp Val
1 5 10 15

Pro Arg Thr

<210> SEQ ID NO 313
<211> LENGTH: 19
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 313

Glu Ser Arg Ser Gly Tyr Ala Asp Ile Pro Phe Pro Ala His Trp Val
1 5 10 15

Pro Arg Thr

<210> SEQ ID NO 314
<211> LENGTH: 19
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 314

Arg Glu Cys Gly Arg Cys Gly Asp Ile Pro Phe Pro Ala His Trp Val
1 5 10 15

Pro Arg Thr

<210> SEQ ID NO 315
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 315

Gly Pro Arg Ser Phe Gly Leu
1 5

<210> SEQ ID NO 316
<211> LENGTH: 6
<212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 316
Gly Pro Arg Ser Phe Gly
1 5

<210> SEQ ID NO 317
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP9 Cleavable Core CM Consensus Sequence 1
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ala, Cys, Asp, Gly, His, Leu, Pro,
    Arg or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Leu, Met, Pro, Ser or Thr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Phe, Gly, Leu, Met, Asn,
    Pro, Arg, Ser, Thr or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Glu, Gly, His, Ile, Met,
    Pro, Ser or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Ala, Cys, Asp, Gly, Leu, Met, Asn,
    Arg, Val, Trp or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Cys, Phe, Gly, His, Pro, Gln, Arg,
    Thr, Val or Trp
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Gly, Leu, Met, Ser, Thr,
    Val or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Cys, His, Leu, Arg, Ser, Val, Trp,
    or Tyr

<400> SEQUENCE: 317
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> SEQ ID NO 318
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP9 Cleavable Core CM Consensus Sequence 1
    subgenus 1.1
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Gly, Pro, Arg or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
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<223> OTHER INFORMATION: Xaa may be Pro or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Leu, Met, Pro or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Ala, Gly, Pro or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Leu, Met or Arg
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Gly or Trp
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Ala, Gly, Ser or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Leu, Arg, Val or Tyr

<400> SEQUENCE: 318

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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1      5

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<210> SEQ ID NO 319
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP9 Cleavable Core CM Consensus Sequence 1
    subgenus 1.2
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Gly, Pro or Arg
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Leu, Met or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Gly, Pro or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Leu, Met or Arg
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Ala, Gly or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Arg, Val or Tyr

<400> SEQUENCE: 319

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Xaa Pro Xaa Xaa Xaa Trp Xaa Xaa
1      5

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<210> SEQ ID NO 320
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP9 Cleavable Core CM Consensus Sequence 1

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subgenus 1.3
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Pro or Arg
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Met or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Gly or Pro
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Leu, Met or Arg
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Ala, Gly or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Arg, Val or Tyr

<400> SEQUENCE: 320
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Xaa Pro Xaa Xaa Xaa Trp Xaa Xaa
1 5

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<210> SEQ ID NO 321
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP9 Cleavable Core CM Consensus Sequence 1
    subgenus 1.4
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Pro or Arg
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Gly or Pro
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Met or Arg
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Ala, Gly or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Val or Tyr

<400> SEQUENCE: 321
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Xaa Pro Ser Xaa Xaa Trp Xaa Xaa
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<210> SEQ ID NO 322
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP9 Cleavable Core CM Consensus Sequence 1
    subgenus 1.5
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
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<223> OTHER INFORMATION: Xaa may be Pro or Arg
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Gly or Pro
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Met or Arg
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Ala or Ser

<400> SEQUENCE: 322

Xaa Pro Ser Xaa Xaa Trp Xaa Tyr
1 5

<210> SEQ ID NO 323
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP9 Cleavable Core CM Consensus Sequence 1
    subgenus 1.6
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Cys, Gly, His, Leu or Arg
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Pro, Ser or Thr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Asn, Arg, Ser or Thr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Pro or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Cys, Met, Arg, Val or Trp
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Cys, Pro, Arg or Trp
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Ala, Asp or Gly
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Cys or Tyr

<400> SEQUENCE: 323

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> SEQ ID NO 324
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP9 Cleavable Core CM Consensus Sequence 2
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Phe, Gly, Val or Trp
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<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Leu, Met, Pro, Arg, Thr
or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Cys, Gly, His, Leu, Gln, Ser, Thr
or Trp
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Asp, Gly, Leu or Pro
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Glu, Gly, Ile, Leu, Asn, Pro, Arg
or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Gly, Leu, Pro, Arg, Ser or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Ala, Ile, Leu, Met, Thr or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Ala, Gly, Leu, Pro, Gln, Arg, Ser
or Val

<400> SEQUENCE: 324

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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

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<210> SEQ ID NO 325
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP9 Cleavable Core CM Consensus Sequence 2
subgenus 2.1
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Asp, Pro or Thr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be His, Gln or Trp
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Asp or Pro
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Ile or Arg
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Leu, Met or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Gly, Leu or Ser

<400> SEQUENCE: 325

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Trp Xaa Xaa Xaa Xaa Ser Xaa Xaa
1 5

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<210> SEQ ID NO 326
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP9 Cleavable Core CM Consensus Sequence 2
    subgenus 2.2
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be His, Gln or Trp
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Asp or Pro
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Ile or Arg
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Gly, Ser or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Leu, Met or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Gly, Leu or Ser

<400> SEQUENCE: 326
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Trp Asp Xaa Xaa Xaa Xaa Xaa Xaa
1 5

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<210> SEQ ID NO 327
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP9 Cleavable Core CM Consensus Sequence 2
    subgenus 2.3
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be His, Gln or Trp
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Ile or Arg
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Leu, Met or Val

<400> SEQUENCE: 327
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Trp Asp Xaa Pro Xaa Ser Xaa Leu
1 5

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<210> SEQ ID NO 328
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable moiety
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<400> SEQUENCE: 328

Trp Asp His Pro Ile Ser Leu Leu
1 5

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<210> SEQ ID NO 329
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP9 Cleavable Core CM Consensus Sequence 3
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Gly, Ile, Leu, Met, Pro, Arg, Ser,
    Thr or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, His, Ile, Leu, Pro, Ser
    or Thr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Phe, Leu, Ser or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be His, Leu, Met, Pro, Gln, Arg, Ser
    or Thr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Phe, Gly, Leu, Met, Arg,
    Ser, Thr or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Ala, Cys, Gly, His, Gln, Thr or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Cys, Gly, Ile, Met, Arg, Ser, Thr,
    Val or Trp
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Phe, Leu, Ser or Tyr

<400> SEQUENCE: 329

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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<210> SEQ ID NO 330
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP9 Cleavable Core CM Consensus Sequence 3
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<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ile, Leu, Met or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Asp, Pro, Ser or Thr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Phe, Leu, Ser or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Leu, Pro or Ser
<220> FEATURE:
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<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Ala, Phe, Arg, Ser or Thr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Gly, His, Thr or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Gly, Ile, Met, Val or Trp
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Phe, Leu or Ser
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<400> SEQUENCE: 330

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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<210> SEQ ID NO 331
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP9 Cleavable Core CM Consensus Sequence 3
  subgenus 3.2
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Leu, Met or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Ser or Thr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Phe or Leu
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Ala, Phe, or Thr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Gly, His, Thr or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Ile, Met or Trp
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<400> SEQUENCE: 331

Xaa Xaa Xaa Pro Xaa Xaa Xaa Phe
1 5

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<210> SEQ ID NO 332
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP9 Cleavable Core CM Consensus Sequence 3
  subgenus 3.3
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Leu, Met or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Ser or Thr
<220> FEATURE:
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<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Ala, Phe or Thr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Gly, His or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Ile, Met or Trp

<400> SEQUENCE: 332

Xaa Xaa Phe Pro Xaa Xaa Xaa Phe
1 5

<210> SEQ ID NO 333
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP9 Cleavable Core CM Consensus Sequence 3
  subgenus 3.4
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Leu or Met
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Ser or Thr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Ala or Thr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be His or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Ile or Trp

<400> SEQUENCE: 333

Xaa Xaa Phe Pro Xaa Xaa Xaa Phe
1 5

<210> SEQ ID NO 334
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP9 Cleavable Core CM Consensus Sequence 3
  subgenus 3.5
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Gly, Ile, Arg or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be His or Thr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Phe, Leu, Ser or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Leu, Pro or Arg
<220> FEATURE:
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<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Phe, Leu or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Ala, Cys or Gly
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Ile, Met or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Phe or Leu
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<400> SEQUENCE: 334

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

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<210> SEQ ID NO 335
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP9 Cleavable Core CM Consensus Sequence 3
  subgenus 3.6
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Phe or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Leu or Pro
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Phe or Leu
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Ile or Met
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<400> SEQUENCE: 335

Ser Thr Xaa Xaa Xaa Gly Xaa Phe
1 5

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<210> SEQ ID NO 336
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable moiety
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<400> SEQUENCE: 336

Leu Thr Phe Pro Thr Tyr Ile Phe
1 5

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<210> SEQ ID NO 337
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable moiety
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<400> SEQUENCE: 337

Met Thr Phe Pro Thr Tyr Ile Phe
1 5

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<210> SEQ ID NO 338
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 338
Leu Thr Phe Pro Thr Tyr Trp Phe
1 5

<210> SEQ ID NO 339
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 339
Met Thr Phe Pro Thr Tyr Trp Phe
1 5

<210> SEQ ID NO 340
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP9 Cleavable Core CM Consensus Sequence 4
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Asp, Gly, His, Leu, Asn, Pro, Gln,
    Arg, Ser, Trp or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Ala, Cys, Asp, Gly, Leu, Arg, Val,
    Trp or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Asp, His, Leu, Pro, Gln, Arg, Ser
    or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Asp, Phe, His, Ile, Leu, Met, Pro,
    Ser or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Ala, Cys, Glu, Phe, Gly, Lys, Met,
    Arg, Ser, Val or Trp
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Ala, Gly, Lys, Leu, Met, Asn, Pro,
    Arg, Ser or Thr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Ala, Phe, Gly, His, Leu, Pro, Arg,
    Ser or Thr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Ala, Gly, His, Ile, Asn, Pro, Ser,
    Thr or Tyr

<400> SEQUENCE: 340
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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

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<210> SEQ ID NO 341
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP9 Cleavable Core CM Consensus Sequence 4
    subgenus 4.1
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Asp, Gly, His, Leu, Pro, Gln, Ser
    or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Asp, Trp or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be His, Leu or Arg
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be His, Leu, Met, Pro or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Glu, Phe, Gly, Met, Arg or Trp
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Ala, Leu, Met, Asn, Pro or Arg
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Gly, Leu, Pro, Arg or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Gly, Ile, Pro, Ser, Thr or Tyr

<400> SEQUENCE: 341
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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

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<210> SEQ ID NO 342
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP9 Cleavable Core CM Consensus Sequence 4
    subgenus 4.2
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Asp or His
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Trp or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be His or Leu
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be His, Leu or Tyr
<220> FEATURE:
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<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Gly or Trp
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Pro or Arg
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Gly, Leu or Pro
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Gly, Ile, Ser or Thr

<400> SEQUENCE: 342

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> SEQ ID NO 343
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP9 Cleavable Core CM Consensus Sequence 4
  subgenus 4.3
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be His or Leu
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be His, Leu or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Gly or Trp
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Leu or Pro
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Gly, Ile, Ser or Thr

<400> SEQUENCE: 343
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His Trp Xaa Xaa Xaa Pro Xaa Xaa
1 5

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<210> SEQ ID NO 344
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP9 Cleavable Core CM Consensus Sequence 4
  subgenus 4.4
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be His or Leu
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Leu or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Leu or Pro
<220> FEATURE:
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<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Gly, Ile, Ser or Thr

<400> SEQUENCE: 344

His Trp Xaa Xaa Gly Pro Xaa Xaa
1 5

<210> SEQ ID NO 345
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP9 Cleavable Core CM Consensus Sequence 4
    subgenus 4.5
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be His or Leu
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Leu or Tyr

<400> SEQUENCE: 345

His Trp Xaa Xaa Gly Pro Pro Thr
1 5

<210> SEQ ID NO 346
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP9 Cleavable Core CM Consensus Sequence 4
    subgenus 4.6
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Asp, Gly, Ser or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Leu or Pro
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Asp or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Cys, Glu, Gly or Trp
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Met or Pro
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Gly, Arg or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be His, Ile or Tyr

<400> SEQUENCE: 346

Xaa Trp Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> SEQ ID NO 347
<211> LENGTH: 8
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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP9 Cleavable Core CM Consensus Sequence 4
    subgenus 4.7
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Asp, Gly or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Glu or Trp
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Met or Pro
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Gly or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Ile or Tyr

<400> SEQUENCE: 347
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Xaa Trp Leu Tyr Xaa Xaa Xaa Xaa
1 5

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<210> SEQ ID NO 348
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable moiety
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<400> SEQUENCE: 348

Asp Trp Leu Tyr Trp Met Gly Ile
1 5

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<210> SEQ ID NO 349
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable moiety
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<400> SEQUENCE: 349

Asp Trp Leu Tyr Trp Met Ser Ile
1 5

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<210> SEQ ID NO 350
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable moiety
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<400> SEQUENCE: 350

Asp Trp Leu Tyr Trp Pro Ser Ile
1 5

```
<210> SEQ ID NO 351
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<223> OTHER INFORMATION: cleavable moiety
<400> SEQUENCE: 351
His Trp His Leu Gly Pro Pro Thr
1 5

<210> SEQ ID NO 352
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 5
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ala, Ile, Gly, Leu, Met, Pro, Gln,
Ser, Thr or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Leu, Pro, Gln, Ser, Thr,
Val or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala, Cys, Glu, Phe, Gly, His, Lys,
Leu, Pro, Gln, Arg, Ser or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Asp, Glu, Gly, Ser or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Ala, Ile, Leu, Met or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Cys, Glu, Gly, Ile, Lys, Leu, Met,
Asn, Gln, Arg or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Ala, Phe, His, Ile, Leu, Met, Asn,
Pro, Arg, Ser or Thr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Ala, Cys, Gly, His, Ile, Leu, Asn,
Pro, Gln, Arg, Ser, Thr, Val or Trp

<400> SEQUENCE: 352
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> SEQ ID NO 353
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 5
    subgenus 5.1
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ala, Gly, Ile, Pro, Gln,
Ser, Thr or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Ala, Leu, Gln, Ser or Val
<220> FEATURE:
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<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala, Glu, Leu, Arg or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Asp or Gly
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Ile or Leu
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Glu, Ile, Leu, Met, Gln, Arg
    or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Phe, His, Leu, Met, Arg or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Ala, Gly, His, Leu, Asn, Pro,
    Gln or Ser

<400> SEQUENCE: 353

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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 1 5

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<210> SEQ ID NO 354
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 5
    subgenus 5.2
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ala, Ile, Ser or Thr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Leu, Gln, Ser or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala, Leu, Arg or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Ile or Leu
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Glu, Leu, Arg or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Phe, His, Leu, Arg or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be His, Leu, Pro or Ser

<400> SEQUENCE: 354

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Xaa Xaa Xaa Gly Xaa Xaa Xaa Xaa
 1 5

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<210> SEQ ID NO 355
<211> LENGTH: 8

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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 5
    subgenus 5.3
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ala, Ile, Ser or Thr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Leu, Ser or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala, Arg or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Glu, Leu or Arg
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Phe, His or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Leu, Pro or Ser

<400> SEQUENCE: 355
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Xaa Xaa Xaa Gly Leu Xaa Xaa Xaa
1 5

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<210> SEQ ID NO 356
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 5
    subgenus 5.4
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ala, Ile, Ser or Thr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Leu, Ser or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Arg or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Leu or Arg
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Phe, His or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Pro or Ser
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<400> SEQUENCE: 356

Xaa Xaa Xaa Gly Leu Xaa Xaa Xaa
1 5

<210> SEQ ID NO 357
<211> LENGTH: 8

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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 5
    subgenus 5.5
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ala, Ile, Ser or Thr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Leu, Ser or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Arg or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Leu or Arg
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Pro or Ser

<400> SEQUENCE: 357
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Xaa Xaa Xaa Gly Leu Xaa Ser Xaa
1 5

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<210> SEQ ID NO 358
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 5
    subgenus 5.6
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Leu, Ser or Val

<400> SEQUENCE: 358
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Thr Xaa Ser Gly Leu Arg Ser Pro
1 5

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<210> SEQ ID NO 359
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 5
    subgenus 5.7
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ala, Gly, Ile, Met, Pro, Ser, Thr
    or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Leu, Gln, Ser or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala, Cys, Phe, Lys, Leu, Gln, Arg
    or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Asp, Gly, Ser or Val
<220> FEATURE:
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<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Leu or Met
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Gly, Ile, Leu, Met, Asn, Gln or Arg
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Ile, Asn, Pro or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Ala, His, Ile, Asn, Gln or Ser

<400> SEQUENCE: 359
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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

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<210> SEQ ID NO 360
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 5
  subgenus 5.8
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ala, Ile or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Leu, Gln, Ser or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Leu, Arg or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Leu, Met or Arg
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Ala, His, Asn, Gln or Ser

<400> SEQUENCE: 360
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Xaa Xaa Xaa Gly Leu Xaa Ser Xaa
1 5

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<210> SEQ ID NO 361
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 5
  subgenus 5.9
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ala, Ile or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Leu, Gln, Ser or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Leu, Arg or Ser
<220> FEATURE:
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<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Leu, Met or Arg
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Ala, His, Asn, Gln or Ser

<400> SEQUENCE: 361

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Xaa Xaa Xaa Gly Leu Xaa Ser Xaa
1 5

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<210> SEQ ID NO 362
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 5
  subgenus 5.10
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ala or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Leu or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Leu or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Leu or Arg
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be His or Ser

<400> SEQUENCE: 362

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Xaa Xaa Xaa Gly Leu Xaa Ser Xaa
1 5

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<210> SEQ ID NO 363
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 5
  subgenus 5.11
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ala or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Leu or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Leu or Arg
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be His or Ser

<400> SEQUENCE: 363

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Xaa Xaa Ser Gly Leu Xaa Ser Xaa
1 5

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<210> SEQ ID NO 364
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 364

Ser Val Ser Gly Leu Leu Ser His
1 5

<210> SEQ ID NO 365
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 365

Ser Val Ser Gly Leu Leu Ser Ser
1 5

<210> SEQ ID NO 366
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 366

Ser Val Ser Gly Leu Arg Ser His
1 5

<210> SEQ ID NO 367
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 367

Ser Val Ser Gly Leu Arg Ser Ser
1 5

<210> SEQ ID NO 368
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 368

Thr Leu Ser Gly Leu Arg Ser Pro
1 5

<210> SEQ ID NO 369
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 369

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Thr Ser Ser Gly Leu Arg Ser Pro
1 5

<210> SEQ ID NO 370
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 370

Thr Val Ser Gly Leu Arg Ser Pro
1 5

<210> SEQ ID NO 371
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 6
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ala, Cys, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Ala, Cys, Glu, Phe, His, Leu, Asn, Arg, Ser or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Glu, Lys, Asn, Pro, Gln, Ser, Thr or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Ala, Glu, Gly, His, Lys, Leu, Asn, Pro, Arg, Ser or Thr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Ile, Lys, Leu, Met, Asn, Arg, Thr, Val or Tyr FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Glu, Ile, Lys, Leu, Pro, Gln, Arg, Ser, Thr, Val or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Ala, Cys, Asp, Glu, Gly, Ile, Leu, Met, Gln, Arg, Ser, Thr or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Ala, Phe, Gly, His, Ile, Leu, Pro, Gln, Arg, Ser, Thr or Tyr

<400> SEQUENCE: 371

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> SEQ ID NO 372
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 6
Subgenus 6.1

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<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ala, Phe, Gly, His, Ile, Leu, Met,
  Gln, Arg or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Ala, Phe, His, Leu or Asn
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala, Glu, Asn, Gln or Ser
<220> FEATURE:
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<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Ala, Glu, Lys, Asn, Ser or Thr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Leu or Met
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Ala, Ile, Lys, Leu, Pro, Arg or Val
<220> FEATURE:
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<223> OTHER INFORMATION: Xaa may be Ala, Asp, Ile, Leu, Met, Arg, Thr
  or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Ala, Phe, Gly, His, Ile, Leu, Pro,
  Gln, Arg or Ser

<400> SEQUENCE: 372

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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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<210> SEQ_ID NO 373
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 6
  Subgenus 6.2
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Gly, Leu, Arg or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Ala or Leu
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala, Glu, Asn, Gln or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Ala, Glu, Asn, Ser or Thr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Leu or Met
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Leu or Arg
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)

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<223> OTHER INFORMATION: Xaa may be Ala, Leu or Thr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Phe, Gly, Leu, Arg or Ser

<400> SEQUENCE: 373

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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<210> SEQ ID NO 374
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 6
Subgenus 6.3
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Ala or Leu
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Glu, Asn, Gln or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Ala or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Leu or Met
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Ala or Thr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Phe, Leu or Arg

<400> SEQUENCE: 374

Leu Xaa Xaa Xaa Xaa Arg Xaa Xaa
1 5

<210> SEQ ID NO 375
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 6
Subgenus 6.4
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Ala or Leu
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Glu, Asn, Gln or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Ala or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Leu or Met
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
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<223> OTHER INFORMATION: Xaa may be Leu or Arg
<400> SEQUENCE: 375
Leu Xaa Xaa Xaa Xaa Arg Ala Xaa
1 5

<210> SEQ ID NO 376
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 6A
Subgenus 6A.1
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ala, Glu, Leu, Asn, Pro or Gln
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Phe, His, Leu, Asn or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Gln or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Leu, Thr, Val or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Asp, Glu, Pro, Gln or Arg
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Ala, Cys, Gly, Ile, Met, Arg, Ser
or Thr

<400> SEQUENCE: 376
Xaa Xaa Xaa Ala Xaa Xaa Xaa
1 5

<210> SEQ ID NO 377
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 6A
Subgenus 6A.2
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ala, Glu, Leu or Gln
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Phe, His or Asn
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Leu or Thr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Gln or Arg
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Ile or Met

<400> SEQUENCE: 377
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Xaa Xaa Gln Ala Xaa Xaa Xaa
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<210> SEQ ID NO 378
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 6A
Subgenus 6A.3
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Phe, His or Asn

<400> SEQUENCE: 378

Ala Xaa Gln Ala Leu Arg Met
1 5

<210> SEQ ID NO 379
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 379

Ala Phe Gln Ala Leu Arg Met
1 5

<210> SEQ ID NO 380
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 380

Ala His Gln Ala Leu Arg Met
1 5

<210> SEQ ID NO 381
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 381

Ala Asn Gln Ala Leu Arg Met
1 5

<210> SEQ ID NO 382
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 382

Ala Asn Gln Ala Leu Arg Met Ala
1 5

<210> SEQ ID NO 383

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<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 383

Leu Leu Glu Ala Leu Arg Ala Leu
1 5

<210> SEQ ID NO 384
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 384

Leu Leu Asn Ala Leu Arg Ala Leu
1 5

<210> SEQ ID NO 385
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 385

Leu Leu Gln Ala Leu Arg Ala Leu
1 5

<210> SEQ ID NO 386
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 386

Leu Leu Ser Ala Leu Arg Ala Leu
1 5

<210> SEQ ID NO 387
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 387

Leu Leu Glu Ser Leu Arg Ala Leu
1 5

<210> SEQ ID NO 388
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 388

Leu Leu Asn Ser Leu Arg Ala Leu
1 5

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<210> SEQ ID NO 389
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 389

Leu Leu Gln Ser Leu Arg Ala Leu
1 5

<210> SEQ ID NO 390
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 390

Leu Leu Ser Ser Leu Arg Ala Leu
1 5

<210> SEQ ID NO 391
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 391

Gln Phe Gln Ala Leu Arg Met
1 5

<210> SEQ ID NO 392
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 392

Gln His Gln Ala Leu Arg Met
1 5

<210> SEQ ID NO 393
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 393

Gln Asn Gln Ala Leu Arg Met
1 5

<210> SEQ ID NO 394
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 7
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ala, Phe, Leu, Gln, Ser, Thr or Val

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<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Ala, Glu, Gly, His, Lys, Gln, Arg,
  Val or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala, Gly, Ile, Lys, Leu, Met, Asn,
  Ser, Thr or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Phe, Gly, Ile, Leu, Asn,
  Pro, Arg, Ser, Thr or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Ala, Pro or Arg
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Gly, Leu, Met, Pro, Arg,
  Ser, Thr, Val, Trp or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Ala, Cys, Glu, Phe, His, Ile, Leu,
  Asn, Arg, Ser, Thr, Trp or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Ala, Phe, Gly, Ile, Leu, Met, Arg,
  Ser, Thr or Val

<400> SEQUENCE: 394

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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

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<210> SEQ ID NO 395
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 7
  Subgenus 7.1
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be His, Lys, Gln, Arg or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala, Leu, Met, Ser, Thr or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Ala, Ile, Leu, Ser or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Ala, Gly, Arg, Ser, Val or Trp
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Ile, Arg, Thr or Trp
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Ala, Phe, Gly, Leu, Ser or Val

<400> SEQUENCE: 395

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Leu Xaa Xaa Xaa Pro Xaa Xaa Xaa

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1 5

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<210> SEQ ID NO 396
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 7
    Subgenus 7.2
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be His, Lys, Arg or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala, Leu or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Ala, Ile or Leu
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Gly, Arg or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Thr or Trp
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Ala, Phe, Leu or Ser

<400> SEQUENCE: 396
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Leu Xaa Xaa Xaa Pro Xaa Xaa Xaa
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<210> SEQ ID NO 397
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 7
    Subgenus 7.3
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Lys, Arg or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Ala or Leu
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Gly, Arg or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Ala or Leu

<400> SEQUENCE: 397
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Leu Xaa Ala Xaa Pro Xaa Trp Xaa
1 5

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<210> SEQ ID NO 398
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 7
      Subgenus 7.4
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ala, Phe, Leu, Gln or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Ala, Glu, Gly, His, Lys, Gln or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala, Gly, Lys, Ser or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Ala, Ile, Leu, Pro or Thr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Ala, Pro or Arg
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Ala, Leu, Met, Arg, Val or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Cys, His, Arg, Thr or Trp
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Ala, Phe, Leu, Arg, Ser or Thr

<400> SEQUENCE: 398
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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

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<210> SEQ ID NO 399
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 7
      Subgenus 7.5
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Phe or Leu
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Gly, Lys, Gln or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala, Gly, Ser or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Ala, Ile or Leu
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Ala, Arg or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Arg or Trp
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Ala, Phe, Leu or Arg
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<400> SEQUENCE: 399

Xaa Xaa Xaa Xaa Pro Xaa Xaa Xaa
1 5

<210> SEQ ID NO 400
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 7
Subgenus 7.6
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Lys or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Ala, Ile or Leu
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Ala, Arg or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Ala or Phe

<400> SEQUENCE: 400

Leu Xaa Xaa Xaa Pro Xaa Trp Xaa
1 5

<210> SEQ ID NO 401
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 7
Subgenus 7.7
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Lys or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Ala or Ile
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Arg or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Ala or Phe

<400> SEQUENCE: 401

Leu Xaa Ala Xaa Pro Xaa Trp Xaa
1 5

<210> SEQ ID NO 402
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:

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<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 402

Leu Pro Ala Gly Leu Leu Leu
1 5

<210> SEQ ID NO 403

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 403

Leu Lys Ala Ala Pro Val Trp Ala
1 5

<210> SEQ ID NO 404

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 404

Leu Lys Ala Ala Pro Arg Trp Phe
1 5

<210> SEQ ID NO 405

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 405

Leu Lys Ala Ala Pro Val Trp Phe
1 5

<210> SEQ ID NO 406

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 406

Leu Tyr Ala Ala Pro Arg Trp Ala
1 5

<210> SEQ ID NO 407

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 407

Leu Tyr Ala Ala Pro Val Trp Ala
1 5

<210> SEQ ID NO 408

<211> LENGTH: 8

<212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 408

Leu Tyr Ala Ala Pro Arg Trp Phe
1 5

<210> SEQ ID NO 409
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 409

Leu Tyr Ala Ala Pro Val Trp Phe
1 5

<210> SEQ ID NO 410
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 8
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Phe, Gly, His, Ile, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val or Trp
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Ala, Pro, Arg or Thr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala, Glu, Phe, Gly, His, Ile, Lys, Leu, Asn, Pro, Gln, Arg, Ser, Thr or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Glu, Gly, His, Lys, Met, Asn, Pro, Arg, Ser or Thr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Cys, Phe, His, Ile, Leu, Met, Pro, Arg, Ser, Val, Trp or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Ala, Cys, Phe, Gly, His, Ile, Lys, Leu, Met, Arg, Ser, Thr, Val, Trp or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Glu, Phe, Gly, His, Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val or Tyr

<400> SEQUENCE: 410

Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> SEQ ID NO 411
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 8

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Subgenus 8.1
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ala, Phe, Gly, Ile, Leu, Met, Asn,
    Ser, Thr, Val or Trp
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala, Glu, Phe, His, Ile, Lys, Asn,
    Pro, Gln, Arg, Ser, Thr or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Glu, Gly, His, Asn, Pro
    or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Cys, Phe, Ile, Leu, Met, Arg, Ser
    or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Cys, Phe, Gly, Ile, Leu, Arg, Ser,
    Thr, Val or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Ala, Phe, Leu, Met, Pro, Gln, Arg,
    Ser, Thr, Val or Tyr

<400> SEQUENCE: 411

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Xaa Pro Xaa Xaa Xaa Xaa Xaa
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<210> SEQ ID NO 412
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 8
    Subgenus 8.2
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Phe, Gly, Leu, Ser, Thr or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala, Glu, His, Lys, Asn, Gln, Arg,
    Ser, Thr or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Ala, Gly, His, Asn, Pro or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Ile, Leu, Met or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Phe, Ile, Leu, Arg, Ser, Thr, Val
    or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Ala, Phe, Leu, Arg, Thr, Val or Tyr

<400> SEQUENCE: 412

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Xaa Pro Xaa Xaa Xaa Xaa Xaa
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<210> SEQ ID NO 413
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 8
    Subgenus 8.3
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Phe, Leu or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala, Lys, Gln, Arg or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Ala, Gly, His or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Ile, Leu, Met or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Phe, Leu, Arg, Ser, Thr, Val or
    Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Phe, Leu, Thr or Val

<400> SEQUENCE: 413
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Xaa Pro Xaa Xaa Xaa Xaa Xaa
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<210> SEQ ID NO 414
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 8
    Subgenus 8.4
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Phe, Leu or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala, Gln or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Gly or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Ile, Leu or Met
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Leu, Ser or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Phe, Leu or Thr

<400> SEQUENCE: 414
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Xaa Pro Xaa Xaa Xaa Xaa Xaa

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1 5

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<210> SEQ ID NO 415
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 8
  Subgenus 8.5
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Phe, Leu or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala, Gln or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Ile, Leu or Met
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Leu or Val

<400> SEQUENCE: 415
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Xaa Pro Xaa Gly Xaa Xaa Leu
1 5

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<210> SEQ ID NO 416
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 8
  Subgenus 8.6
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Phe, Leu or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Ile, Leu or Met
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Leu or Val
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<400> SEQUENCE: 416

Xaa Pro Xaa Gly Xaa Xaa Leu
1 5

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<210> SEQ ID NO 417
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 8
  Subgenus 8.7
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Phe, Gly, Leu, Met, Pro, Ser, Val
  or Trp
<220> FEATURE:
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<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala, Asn, Gln or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Gly, His, Met, Asn, Pro
    or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Phe, Ile, Leu, Met or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Ala, Ile, Leu, Met, Ser or Val and
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Ala, Gly, Ile, Leu, Met, Asn, Pro,
    Gln, Arg, Ser, Thr or Tyr

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<400> SEQUENCE: 417

Xaa Pro Xaa Xaa Xaa Xaa Xaa
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<210> SEQ ID NO 418
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Leu, Ser or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala, Asn, Gln or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be His, Asn, Pro or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Phe, Ile, Leu or Met
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Ile, Leu, Ser or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Ala, Leu or Gln

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<400> SEQUENCE: 418

Xaa Pro Xaa Xaa Xaa Xaa Xaa
 1 5

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<210> SEQ ID NO 419
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 8
    Subgenus 8.9
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)

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<223> OTHER INFORMATION: Xaa may be Ala, Asn, Gln or Ser

<220> FEATURE:

<221> NAME/KEY: misc_feature

<222> LOCATION: (5)..(5)

<223> OTHER INFORMATION: Xaa may be Ile or Leu

<400> SEQUENCE: 419

Leu Pro Xaa His Xaa Val Leu
1 5

<210> SEQ ID NO 420

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 420

Leu Pro Ala Gly Leu Leu Leu Arg
1 5

<210> SEQ ID NO 421

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 421

Leu Pro Ala His Leu Val Leu Leu
1 5

<210> SEQ ID NO 422

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 422

Leu Pro Ser His Leu Val Leu Leu
1 5

<210> SEQ ID NO 423

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 423

Leu Pro Ala His Leu Val Leu Val
1 5

<210> SEQ ID NO 424

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 424

Leu Pro Ser His Leu Val Leu Val
1 5

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<210> SEQ ID NO 425
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 9
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Phe, Gly, His, Ile, Leu,
Met, Pro, Arg, Ser, Thr or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Glu, Leu, Met, Pro, Gln,
Arg, Ser, Thr, Val or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala, Gly, His, Leu, Asn, Pro, Arg,
Ser, Thr or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Glu, His, Leu, Met, Asn,
Pro, Gln, Arg, Ser, Thr or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Ala, Gly, Arg, Ser or Thr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Cys, Phe, Leu, Met, Ser, Val, Trp
or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Ala, Glu, Phe, Gly, His, Ile, Leu,
Met, Asn, Gln, Arg, Ser, Val, Trp or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Ala, Glu, Gly, Leu, Pro, Arg, Ser
or Val

<400> SEQUENCE: 425

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1      5
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<210> SEQ ID NO 426
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 9
Subgenus 9.1
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Phe, Gly, Ile, Arg or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Asp, Glu, Leu, Met, Pro, Arg, Ser,
Thr, Val or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala, His, Pro or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
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<223> OTHER INFORMATION: Xaa may be Ala, Asp, Glu, His, Leu, Met, Asn,  
      Arg, Thr or Val  
<220> FEATURE:  
<221> NAME/KEY: misc_feature  
<222> LOCATION: (5)..(5)  
<223> OTHER INFORMATION: Xaa may be Ala, Gly or Arg  
<220> FEATURE:  
<221> NAME/KEY: misc_feature  
<222> LOCATION: (6)..(6)  
<223> OTHER INFORMATION: Xaa may be Phe, Leu, Met, Ser, Val or Trp  
<220> FEATURE:  
<221> NAME/KEY: misc_feature  
<222> LOCATION: (7)..(7)  
<223> OTHER INFORMATION: Xaa may be Ala, Glu, His, Leu, Met, Arg, Ser  
      or Val  
<220> FEATURE:  
<221> NAME/KEY: misc_feature  
<222> LOCATION: (8)..(8)  
<223> OTHER INFORMATION: Xaa may be Ala, Gly, Leu, Pro, Arg, Ser or Val  
  
<400> SEQUENCE: 426
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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

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<210> SEQ ID NO 427  
<211> LENGTH: 8  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 9  
      Subgenus 9.2  
<220> FEATURE:  
<221> NAME/KEY: misc_feature  
<222> LOCATION: (1)..(1)  
<223> OTHER INFORMATION: Xaa may be Phe, Gly, Ile, Arg or Ser  
<220> FEATURE:  
<221> NAME/KEY: misc_feature  
<222> LOCATION: (2)..(2)  
<223> OTHER INFORMATION: Xaa may be Leu, Pro, Arg or Val  
<220> FEATURE:  
<221> NAME/KEY: misc_feature  
<222> LOCATION: (3)..(3)  
<223> OTHER INFORMATION: Xaa may be Ala or His  
<220> FEATURE:  
<221> NAME/KEY: misc_feature  
<222> LOCATION: (4)..(4)  
<223> OTHER INFORMATION: Xaa may be Ala, Asp or Arg  
<220> FEATURE:  
<221> NAME/KEY: misc_feature  
<222> LOCATION: (5)..(5)  
<223> OTHER INFORMATION: Xaa may be Ala or Gly  
<220> FEATURE:  
<221> NAME/KEY: misc_feature  
<222> LOCATION: (6)..(6)  
<223> OTHER INFORMATION: Xaa may be Leu or Val  
<220> FEATURE:  
<221> NAME/KEY: misc_feature  
<222> LOCATION: (7)..(7)  
<223> OTHER INFORMATION: Xaa may be His, Leu, Met, Arg, Ser or Val  
<220> FEATURE:  
<221> NAME/KEY: misc_feature  
<222> LOCATION: (8)..(8)  
<223> OTHER INFORMATION: Xaa may be Ala, Leu, Ser or Val  
  
<400> SEQUENCE: 427
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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

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<210> SEQ ID NO 428  
<211> LENGTH: 8  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence
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<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 9
  Subgenus 9.3
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Gly, Arg or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Arg or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala or His
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Ala, Asp or Arg
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Ala or Gly
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Leu or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be His or Arg
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Ala, Leu, Ser or Val

<400> SEQUENCE: 428

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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<210> SEQ ID NO 429
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 9
  Subgenus 9.4
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala or His
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Ala or Asp
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Leu or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Ala, Ser or Val

<400> SEQUENCE: 429

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Arg Arg Xaa Xaa Gly Xaa Arg Xaa
1          5

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<210> SEQ ID NO 430
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:  
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 9  
Subgenus 9.5  
<220> FEATURE:  
<221> NAME/KEY: misc_feature  
<222> LOCATION: (1)..(1)  
<223> OTHER INFORMATION: Xaa may be Asp, Phe, Gly, Ile, Leu, Arg, Ser  
or Thr  
<220> FEATURE:  
<221> NAME/KEY: misc_feature  
<222> LOCATION: (2)..(2)  
<223> OTHER INFORMATION: Xaa may be Glu, Leu, Met, Arg, Ser, Thr or Val  
<220> FEATURE:  
<221> NAME/KEY: misc_feature  
<222> LOCATION: (3)..(3)  
<223> OTHER INFORMATION: Xaa may be His or Asn  
<220> FEATURE:  
<221> NAME/KEY: misc_feature  
<222> LOCATION: (4)..(4)  
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Leu, Met, Arg or Thr  
<220> FEATURE:  
<221> NAME/KEY: misc_feature  
<222> LOCATION: (5)..(5)  
<223> OTHER INFORMATION: Xaa may be Ala, Gly, Arg or Thr  
<220> FEATURE:  
<221> NAME/KEY: misc_feature  
<222> LOCATION: (6)..(6)  
<223> OTHER INFORMATION: Xaa may be Cys, Leu, Met, Ser, Val or Trp  
<220> FEATURE:  
<221> NAME/KEY: misc_feature  
<222> LOCATION: (7)..(7)  
<223> OTHER INFORMATION: Xaa may be Ala, Glu, Phe, Gly, Leu, Arg, Ser or  
Trp  
<220> FEATURE:  
<221> NAME/KEY: misc_feature  
<222> LOCATION: (8)..(8)  
<223> OTHER INFORMATION: Xaa may be Ala, Gly, Leu, Pro, Arg, Ser or Val  
  
<400> SEQUENCE: 430
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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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<210> SEQ ID NO 431  
<211> LENGTH: 8  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 9  
Subgenus 9.6  
<220> FEATURE:  
<221> NAME/KEY: misc_feature  
<222> LOCATION: (1)..(1)  
<223> OTHER INFORMATION: Xaa may be Phe, Ile, Arg or Ser  
<220> FEATURE:  
<221> NAME/KEY: misc_feature  
<222> LOCATION: (2)..(2)  
<223> OTHER INFORMATION: Xaa may be Glu, Leu, Arg or Val  
<220> FEATURE:  
<221> NAME/KEY: misc_feature  
<222> LOCATION: (4)..(4)  
<223> OTHER INFORMATION: Xaa may be Asp, Met, Arg or Thr  
<220> FEATURE:  
<221> NAME/KEY: misc_feature  
<222> LOCATION: (5)..(5)  
<223> OTHER INFORMATION: Xaa may be Ala or Gly  
<220> FEATURE:  
<221> NAME/KEY: misc_feature  
<222> LOCATION: (6)..(6)  
<223> OTHER INFORMATION: Xaa may be Leu, Met, Ser or Val  
<220> FEATURE:  
<221> NAME/KEY: misc_feature  
<222> LOCATION: (7)..(7)  
<223> OTHER INFORMATION: Xaa may be Glu, Arg or Ser  
<220> FEATURE:
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<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Ala, Pro, Ser or Val

<400> SEQUENCE: 431
Xaa Xaa His Xaa Xaa Xaa Xaa Xaa
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<210> SEQ ID NO 432
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 9
  Subgenus 9.7
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ile or Arg
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Glu, Arg or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Asp, Met, Arg or Thr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Ala or Gly
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Leu or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Arg or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Ala, Pro, Ser or Val

<400> SEQUENCE: 432
Xaa Xaa His Xaa Xaa Xaa Xaa Xaa
1 5

<210> SEQ ID NO 433
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 9
  Subgenus 9.8
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ile or Arg
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Ala or Gly
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Leu or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Arg or Ser
<220> FEATURE:
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<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Ala or Ser

<400> SEQUENCE: 433

Xaa Arg His Asp Xaa Xaa Xaa Xaa
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<210> SEQ ID NO 434
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 434

Arg Arg His Asp Gly Leu Arg Ala
1 5

<210> SEQ ID NO 435
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 435

Arg Arg His Asp Gly Leu Arg Ser
1 5

<210> SEQ ID NO 436
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 10
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Gly, His, Ile, Leu, Asn,
Pro, Arg, Ser, Thr, Val, Trp or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Gly, His, Leu, Met, Asn,
Pro, Gln, Arg, Ser, Val or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala, His, Lys, Leu, Asn, Pro, Gln,
Arg, Ser, Thr or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Phe, Gly, His, Ile, Leu,
Pro, Arg, Ser, Val or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Cys, Phe, Ile, Leu, Pro, Val or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Glu, Phe, Gly, Ile, Lys,
Met, Asn, Arg, Ser, Thr, Val or Trp
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Glu, Phe, His, Lys, Leu,
Met, Asn, Gln, Arg, Val or Tyr
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<220> FEATURE:  
<221> NAME/KEY: misc_feature  
<222> LOCATION: (8)..(8)  
<223> OTHER INFORMATION: Xaa may be Ala, Phe, Ile, Leu, Met or Val  
  
<400> SEQUENCE: 436  
  
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa  
1 5  
  
<210> SEQ ID NO 437  
<211> LENGTH: 8  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 10  
Subgenus 10.1  
<220> FEATURE:  
<221> NAME/KEY: misc_feature  
<222> LOCATION: (1)..(1)  
<223> OTHER INFORMATION: Xaa may be Ala, Ile, Pro, Ser, Thr, Val or Tyr  
<220> FEATURE:  
<221> NAME/KEY: misc_feature  
<222> LOCATION: (2)..(2)  
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Gly, Leu, Met, Gln, Arg,  
Ser, Val or Tyr  
<220> FEATURE:  
<221> NAME/KEY: misc_feature  
<222> LOCATION: (3)..(3)  
<223> OTHER INFORMATION: Xaa may be Ala, His, Lys, Leu, Asn, Ser or Thr  
<220> FEATURE:  
<221> NAME/KEY: misc_feature  
<222> LOCATION: (4)..(4)  
<223> OTHER INFORMATION: Xaa may be Gly, His, Ile, Leu, Ser or Val  
<220> FEATURE:  
<221> NAME/KEY: misc_feature  
<222> LOCATION: (5)..(5)  
<223> OTHER INFORMATION: Xaa may be Ile, Leu or Val  
<220> FEATURE:  
<221> NAME/KEY: misc_feature  
<222> LOCATION: (6)..(6)  
<223> OTHER INFORMATION: Xaa may be Ala, Phe, Gly, Lys, Arg, Ser or Trp  
<220> FEATURE:  
<221> NAME/KEY: misc_feature  
<222> LOCATION: (7)..(7)  
<223> OTHER INFORMATION: Xaa may be Asp, His, Leu, Met, Asn, Gln, Arg  
or Val  
<220> FEATURE:  
<221> NAME/KEY: misc_feature  
<222> LOCATION: (8)..(8)  
<223> OTHER INFORMATION: Xaa may be Ala, Ile, Leu or Val  
  
<400> SEQUENCE: 437  
  
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa  
1 5  
  
<210> SEQ ID NO 438  
<211> LENGTH: 8  
<212> TYPE: PRT  
<213> ORGANISM: Artificial Sequence  
<220> FEATURE:  
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 10  
Subgenus 10.2  
<220> FEATURE:  
<221> NAME/KEY: misc_feature  
<222> LOCATION: (1)..(1)  
<223> OTHER INFORMATION: Xaa may be Ala, Ile, Thr or Val  
<220> FEATURE:  
<221> NAME/KEY: misc_feature  
<222> LOCATION: (2)..(2)  
<223> OTHER INFORMATION: Xaa may be Ala, Leu, Met, Gln, Arg, Val or Tyr  
<220> FEATURE:  
<221> NAME/KEY: misc_feature
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<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala, Asn, Ser or Thr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Gly, Leu, Ser or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Leu or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Ala, Phe, Gly, Lys or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Met, Asn, Gln, Arg or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Ile, Leu or Val

<400> SEQUENCE: 438

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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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<210> SEQ ID NO 439
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 10
  Subgenus 10.3
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ala, Ile, Thr or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Met, Gln or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala, Asn or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Gly, Leu, Ser or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Leu or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Ala, Phe, Gly or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Met, Asn, Gln or Arg
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Ile, Leu or Val

<400> SEQUENCE: 439

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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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<210> SEQ ID NO 440

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<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 10
    Subgenus 10.4
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ala, Ile or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Asn or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Gly, Leu or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Ala, Gly or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Met, Gln or Arg
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Leu or Val

<400> SEQUENCE: 440
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Xaa Tyr Xaa Xaa Leu Xaa Xaa Xaa
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<210> SEQ_ID NO 441
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 10
    Subgenus 10.5
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ala, Ile or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Asn or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Gly, Leu or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Gly or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Met or Arg
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Leu or Val

<400> SEQUENCE: 441
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Xaa Tyr Xaa Xaa Leu Xaa Xaa Xaa
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<210> SEQ_ID NO 442

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<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 10
  Subgenus 10.6
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ala, Ile or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Asn or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Gly, Leu or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Met or Arg
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Leu or Val

<400> SEQUENCE: 442
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Xaa Tyr Xaa Xaa Leu Ser Xaa Xaa
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<210> SEQ ID NO 443
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 10
  Subgenus 10.7
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Asn or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Gly or Leu
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Leu or Val
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<400> SEQUENCE: 443

Ala Tyr Xaa Xaa Leu Ser Arg Xaa
1 5

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<210> SEQ ID NO 444
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 10
  Subgenus 10.8
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Gly, Ile, Leu, Asn, Pro,
  Ser, Thr, Val, Trp or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Gly, Leu, Met, Gln, Ser
  or Val
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<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be His, Lys, Asn, Pro, Gln, Arg, Ser
    or Thr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be His, Ile, Leu, Arg or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Ile, Leu, Pro or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Glu, Gly, Ile, Lys, Met,
    Asn, Ser or Thr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Asp, Phe, Leu, Met, Gln, Arg or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Ala, Phe, Ile, Leu or Val

<400> SEQUENCE: 444

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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 1 5

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<210> SEQ ID NO 445
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 10
    Subgenus 10.9
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ala, Ile, Thr or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Gly, Leu, Met, Gln, Ser
    or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be His, Lys, Asn, Ser or Thr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be His, Ile, Leu or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Ala, Gly, Lys or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Leu, Met, Gln, Arg or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Ala, Leu or Val

<400> SEQUENCE: 445

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Xaa Xaa Xaa Xaa Leu Xaa Xaa Xaa
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<210> SEQ_ID NO 446
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 10
    Subgenus 10.10
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ala or Ile
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Ala, Leu or Gln
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Asn, Ser or Thr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Leu or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Ala, Gly, Lys or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Met, Arg or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Leu or Val

<400> SEQUENCE: 446

Xaa Xaa Xaa Xaa Leu Xaa Xaa Xaa
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<210> SEQ_ID NO 447
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 10
    Subgenus 10.11
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ala or Ile
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Ala, Leu or Gln
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Asn or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Leu or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Ala or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Met or Arg
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
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<223> OTHER INFORMATION: Xaa may be Leu or Val

<400> SEQUENCE: 447

Xaa Xaa Xaa Xaa Leu Xaa Xaa Xaa
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<210> SEQ ID NO 448

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 10
Subgenus 10.12

<220> FEATURE:

<221> NAME/KEY: misc_feature

<222> LOCATION: (2)..(2)

<223> OTHER INFORMATION: Xaa may be Ala, Leu or Gln

<220> FEATURE:

<221> NAME/KEY: misc_feature

<222> LOCATION: (4)..(4)

<223> OTHER INFORMATION: Xaa may be Leu or Val

<220> FEATURE:

<221> NAME/KEY: misc_feature

<222> LOCATION: (6)..(6)

<223> OTHER INFORMATION: Xaa may be Ala or Ser

<220> FEATURE:

<221> NAME/KEY: misc_feature

<222> LOCATION: (7)..(7)

<223> OTHER INFORMATION: Xaa may be Met or Arg

<220> FEATURE:

<221> NAME/KEY: misc_feature

<222> LOCATION: (8)..(8)

<223> OTHER INFORMATION: Xaa may be Leu or Val

<400> SEQUENCE: 448

Ile Xaa Asn Xaa Leu Xaa Xaa Xaa
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<210> SEQ ID NO 449

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 10
Subgenus 10.13

<220> FEATURE:

<221> NAME/KEY: misc_feature

<222> LOCATION: (2)..(2)

<223> OTHER INFORMATION: Xaa may be Ala, Leu or Gln

<220> FEATURE:

<221> NAME/KEY: misc_feature

<222> LOCATION: (4)..(4)

<223> OTHER INFORMATION: Xaa may be Leu or Val

<220> FEATURE:

<221> NAME/KEY: misc_feature

<222> LOCATION: (8)..(8)

<223> OTHER INFORMATION: Xaa may be Leu or Val

<400> SEQUENCE: 449

Ile Xaa Asn Xaa Leu Ser Met Xaa
1 5

<210> SEQ ID NO 450

<211> LENGTH: 8

<212> TYPE: PRT

<213> ORGANISM: Artificial Sequence

<220> FEATURE:

<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 450

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Ile Ala Asn Leu Leu Ser Met Val
1 5

<210> SEQ ID NO 451
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 451

Ile Leu Asn Leu Leu Ser Met Val
1 5

<210> SEQ ID NO 452
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 452

Ile Gln Asn Leu Leu Ser Met Val
1 5

<210> SEQ ID NO 453
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 11
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ala, Gly, His, Leu, Pro, Arg, Ser or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Ala, Gly, Arg, Ser, Thr or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala, Gly, Pro, Arg, Ser or Thr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Ala, Gly, Pro, Arg, Ser or Thr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Leu or Trp
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Phe, His, Leu, Met, Gln, Ser, Val or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Glu, Ile, Lys, Pro, Arg, Ser, Thr or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Ala, Glu, Phe, Gly, His, Ile, Leu, Asn, Pro, Gln, Arg or Val

<400> SEQUENCE: 453

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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

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<210> SEQ ID NO 454
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 11
    Subgenus 11.1
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ala, Gly, Pro, Arg or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Ala, Arg or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Gly, Pro, Ser or Thr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Leu or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Leu, Ser, Val or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Asp, Glu, Pro or Thr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Pro, Gln or Val

<400> SEQUENCE: 454
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Xaa Xaa Xaa Xaa Trp Xaa Xaa Xaa
1 5

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<210> SEQ ID NO 455
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 11
    Subgenus 11.2
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Gly, Pro, Arg or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Ala or Arg
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Gly, Pro or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Leu or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Leu or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
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<223> OTHER INFORMATION: Xaa may be Glu or Thr
<400> SEQUENCE: 455
Xaa Xaa Xaa Xaa Trp Xaa Xaa Gln
1 5

<210> SEQ ID NO 456
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 11
Subgenus 11.3
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Pro or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Leu or Val

<400> SEQUENCE: 456
Pro Ala Xaa Xaa Trp Tyr Thr Gln
1 5

<210> SEQ ID NO 457
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 457
Pro Ala Ser Leu Trp Tyr Thr Gln
1 5

<210> SEQ ID NO 458
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 12
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Glu, Phe, Gly, His, Ile,
Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Ala, Glu, Phe, Gly, His, Ile, Lys,
Leu, Met, Pro, Gln, Arg, Ser, Thr, Val, Trp or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala, Glu, Gly, His, Lys, Asn, Pro,
Arg, Ser, Thr, Val or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Ala, Gly, His, Ile, Leu, Asn, Pro,
Arg, Ser, Thr or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Ile, Leu, Met, Gln, Thr, Val, Trp
or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
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<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Gly, His, Lys, Leu, Asn,
  Pro, Gln, Arg, Ser, Thr or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Glu, Phe, Gly, Ile, Lys,
  Leu, Met, Pro, Gln, Arg, Ser, Val, Trp or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Ala, Phe, Gly, Ile, Leu, Met, Asn,
  Pro, Gln, Arg, Ser, Thr, Val or Tyr

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<400> SEQUENCE: 458

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

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<210> SEQ ID NO 459
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 12
  Subgenus 12.1
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ala, Gly, Leu, Pro or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Ala, Glu, Gly, His, Leu, Pro, Gln,
  Ser, Thr or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Gly, Asn, Arg or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Leu, Pro or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Ile or Leu
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Ala, Gly, Asn, Gln, Arg or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Asp, Phe, Gly, Ile, Leu, Met, Pro,
  Ser or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Phe, Gly, Leu, Pro, Gln, Arg or Ser

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<400> SEQUENCE: 459

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
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<210> SEQ ID NO 460
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 12
  Subgenus 12.2
<220> FEATURE:

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<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ala, Pro or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Leu, Ser or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Gly, Asn, Arg or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Leu, Pro or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Ala, Gly, Arg or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Leu, Pro or Val and
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Phe, Leu, Pro or Ser

<400> SEQUENCE: 460
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Xaa Xaa Xaa Xaa Leu Xaa Xaa Xaa
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<210> SEQ ID NO 461
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 12
  Subgenus 12.3
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ala, Pro or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Leu, Ser or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Gly, Asn, Arg or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Leu, Pro or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Ala, Gly, Arg or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Leu or Pro
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Phe, Pro or Ser

<400> SEQUENCE: 461
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Xaa Xaa Xaa Xaa Leu Xaa Xaa Xaa
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<210> SEQ ID NO 462
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 12
    Subgenus 12.4
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ala, Pro or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Leu or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Gly, Asn or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Leu or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Ala, Gly, Arg or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Leu or Pro
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Pro or Ser

<400> SEQUENCE: 462

Xaa Xaa Xaa Xaa Leu Xaa Xaa Xaa
1           5
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<210> SEQ ID NO 463
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 12
    Subgenus 12.5
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ala or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Leu
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Gly, Asn or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Leu or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Leu
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Arg or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
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<223> OTHER INFORMATION: Xaa may be Leu
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Pro

<400> SEQUENCE: 463

Xaa Leu Xaa Xaa Leu Xaa Leu Pro
1 5

<210> SEQ ID NO 464
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 12
    Subgenus 12.6
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ala, Glu, Gly, His, Ile, Leu, Met,
    Pro or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Ala, Glu, Gly, His, Ile, Lys, Leu,
    Pro, Gln, Arg, Ser, Thr, Val, Trp or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala, Gly, Asn, Arg, Ser, Thr or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Ala, Gly, His, Leu, Asn, Pro, Arg,
    Ser, Thr or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Ile, Leu, Met or Gln
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Gly, Lys, Leu, Asn, Gln,
    Arg, Ser or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Glu, Phe, Gly, Ile, Lys,
    Leu, Met, Pro, Arg, Val, Trp or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Ala, Phe, Gly, Met, Pro, Gln, Arg,
    Ser, Val or Tyr

<400> SEQUENCE: 464

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> SEQ ID NO 465
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 12
    Subgenus 12.7
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ala, Pro or Ser
<220> FEATURE:
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<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Ala, His, Gln, Ser or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Gly, Asn or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Leu, Pro or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Gly, Arg or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Phe, Ile, Leu, Met or Pro
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Phe, Pro, Gln or Arg

<400> SEQUENCE: 465

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Xaa Xaa Xaa Xaa Leu Xaa Xaa Xaa
1 5

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<210> SEQ ID NO 466
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 12
Subgenus 12.8
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ala, Pro or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be His, Ser or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Gly, Asn or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Leu, Pro or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Ala, Gly, Arg or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Phe, Ile, Met or Pro
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Pro or Arg

<400> SEQUENCE: 466

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Xaa Xaa Xaa Xaa Leu Xaa Xaa Xaa
1 5

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<210> SEQ ID NO 467
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence

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<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 12
  Subgenus 12.9
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ala, Pro or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Ser or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Gly, Asn or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Ala, Gly or Arg
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Phe, Ile or Pro

<400> SEQUENCE: 467

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Xaa Xaa Xaa Leu Leu Xaa Xaa Pro
1 5

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<210> SEQ ID NO 468
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 12
  Subgenus 12.10
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ala, Pro or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Ser or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Gly, Asn or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Ala or Arg
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Phe or Pro

<400> SEQUENCE: 468

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Xaa Xaa Xaa Leu Leu Xaa Xaa Pro
1 5

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<210> SEQ ID NO 469
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 12
  Subgenus 12.11
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ala or Pro
<220> FEATURE:

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<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Gly or Asn

<400> SEQUENCE: 469

Xaa Ser Xaa Leu Leu Arg Phe Pro
1 5

<210> SEQ ID NO 470
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 470

Ala Leu Gly Leu Leu Arg Leu Pro
1 5

<210> SEQ ID NO 471
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 471

Ala Leu Gly Leu Leu Ser Leu Pro
1 5

<210> SEQ ID NO 472
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 472

Ala Ser Gly Leu Leu Arg Phe Pro
1 5

<210> SEQ ID NO 473
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 13
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Phe, Ile, Leu, Met, Arg, Ser, Thr
or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Ala, Glu, Gly, His, Ile, Lys, Leu,
Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Glu, Phe, Gly, His, Ile,
Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Ala, Glu, Gly, Asn, Pro, Gln, Ser,
Thr, Val or Trp
<220> FEATURE:
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<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Ala, Phe, Gly, His, Ile, Lys, Leu,
    Met, Asn, Pro, Gln, Arg, Ser, Thr, Val or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Glu, Phe, Gly, His, Ile,
    Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Ala, Cys, Asp, Glu, Phe, Gly, His,
    Ile, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Phe, Gly, His, Ile, Leu,
    Met, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp or Tyr

<400> SEQUENCE: 473
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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

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<210> SEQ ID NO 474
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable moiety
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<400> SEQUENCE: 474

Leu Leu Leu Pro Ala His Gly Gly
1 5

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<210> SEQ ID NO 475
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 13
    Subgenus 13.1
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Phe, Ile, Leu, Met, Ser or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Ala, Glu, His, Lys, Leu, Met, Asn,
    Gln, Ser, Thr, Val or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala, Phe, His, Leu, Met, Gln, Ser,
    Thr or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Ala, Gly or Pro
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Ala, Phe, Gly, His, Ile, Leu, Met,
    Asn, Arg, Ser, Val or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Ala, Glu, Gly, His, Leu, Met, Pro,
    Gln, Arg, Ser, Thr or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
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<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Glu, Phe, Gly, His, Leu,
      Met, Asn, Arg, Ser, Val or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Ala, Phe, Gly, Ile, Leu, Met, Pro,
      Gln, Arg, Ser, Trp or Tyr

<400> SEQUENCE: 475

Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1           5

<210> SEQ ID NO 476
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 13
      Subgenus 13.2
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Leu, Met or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Ala, His, Leu, Asn, Gln, Ser or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala, Leu, Met, Gln, Ser, Thr or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Ala, Phe, Gly, Ile, Leu, Arg, Ser,
      Val or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be His, Leu, Met, Gln or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Gly, His, Arg or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Ala, Phe, Gly, Leu, Arg or Ser

<400> SEQUENCE: 476

Xaa Xaa Xaa Pro Xaa Xaa Xaa Xaa
1           5

<210> SEQ ID NO 477
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 13
      Subgenus 13.3
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Leu, Met or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Ala or Leu
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)

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<223> OTHER INFORMATION: Xaa may be Ala, Leu or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Leu or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be His, Leu or Gln
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Gly or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Gly, Arg or Ser

<400> SEQUENCE: 477
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Xaa Xaa Xaa Pro Xaa Xaa Xaa Xaa
1 5

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<210> SEQ ID NO 478
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 13
Subgenus 13.4
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Leu or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Ala or Leu
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Leu or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Leu or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be His or Leu
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Gly or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Arg or Ser

<400> SEQUENCE: 478
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Xaa Xaa Xaa Pro Xaa Xaa Xaa Xaa
1 5

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<210> SEQ ID NO 479
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 13
Subgenus 13.5
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
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<223> OTHER INFORMATION: Xaa may be Leu or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Ala or Leu
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Leu or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be His or Leu

<400> SEQUENCE: 479

Xaa Xaa Xaa Pro Leu Xaa Gly Ser
1 5

<210> SEQ ID NO 480
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 13
Subgenus 13.6
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Phe, Ile, Leu, Met, Ser, Thr or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Ala, Glu, Gly, His, Leu, Met, Ser,
Val, Trp or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Glu, Gly, Lys, Leu, Met,
Asn, Gln, Arg, Ser, Thr or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Glu, Gly, Asn, Pro, Ser, Thr or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Ala, Phe, Gly, Leu, Asn, Pro, Gln,
Arg, Ser, Val or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Ala, Glu, His, Pro, Gln or Arg
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Asp, Glu, Gly, Asn, Arg, Ser or Thr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Gly, Gln, Ser, Thr or Val

<400> SEQUENCE: 480
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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

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<210> SEQ ID NO 481
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 13
Subgenus 13.
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<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Leu, Met or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Ala or Leu
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala, Leu, Gln or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Gly, Pro or Thr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Ala, Ser or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be His or Pro
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Asp or Gly
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Ala, Gly or Ser

<400> SEQUENCE: 481

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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

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<210> SEQ ID NO 482
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 13
  Subgenus 13.7
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Leu or Met
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Ala or Leu
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Gly or Pro
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Ala or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Ala or Gly

<400> SEQUENCE: 482

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Xaa Xaa Leu Xaa Xaa His Gly Xaa
1 5

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<210> SEQ ID NO 483
<211> LENGTH: 8
<212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 483
Leu Leu Leu Pro Leu Leu Gly Ser
1 5

<210> SEQ ID NO 484
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: cleavable moiety

<400> SEQUENCE: 484
Val Ala Gly Arg Ser Met Arg Pro
1 5

<210> SEQ ID NO 485
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Core CM Consensus Sequence 6A
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ala, Cys, Asp, Glu, Phe, Gly, His,
Ile, Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Ala, Cys, Glu, Phe, His, Leu, Asn,
Arg, Ser or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Glu, Lys, Asn, P Gln, Ser,
Thr or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Ala, Glu, Gly, His, Lys, Leu, Asn,
Pro, Arg, Ser or Thr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Ile, Lys, Leu, Met, Asn, Arg, Thr,
Val or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Glu, Ile, Lys, Leu, Pro,
Gln, Arg, Ser, Thr, Val or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Ala, Cys, Asp, Glu, Gly, Ile, Leu,
Met, Gln, Arg, Ser, Thr or Val

<400> SEQUENCE: 485
Xaa Xaa Xaa Xaa Xaa Xaa Xaa
1 5

<210> SEQ ID NO 486
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
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<223> OTHER INFORMATION: MMP14 Cleavable Extended Core CM Consensus
      Sequence 8A
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Phe, Gly, His, Ile, Leu,
      Met, Asn, Pro, Gln, Arg, Ser, Thr, Val or Trp
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa may be Ala, Pro, Arg or Thr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala, Glu, Phe, Gly, His, Ile, Lys,
      Leu, Asn, Pro, Gln, Arg, Ser, Thr or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Glu, Gly, His, Lys, Met,
      Asn, Pro, Arg, Ser or Thr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Cys, Phe, His, Ile, Leu, Met, Pro,
      Arg, Ser, Val, Trp or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Ala, Cys, Phe, Gly, His, Ile, Lys,
      Leu, Met, Arg, Ser, Thr, Val, Trp or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Glu, Phe, Gly, His, Ile,
      Lys, Leu, Met, Asn, Pro, Gln, Arg, Ser, Thr, Val or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Glu, Phe, Gly, His, Ile,
      Lys, Leu, Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp or Tyr

<400> SEQUENCE: 486

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Xaa Xaa Xaa Xaa Xaa Xaa Xaa Xaa
 1 5

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<210> SEQ ID NO 487
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Extended Core CM Consensus
      Sequence 8A Subgenus 8A.1
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Ala, Phe, Gly, Ile, Leu, Met, Asn,
      Ser, Thr, Val or Trp
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala, Glu, Phe, His, Ile, Lys, Asn,
      Pro, Gln, Arg, Ser, Thr or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Glu, Gly, His, Asn, Pro
      or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Cys, Phe, Ile, Leu, Met, Arg, Ser
      or Val
<220> FEATURE:

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<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Cys, Phe, Gly, Ile, Leu, Arg, Ser,
    Thr, Val or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Ala, Phe, Leu, Met, Pro, Gln, Arg,
    Ser, Thr, Val or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Glu, Gly, His, Ile, Leu,
    Asn, Pro, Gln, Arg, Ser, Thr, Val, Trp or Tyr

<400> SEQUENCE: 487

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Xaa Pro Xaa Xaa Xaa Xaa Xaa Xaa
1           5

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<210> SEQ ID NO 488
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Extended Core CM Consensus
    Sequence 8A Subgenus 8A.2
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Phe, Gly, Leu, Ser, Thr or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala, Glu, His, Lys, Asn, Gln, Arg,
    Ser, Thr or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Ala, Gly, His, Asn, Pro or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Ile, Leu, Met or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Phe, Ile, Leu, Arg, Ser, Thr, Val
    or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Ala, Phe, Leu, Arg, Thr, Val or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Glu, Leu, Pro, Arg, Ser,
    Thr, Val or Tyr

<400> SEQUENCE: 488

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Xaa Pro Xaa Xaa Xaa Xaa Xaa Xaa
1           5

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<210> SEQ ID NO 489
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Extended Core CM Consensus
    Sequence 8A Subgenus 8A.3
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)

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<223> OTHER INFORMATION: Xaa may be Phe, Leu or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala, Lys, Gln, Arg or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Ala, Gly, His or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Ile, Leu, Met or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Phe, Leu, Arg, Ser, Thr, Val or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Phe, Leu, Thr or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Gly, Leu, Arg, Thr or Val

<400> SEQUENCE: 489
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Xaa Pro Xaa Xaa Xaa Xaa Xaa Xaa
1 5

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<210> SEQ ID NO 490
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Extended Core CM Consensus
Sequence 8A Subgenus 8A.4
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Phe, Leu or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala, Gln or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Gly or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Ile, Leu or Met
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Leu, Ser or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Phe, Leu or Thr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Ala, Arg or Thr
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<400> SEQUENCE: 490

Xaa Pro Xaa Xaa Xaa Xaa Xaa Xaa
1 5

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<210> SEQ ID NO 491
<211> LENGTH: 8
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<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Extended Core CM Consensus
  Sequence 8A Subgenus 8A.5
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Phe, Leu or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala, Gln or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Ile, Leu or Met
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Leu or Val

<400> SEQUENCE: 491
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Xaa Pro Xaa Gly Xaa Xaa Leu Arg
1 5

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<210> SEQ ID NO 492
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Extended Core CM Consensus
  Sequence 8A Subgenus 8A.6
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Phe, Leu or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Ile, Leu or Met
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Leu or Val

<400> SEQUENCE: 492
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Xaa Pro Xaa Gly Xaa Xaa Leu Arg
1 5

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<210> SEQ ID NO 493
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Extended Core CM Consensus
  Sequence 8A Subgenus 8A.7
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Phe, Gly, Leu, Met, Pro, Ser, Val
  or Trp
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala, Asn, Gln or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
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<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be Ala, Asp, Gly, His, Met, Asn, Pro
      or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Phe, Ile, Leu, Met or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Ala, Ile, Leu, Met, Ser or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Ala, Gly, Ile, Leu, Met, Asn, Pro,
      Gln, Arg, Ser, Thr or Tyr
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Ala, Phe, His, Ile, Leu, Gln, Arg,
      Thr, Val, Trp or Tyr

<400> SEQUENCE: 493

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Xaa Pro Xaa Xaa Xaa Xaa Xaa Xaa
1          5

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<210> SEQ ID NO 494
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (1)..(1)
<223> OTHER INFORMATION: Xaa may be Leu, Ser or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala, Asn, Gln or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (4)..(4)
<223> OTHER INFORMATION: Xaa may be His, Asn, Pro or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Phe, Ile, Leu or Met
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (6)..(6)
<223> OTHER INFORMATION: Xaa may be Ile, Leu, Ser or Val
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (7)..(7)
<223> OTHER INFORMATION: Xaa may be Ala, Leu or Gln
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Leu, Thr, Val or Tyr

<400> SEQUENCE: 494

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Xaa Pro Xaa Xaa Xaa Xaa Xaa Xaa
1          5

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<210> SEQ ID NO 495
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: MMP14 Cleavable Extended Core CM Consensus

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Sequence 8A Subgenus 8A.9
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (3)..(3)
<223> OTHER INFORMATION: Xaa may be Ala, Asn, Gln or Ser
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (5)..(5)
<223> OTHER INFORMATION: Xaa may be Ile or Leu
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (8)..(8)
<223> OTHER INFORMATION: Xaa may be Leu or Val

<400> SEQUENCE: 495

Leu Pro Xaa His Xaa Val Leu Xaa
1 5

<210> SEQ ID NO 496
<211> LENGTH: 21
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 496

Gln Gly Gln Ser Gly Gln Cys Asn Ile Trp Leu Val Gly Gly Asp Cys
1 5 10 15

Arg Gly Trp Gln Gly
20

<210> SEQ ID NO 497
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: masking moiety

<400> SEQUENCE: 497

Cys Ile Ser Pro Arg Gly Cys
1 5

<210> SEQ ID NO 498
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: anti-Jagged antigen binding fragment VH CDR1 sequence

<400> SEQUENCE: 498

Ser Tyr Ala Met Ser
1 5

<210> SEQ ID NO 499
<211> LENGTH: 17
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: anti-Jagged antigen binding fragment VH CDR2 sequence

<400> SEQUENCE: 499

Ser Ile Asp Pro Glu Gly Arg Gln Thr Tyr Tyr Ala Asp Ser Val Lys
1 5 10 15

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Gly

<210> SEQ ID NO 500
<211> LENGTH: 10
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: anti-Jagged antigen binding fragment VH CDR3 sequence

<400> SEQUENCE: 500

Asp Ile Gly Gly Arg Ser Ala Phe Asp Tyr
1 5 10

<210> SEQ ID NO 501
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: anti-Jagged antigen binding fragment VL CDR1 sequence

<400> SEQUENCE: 501

Arg Ala Ser Gln Ser Ile Ser Ser Tyr
1 5

<210> SEQ ID NO 502
<211> LENGTH: 7
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: anti-Jagged antigen binding fragment VL CDR2 sequence

<400> SEQUENCE: 502

Ala Ala Ser Ser Leu Gln Ser
1 5

<210> SEQ ID NO 503
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: anti-Jagged antigen binding fragment VL CDR3 sequence

<400> SEQUENCE: 503

Gln Gln Thr Val Val Ala Pro Pro Leu
1 5

<210> SEQ ID NO 504
<211> LENGTH: 5
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: anti-EGFR antigen binding fragment VH CDR1 sequence

<400> SEQUENCE: 504

Asn Tyr Gly Val His
1 5

<210> SEQ ID NO 505
<211> LENGTH: 16
<212> TYPE: PRT

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<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: anti-EGFR antigen binding fragment VH CDR2 sequence

<400> SEQUENCE: 505

Val Ile Trp Ser Gly Gly Asn Thr Asp Tyr Asn Thr Pro Phe Thr Ser
1 5 10 15

<210> SEQ ID NO 506
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: anti-EGFR antigen binding fragment VH CDR3 sequence

<400> SEQUENCE: 506

Ala Leu Thr Tyr Tyr Asp Tyr Glu Phe Ala Tyr
1 5 10

<210> SEQ ID NO 507
<211> LENGTH: 11
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: anti-EGFR antigen binding fragment VL CDR1 sequence

<400> SEQUENCE: 507

Arg Ala Ser Gln Ser Ile Gly Thr Asn Ile His
1 5 10

<210> SEQ ID NO 508
<211> LENGTH: 8
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: anti-EGFR antigen binding fragment VL CDR2 sequence

<400> SEQUENCE: 508

Lys Tyr Ala Ser Glu Ser Ile Ser
1 5

<210> SEQ ID NO 509
<211> LENGTH: 9
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: anti-EGFR antigen binding fragment VL CDR3 sequence

<400> SEQUENCE: 509

Gln Gln Asn Asn Asn Trp Pro Thr Thr
1 5

<210> SEQ ID NO 510
<211> LENGTH: 273
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: anti-CTLA-4 scFv

<400> SEQUENCE: 510

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Gly Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Gly Ser Gly
 1 5 10 15

Gly Gly Gly Ser Gly Gly Glu Ile Val Leu Thr Gln Ser Pro Gly
 20 25 30

Thr Leu Ser Leu Ser Pro Gly Glu Arg Ala Thr Leu Ser Cys Arg Ala
 35 40 45

Ser Gln Ser Val Ser Ser Tyr Leu Ala Trp Tyr Gln Gln Lys Pro
 50 55 60

Gly Gln Ala Pro Arg Leu Leu Ile Tyr Gly Ala Ser Ser Arg Ala Thr
 65 70 75 80

Gly Ile Pro Asp Arg Phe Ser Gly Ser Gly Thr Asp Phe Thr
 85 90 95

Leu Thr Ile Ser Arg Leu Glu Pro Glu Asp Phe Ala Val Tyr Tyr Cys
 100 105 110

Gln Gln Tyr Gly Ser Ser Pro Leu Thr Phe Gly Gly Thr Lys Val
 115 120 125

Glu Ile Lys Arg Ser Gly Gly Ser Thr Ile Thr Ser Tyr Asn Val Tyr
 130 135 140

Tyr Thr Lys Leu Ser Ser Gly Thr Gln Val Gln Leu Val Gln Thr
 145 150 155 160

Gly Gly Val Val Gln Pro Gly Arg Ser Leu Arg Leu Ser Cys Ala
 165 170 175

Ala Ser Gly Ser Thr Phe Ser Ser Tyr Ala Met Ser Trp Val Arg Gln
 180 185 190

Ala Pro Gly Lys Gly Leu Glu Trp Val Ser Ala Ile Ser Gly Ser Gly
 195 200 205

Gly Ser Thr Tyr Tyr Ala Asp Ser Val Lys Gly Arg Phe Thr Ile Ser
 210 215 220

Arg Asp Asn Ser Lys Asn Thr Leu Tyr Leu Gln Met Asn Ser Leu Arg
 225 230 235 240

Ala Glu Asp Thr Ala Val Tyr Tyr Cys Ala Thr Asn Ser Leu Tyr Trp
 245 250 255

Tyr Phe Asp Leu Trp Gly Arg Gly Thr Leu Val Thr Val Ser Ser Ala
 260 265 270

Ser

<210> SEQ ID NO 511
 <211> LENGTH: 264
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: anti-CD3 epsilon scFv

<400> SEQUENCE: 511

Gly Gly Gly Ser Gly Gly Gly Ser Gly Ser Gly Gly Ser Gly
 1 5 10 15

Gly Gly Gly Ser Gly Gly Gln Val Gln Leu Gln Gln Ser Gly Ala
 20 25 30

Glu Leu Ala Arg Pro Gly Ala Ser Val Lys Met Ser Cys Lys Ala Ser
 35 40 45

Gly Tyr Thr Phe Thr Arg Tyr Thr Met His Trp Val Lys Gln Arg Pro
 50 55 60

Gly Gln Gly Leu Glu Trp Ile Gly Tyr Ile Asn Pro Ser Arg Gly Tyr

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65	70	75	80
Thr Asn Tyr Asn Gln Lys Phe Lys Asp Lys Ala Thr Leu Thr Thr Asp			
85	90	95	
Lys Ser Ser Ser Thr Ala Tyr Met Gln Leu Ser Ser Leu Thr Ser Glu			
100	105	110	
Asp Ser Ala Val Tyr Tyr Cys Ala Arg Tyr Tyr Asp Asp His Tyr Cys			
115	120	125	
Leu Asp Tyr Trp Gly Gln Gly Thr Thr Leu Thr Val Ser Ser Gly Gly			
130	135	140	
Gly Gly Ser Gly Gly Gly Ser Gly Gly Gly Ser Gln Ile Val			
145	150	155	160
Leu Thr Gln Ser Pro Ala Ile Met Ser Ala Ser Pro Gly Glu Lys Val			
165	170	175	
Thr Met Thr Cys Ser Ala Ser Ser Ser Val Ser Tyr Met Asn Trp Tyr			
180	185	190	
Gln Gln Lys Ser Gly Thr Ser Pro Lys Arg Trp Ile Tyr Asp Thr Ser			
195	200	205	
Lys Leu Ala Ser Gly Val Pro Ala His Phe Arg Gly Ser Gly Ser Gly			
210	215	220	
Thr Ser Tyr Ser Leu Thr Ile Ser Gly Met Glu Ala Glu Asp Ala Ala			
225	230	235	240
Thr Tyr Tyr Cys Gln Gln Trp Ser Ser Asn Pro Phe Thr Phe Gly Ser			
245	250	255	
Gly Thr Lys Leu Glu Ile Asn Arg			
260			

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<210> SEQ ID NO 512
<211> LENGTH: 194
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Display Platform CYTX-DP-XXXXXXXX peptide
<220> FEATURE:
<221> NAME/KEY: misc_feature
<222> LOCATION: (17)..(24)
<223> OTHER INFORMATION: Xaa may be any amino acid

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<400> SEQUENCE: 512			
Gly Gln Ser Gly Gln Glu Tyr Met Pro Met Glu Gly Gly Ser Gly Gln			
1	5	10	15
Xaa Xaa Xaa Xaa Xaa Xaa Xaa Ser Gly Gly Gln Gly Gly Ser Gly			
20	25	30	
Gly Ser Gly Gly Ser Gly Gly Ser Gly Ser Ala Tyr Tyr Gly Ile			
35	40	45	
Thr Ala Gly Pro Ala Tyr Arg Ile Asn Asp Trp Ala Ser Ile Tyr Gly			
50	55	60	
Val Val Gly Val Gly Tyr Gly Ser Gly Pro Gly Gly Ser Tyr Gly Phe			
65	70	75	80
Ser Tyr Gly Ala Gly Leu Gln Phe Asn Pro Met Glu Asn Val Ala Leu			
85	90	95	
Asp Phe Ser Tyr Glu Gln Ser Arg Ile Arg Ser Val Asp Val Gly Thr			
100	105	110	
Trp Ile Leu Ser Val Gly Tyr Arg Phe Gly Ser Lys Ser Arg Arg Ala			
115	120	125	

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Thr	Ser	Thr	Val	Thr	Gly	Gly	Tyr	Ala	Gln	Ser	Asp	Ala	Gln	Gly	Gln
130					135					140					

Met	Asn	Lys	Met	Gly	Gly	Phe	Asn	Leu	Lys	Tyr	Arg	Tyr	Glu	Glu	Asp
145					150					155					160

Asn	Ser	Pro	Leu	Gly	Val	Ile	Gly	Ser	Phe	Thr	Tyr	Thr	Gly	Gly	Ser
						165			170				175		

Gly	Gly	Ser	Ser	Gly	Gly	Gln	Ala	Ala	Ala	Gly	His	His	His	His	His
						180			185				190		

His	His														
-----	-----	--	--	--	--	--	--	--	--	--	--	--	--	--	--

<210> SEQ ID NO 513
 <211> LENGTH: 217
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:
 <223> OTHER INFORMATION: SP-CYTX-DP-XXXXXXX peptide
 <220> FEATURE:
 <221> NAME/KEY: misc_feature
 <222> LOCATION: (40)..(47)
 <223> OTHER INFORMATION: Xaa may be any amino acid

<400> SEQUENCE: 513

Met	Lys	Lys	Ile	Ala	Cys	Leu	Ser	Ala	Leu	Ala	Ala	Val	Leu	Ala	Phe
1									10						15

Thr	Ala	Gly	Thr	Ser	Val	Ala	Gly	Gln	Ser	Gly	Gln	Glu	Tyr	Met	Pro
					20				25				30		

Met	Glu	Gly	Gly	Ser	Gly	Gln	Xaa	Ser						
							35	40		45				

Gly	Gly	Gly	Gly	Ser	Gly									
							50	55		60				

Gly	Ser	Ala	Tyr	Tyr	Gly	Ile	Thr	Ala	Gly	Pro	Ala	Tyr	Arg	Ile	Asn
						65			70			75			80

Asp	Trp	Ala	Ser	Ile	Tyr	Gly	Val	Val	Gly	Val	Gly	Tyr	Gly	Ser	Gly
							85	90		95					

Pro	Gly	Gly	Ser	Tyr	Gly	Phe	Ser	Tyr	Gly	Ala	Gly	Leu	Gln	Phe	Asn
							100		105		110				

Pro	Met	Glu	Asn	Val	Ala	Leu	Asp	Phe	Ser	Tyr	Glu	Gln	Ser	Arg	Ile
							115		120		125				

Arg	Ser	Val	Asp	Val	Gly	Thr	Trp	Ile	Leu	Ser	Val	Gly	Tyr	Arg	Phe
							130		135		140				

Gly	Ser	Lys	Ser	Arg	Arg	Ala	Thr	Ser	Thr	Val	Thr	Gly	Gly	Tyr	Ala
							145		150		155		160		

Gln	Ser	Asp	Ala	Gln	Gly	Gln	Met	Asn	Lys	Met	Gly	Gly	Phe	Asn	Leu
							165		170		175				

Lys	Tyr	Arg	Tyr	Glu	Glu	Asp	Asn	Ser	Pro	Leu	Gly	Val	Ile	Gly	Ser
							180		185		190				

Phe	Thr	Tyr	Thr	Gly	Gly	Ser	Gly	Gly	Ser	Ser	Gly	Gln	Ala	Ala	Ala
							195		200		205				

Gly	His														
							210		215						

<210> SEQ ID NO 514
 <211> LENGTH: 8
 <212> TYPE: PRT
 <213> ORGANISM: Artificial Sequence
 <220> FEATURE:

-continued

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What is claimed:

1. An isolated polypeptide comprising a cleavable moiety (CM) comprising an amino acid sequence selected from the group consisting of SEQ ID NOS: 353-363, 372-375, 376-378, 395-401, 411-419, 426-433, 437-449, 454-456, 459-469, 475-482, 487-495, 318-323, 325-327, 330-335, 341-347, 14-33, and 159, wherein the cleavable moiety is a substrate for a protease.

2. The isolated polypeptide of claim 1, wherein the CM comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 353-363, 372-375, 376-378, 395-401, 411-419, 426-433, 437-449, 454-456, 459-469, 475-482, and 487-495.

3. The isolated polypeptide of claim 1, wherein the CM comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 318-323, 325-327, 330-335, and 341-347.

4. The isolated polypeptide of claim 1, wherein the CM comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 14-33, and 159.

5. The isolated polypeptide of claim 1, wherein the CM comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 353-363, wherein the cleavable moiety is a substrate for a protease.

6. The isolated polypeptide of claim 1, wherein the CM comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 372-375, wherein the cleavable moiety is a substrate for a protease.

7. The isolated polypeptide of claim 1, wherein the CM comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 376-378, wherein the cleavable moiety is a substrate for a protease.

8. The isolated polypeptide of claim 1, wherein the CM comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 395-401, wherein the cleavable moiety is a substrate for a protease.

9. The isolated polypeptide of claim 1, wherein the CM comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 411-419, wherein the cleavable moiety is a substrate for a protease.

10. The isolated polypeptide of claim 1, wherein the CM comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 426-433, wherein the cleavable moiety is a substrate for a protease.

11. The isolated polypeptide of claim 1, wherein the CM comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 437-449, wherein the cleavable moiety is a substrate for a protease.

12. The isolated polypeptide of claim 1, wherein the CM comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 454-456, wherein the cleavable moiety is a substrate for a protease.

13. The isolated polypeptide of claim 1, wherein the CM comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 459-469, wherein the cleavable moiety is a substrate for a protease.

14. The isolated polypeptide of claim 1, wherein the CM comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 475-482, wherein the cleavable moiety is a substrate for a protease.

15. The isolated polypeptide of claim 1, wherein the CM comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 487-495, wherein the cleavable moiety is a substrate for a protease.

16. The isolated polypeptide of claim 1, wherein the CM comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 318-323, wherein the cleavable moiety is a substrate for a protease.

17. The isolated polypeptide of claim 1, wherein the CM comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 325-327, wherein the cleavable moiety is a substrate for a protease.

18. The isolated polypeptide of claim 1, wherein the CM comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 330-335, wherein the cleavable moiety is a substrate for a protease.

19. The isolated polypeptide of claim 1, wherein the CM comprises an amino acid sequence selected from the group consisting of SEQ ID NOS: 341-347, wherein the cleavable moiety is a substrate for a protease.

20. An isolated polypeptide comprising a cleavable moiety (CM) comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 364-370, 379-393, 402-409, 420-424, 434, 435, 450-452, 457, 470-472, 474, and 483, wherein the cleavable moiety is a substrate for a protease.

21. An isolated polypeptide comprising a cleavable moiety (CM) comprising an amino acid sequence selected from the group consisting of SEQ ID NOs: 328, 336-339, and 348-351, wherein the cleavable moiety is a substrate for a protease.

22. The isolated polypeptide of claim 1, wherein the CM is cleaved by at least one matrix metalloprotease (MMP).

23. The isolated polypeptide of claim 22, wherein the CM is cleaved by at least one of MMP9 or MMP14.

24. The isolated polypeptide of claim 2, wherein the CM is cleaved by at least MMP14.

25. The isolated polypeptide of claim 3, wherein the CM is cleaved by at least MMP9.

26. The isolated polypeptide of claim 1, wherein the polypeptide comprises an antibody or antigen binding fragment thereof (AB) that binds a target.

27. The isolated polypeptide of claim 26, wherein the CM is a substrate for a protease that is co-localized in a tissue with the target.

28. The isolated polypeptide of claim 26, wherein the antigen binding fragment thereof is selected from the group consisting of a Fab fragment, a F(ab')₂ fragment, a scFv, a scab, a dAb, a single domain heavy chain antibody, and a single domain light chain antibody.

29. The isolated polypeptide of claim 26, wherein the AB is linked to the CM.

30. The isolated polypeptide of claim 29, wherein the AB is linked directly to the CM.

31. The isolated polypeptide of claim 29, wherein the AB is linked to the CM via a linking peptide.

32. The isolated polypeptide of claim 26, wherein the isolated polypeptide comprises a masking moiety (MM),

wherein the MM has an equilibrium dissociation constant for binding to the AB that is greater than the equilibrium dissociation constant of the AB for binding to the target.

33. The isolated polypeptide of claim 32, wherein the MM is a polypeptide of no more than 40 amino acids in length.

34. The isolated polypeptide of claim 32, wherein the MM is linked to the CM such that the isolated polypeptide in an uncleaved state comprises the structural arrangement from N-terminus to C-terminus as follows: MM-CM-AB or AB-CM-MM.

35. The isolated polypeptide of claim 34, wherein the isolated polypeptide comprises a linking peptide between the MM and the CM.

36. The isolated polypeptide of claim 34, wherein the isolated polypeptide comprises a linking peptide between the CM and the AB.

37. The isolated polypeptide of claim 34, wherein the isolated polypeptide comprises a first linking peptide (LP1) and a second linking peptide (LP2), and wherein the isolated polypeptide has the structural arrangement from N-terminus to C-terminus as follows in the uncleaved state: MM-LP1-CM-LP2-AB or AB-LP2-CM-LP1-MM.

38. The isolated polypeptide of claim 37, wherein the two linking peptides need not be identical to each other.

39. The isolated polypeptide of claim 37, wherein each of LP1 and LP2 is a peptide of about 1 to 20 amino acids in length.

40. The isolated polypeptide of claim 32, wherein the amino acid sequence of the MM is different from that of the target and is no more than 50% identical to the amino acid sequence of a natural binding partner of the AB.

41. The isolated polypeptide of claim 32, wherein the MM does not interfere or compete with the AB for binding to the target in a cleaved state.

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