What is claimed:

1. An isolated polypeptide comprising a CM1-CM2 substrate comprising at least a first cleavable moiety (CM1) that is a substrate for at least one matrix metalloprotease (MMP) and at least a second cleavable moiety (CM2) that is a substrate for at least one serine protease (SP), wherein the CM1-CM2 substrate comprises an amino acid sequence selected from the group consisting of: SEQ ID NOs: 1, 7, 555, and 557.

2. The isolated polypeptide of claim 1, wherein the MMP is MMP2, MMP9, or MMP14.

3. The isolated polypeptide of any one of claims 1 or 2, wherein the SP is uPA or matriptase.

4. An isolated polypeptide comprising an antibody or antigen binding fragment thereof (AB) that binds a target, and at least a first cleavable moiety (CM1) that is a substrate for at least one matrix metalloprotease (MMP) and at least a second cleavable moiety (CM2) that is a substrate for at least one serine protease (SP) wherein the CM1-CM2 substrate comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 1, 7, 555 and 557.

5. The isolated polypeptide of claim 4, wherein the MMP, the SP, or both the MMP and the SP are co-localized in a tissue with the target.

6. The isolated polypeptide of any one of claims 4-5, 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.

7. The isolated polypeptide of any one of claims 4-6, wherein the AB is linked to the CM1, and/or optionally

wherein the AB is linked directly to the CM1 and/or optionally;

wherein the AB is linked to the CM1 via a linking peptide.

8. The isolated polypeptide of any one of claims 4-7, wherein the AB is linked to CM2; and/or optionally

wherein the AB is linked directly to the CM2 and/or optionally;
wherein the AB is linked to the CM2 via a linking peptide.

9. The isolated polypeptide of any one of claims 4-8, wherein the MMP is MMP2, MMP9, or MMP14; and/or optionally wherein the SP is uPA or matriptase.

10. The isolated polypeptide of any one of claims 4-9, wherein the isolated polypeptide comprises a masking moiety (MM); and/or optionally

wherein the MM has a dissociation constant for binding to the AB that is greater than the dissociation constant of the AB for binding to the target; and/or optionally
wherein the MM is a polypeptide of no more than 40 amino acids in length.

11. The isolated polypeptide of claim 10, wherein the MM is linked to the CM1 such that the isolated polypeptide in an uncleaved state comprises the structural arrangement from N-terminus to C-terminus as follows: MM-CM1-CM2-AB or AB-CM2-CM1-MM; and/or optionally

wherein the isolated polypeptide comprises a linking peptide between the MM and the CM1; and/or optionally
wherein the isolated polypeptide comprises a linking peptide between CM2 and the AB.

12. The isolated polypeptide of claim 10, wherein the MM is linked to CM2 such that the isolated polypeptide in an uncleaved state comprises the structural arrangement from N-terminus to C-terminus as follows: MM-CM2-CM1-AB or AB-CM1-CM2-MM; and/or optionally

wherein the isolated polypeptide comprises a linking peptide between the MM and the CM2; and/or optionally

wherein the isolated polypeptide comprises a linking peptide between CM1 and the AB.

13. The isolated polypeptide of claim 10, 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-CM1-CM2-LP2-AB, AB-LP2-CM2-CM1-LP1-MM, MM-LP1-CM2-CM1-LP2-AB, or AB-LP2-CM1-CM2-LP1-MM; and/or optionally

wherein the two linking peptides need not be identical to each other; and/or optionally

wherein each of LP1 and LP2 is a peptide of about 1 to 20 amino acids in length.

14. The isolated polypeptide of any one of claims 10-13, wherein the amino acid sequence of the MM is different from that of the target and is no more than 10% identical to the amino acid sequence of a natural binding partner of the AB.

15. The isolated polypeptide of any one of claims 10-14, wherein the MM does not interfere or compete with the AB for binding to the target in a cleaved state.

16. The isolated polypeptide of any one of claims 4-15, wherein the isolated polypeptide comprises a light chain amino acid sequence selected from the group consisting of SEQ ID NOs: 420, 432, 561, and 562, and a heavy chain amino acid sequence comprising SEQ ID NO: 67; and/or optionally

wherein the isolated polypeptide comprises a light chain amino acid sequence selected from the group consisting of SEQ ID NOs: 449, 559, and 560, and a heavy chain amino acid sequence comprising SEQ ID NO: 108.

17. The isolated polypeptide of any one of claims 1-15, wherein the isolated polypeptide comprises an amino acid sequence selected from the group consisting of SEQ ID NOs: 420, 432, 561, and 562; and/or optionally

wherein the isolated polypeptide comprises an amino acid sequence selected from

the group consisting of SEQ ID NOs: 449, 559, and 560.

18. The isolated polypeptide of any one of claims 10-17, wherein the MMP is MMP2, MMP9, or MMP14; and/or optionally wherein the SP is uPA or matriptase.

19. A conjugated activatable antibody comprising the isolated polypeptide as in any of claims 4-18 conjugated to an agent; and/or optionally

wherein the agent is conjugated to the AB via a linker; and/or optionally
wherein the linker is a cleavable or non-cleavable linker.

20. The conjugated activatable antibody of claim 19, wherein the agent is a toxin; and/or optionally.

wherein the agent is a microtubule inhibitor; and/or optionally
wherein the agent is a nucleic acid damaging agent; and/or optionally
wherein the agent is selected from the group consisting of a dolastatin or a derivative thereof, an auristatin, a maytansinoid, a duocarmycin, and a calicheamicin; and/or optionally.
wherein the agent is auristatin E; and/or optionally
wherein the agent is monomethyl auristatin E (MMAE); and/or optionally
wherein the agent is monomethyl auristatin D (MMAD); and/or optionally
wherein the agent is a maytansinoid selected from the group consisting of DM1 and DM4.

21. The conjugated activatable antibody of any one of claim 19 or claim 20, wherein the agent is a detectable moiety; and/or optionally
wherein the detectable moiety is a diagnostic agent.

22. A pharmaceutical composition comprising the isolated polypeptide as in any of claims 4-18 and a carrier; and/or optionally

comprising an additional agent; and/or optionally

wherein the additional agent is a therapeutic agent.

23. An isolated nucleic acid molecule encoding the isolated polypeptide as in any of claims 1-18.

24. A vector comprising the isolated nucleic acid molecule of claim 23.

25. A method of producing an antibody or an activatable antibody by culturing a cell under conditions that lead to expression of the isolated polypeptide as in any of claims 4-18, wherein the cell comprises the nucleic acid molecule of claim 23.

26. A method of manufacturing an activatable antibody that, in an activated state, binds a target, the method comprising:

(a) culturing a cell comprising a nucleic acid construct that encodes the isolated polypeptide as in any of claims 4-18;

and

(b) recovering the activatable antibody.

27. The isolated polypeptide as in any of claims 4-18, the conjugated activatable antibody as in any of claims 19-21, or the pharmaceutical composition as in claim 22 for use in treating cancer, optionally with an additional agent which is optionally a therapeutic agent.