

## CLAIMS

1. A protein comprising a first moiety and a second moiety and a peptide linker between the first moiety and the second moiety,  
wherein the peptide linker comprises an amino acid sequence from a human immunoglobulin hinge region or an amino acid sequence or an amino acid sequence having from 1 to about 7 amino acid substitutions compared to a human immunoglobulin hinge region;  
wherein the peptide linker is cleavable by a protease expressed in a diseased tissue;  
wherein the second moiety is capable of specifically binding to a molecule expressed in the diseased tissue; and  
wherein the binding of the second moiety to the molecule expressed in the diseased tissue is reduced or inhibited when the peptide linker is uncleaved.
2. The protein of claim 1, wherein the peptide linker is between about 5 and about 15 amino acids in length.
3. The protein of claim 1 or 2, wherein the peptide linker comprises or consists of the amino acid sequence of SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4, SEQ ID NO:5, SEQ ID NO:69, SEQ ID NO:70, SEQ ID NO:71, SEQ ID NO:72, SEQ ID NO:81, SEQ ID NO:82, SEQ ID NO:83, SEQ ID NO:84, SEQ ID NO:85, SEQ ID NO:86, or SEQ ID NO:87.
4. The protein of any one of claims 1-3, wherein the protease is a human matrix metalloprotease (MMP), a human cathepsin, human enterokinase, human thrombin, human tPA, human Granzyme B, human uPA, or human ADAMTs-5.
5. The protein of any one of claims 1-4, wherein the peptide linker comprises a human MMP cleavage site, a human cathepsin, human enterokinase, human thrombin, human tPA, human Granzyme B, human uPA, or human ADAMTs-5 cleavage site.
6. The protein of any one of claims 1-5, wherein the human MMP is MMP-2, MMP-3, MMP-7, MMP-8, MMP-9, MMP-10, MMP-12, MMP-13 or MMP14.
7. The protein of any one of claims 1-6, wherein the level or the activity of the human MMP is elevated in the diseased tissue compared to the level or the activity of the human MMP in a non-diseased tissue.

8. The protein of any one of claims 1-5, wherein the human cathepsin is Cathepsin A, Cathepsin C, Cathepsin D, Cathepsin G, Cathepsin L or Cathepsin K.
9. The protein of any one of claims 1-5 and 8, wherein the level or the activity of the human cathepsin is elevated in the diseased tissue compared to the level or the activity of the human cathepsin in a non-diseased tissue.
10. The protein of any one of claims 1-9, wherein the first moiety comprises an antibody, an antigen-binding portion of an antibody or a receptor ectodomain.
11. The protein of claim 10, wherein the first moiety is a Fab, a single-chain Fab, a VH domain, a VL domain, an immunoglobulin new antigen receptor (IgNAR), a single-chain variable fragment (scFv), a diabody, or a T cell receptor domain.
12. The protein of any one of claims 1-11, wherein the first moiety specifically binds to a molecule expressed in a diseased tissue.
13. The protein of any one of claims 1-12, wherein the first moiety specifically binds to a first molecule expressed in a diseased tissue and the second moiety is capable of specifically binding to a second molecule expressed in a diseased tissue, wherein the first molecule expressed in a diseased tissue and the second molecule expressed in a diseased tissue are different molecules.
14. The protein of claim 13, wherein the first molecule expressed in a diseased tissue and the second molecule expressed in a diseased tissue are expressed by the same cell.
15. The protein of claim 13, wherein the first molecule expressed in a diseased tissue and the second molecule expressed in a diseased tissue are expressed by different cells.
16. The protein of claim 13, wherein the first molecule expressed in a diseased tissue and/or the second molecule expressed in a diseased tissue is expressed on the surface of a cell.
17. The protein of claim 13, wherein the first molecule expressed in a diseased tissue and/or the second molecule expressed in a diseased tissue is a soluble molecule.

18. The protein of any one of claims 1-17, wherein the first moiety binds specifically to human EGFR, human HER2, human HER3, human CD105, human C-KIT, human PD1, human PD-L1, human PSMA, human EpCAM, human Trop2, human EphA2, human CD20, human BCMA, human GITR, human OX40, human CSF1R, human Lag3 or human cMET.
19. The protein of any one of claims 1-17, wherein the second moiety specifically binds to a molecule expressed by a human immune cell.
20. The protein of claim 19, wherein the molecule expressed by a human immune cell is human CD3, human CD16A, human CD16B, human CD28, human CD89, human CTLA4, human NKG2D, human SIRP $\alpha$ , human SIRP $\gamma$ , human PD1, human Lag3, human 4-1BB, human OX40, or human GITR.
21. The protein of any one of claims 1-20, wherein the first moiety comprises a heavy chain variable (VH) region and a light chain variable (VL) region.
22. The protein of any one of claims 1-21, wherein the first moiety comprises an immunoglobulin constant region or a portion of an immunoglobulin constant region.
23. The protein of claim 22, wherein the immunoglobulin constant region is IgG, IgE, IgM, IgD, IgA, or IgY.
24. The protein of claim 22, wherein the immunoglobulin constant region is IgG1, IgG2, IgG3, IgG4, IgA1, or IgA2.
25. The protein of claim 22, wherein the immunoglobulin constant region is immunologically inert.
26. The protein of claim 22, wherein the immunoglobulin constant region is a wild-type human IgG4 constant region, a human IgG4 constant region comprising the amino acid substitution S228P, a wild-type human IgG1 constant region, a human IgG1 constant region comprising the amino acid substitutions L234A and L235A, a human IgG1 constant region comprising the amino acid substitutions L234A, L235A and G237A, a human IgG1 constant region comprising the amino acid substitutions L234A, L235A, G237A and P331S, or a wild-type human IgG2 constant region, wherein numbering is according to the EU index as in Kabat.

27. The protein of any one of claims 1-26, wherein the second moiety comprises an antibody, an antigen-binding portion of an antibody or a receptor ectodomain.
28. The protein of claim 27, wherein the second moiety is a Fab, a single-chain Fab, a VH domain, a VL domain, an immunoglobulin new antigen receptor (IgNAR), a single-chain variable fragment (scFv), or a T cell receptor domain.
29. The protein of any one of claims 1-28, wherein the second moiety binds specifically to human CD47.
30. The protein of any one of claims 1-28, wherein the second moiety binds specifically to human CD3 or human PD-L1.
31. The protein of any one of claims 1-30, wherein the second moiety comprises a heavy chain variable (VH) region and a light chain variable (VL) region.
32. The protein of any one of claims 1-31, wherein the second moiety comprises an immunoglobulin constant region or a portion of an immunoglobulin constant region.
33. The protein of claim 32, wherein the immunoglobulin constant region is IgG, IgE, IgM, IgD, IgA or IgY.
34. The protein of claim 32, wherein the immunoglobulin constant region is IgG1, IgG2, IgG3, IgG4, IgA1 or IgA2.
35. The protein of claim 32, wherein the immunoglobulin constant region is immunologically inert.
36. The protein of claim 32, wherein the immunoglobulin constant region is a wild-type human IgG4 constant region, a human IgG4 constant region comprising the amino acid substitution S228P, a wild-type human IgG1 constant region, a human IgG1 constant region comprising the amino acid substitutions L234A and L235A, a human IgG1 constant region comprising the amino acid substitutions L234A, L235A and G237A, a human IgG1 constant region comprising the amino acid substitutions L234A, L235A, G237A and P331S, or a wild-type human IgG2 constant region, wherein numbering is according to the EU index as in Kabat.

37. The protein of claim 1, wherein the protein has an immune effector function or two, three or more immune effector functions.
38. The protein of claim 37, wherein the immune effector function is ADCC, CDC or ADCP.
39. The protein of any one of claims 1-38, wherein the first moiety prevents or reduces specific binding of the second moiety to the molecule expressed in the diseased tissue.
40. The protein of any one of claims 1-39, wherein the peptide linker is cleaved in the vicinity of the diseased tissue or inside the diseased tissue.
41. The protein of any one of claims 1-40, wherein the peptide linker is cleaved in the vicinity of the diseased tissue or inside the diseased tissue, wherein the first moiety dissociates from the second moiety in the vicinity of the diseased tissue or inside the diseased tissue and wherein the second moiety specifically binds to the molecule expressed in the diseased tissue in the vicinity of the diseased tissue or inside the diseased tissue.
42. The protein of any one of claims 1-41, wherein the diseased tissue is a tumour or an inflamed tissue.
43. The protein of claim 1, wherein the first moiety binds specifically to human cMET, wherein the second moiety binds specifically to human CD47, and wherein the protein comprises a first polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:16 and a second polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:17.
44. The protein of claim 1, wherein the first moiety binds specifically to human HER2, wherein the second moiety binds specifically to human CD3, and wherein the protein comprises a first polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:26 and a second polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:27.
45. The protein of claim 1, wherein the first moiety binds specifically to human HER2, wherein the second moiety binds specifically to human CD47, and wherein the protein comprises a first polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:34 and a second polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:35.

46. The protein of claim 1, wherein the first moiety binds specifically to human cMET, wherein the second moiety binds specifically to human CD47, and wherein the protein comprises a first polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:36 and a second polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:37.

47. The protein of claim 1, wherein the first moiety binds specifically to human Her2, wherein the second moiety binds specifically to human CD3, and wherein the protein comprises a first polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:38 and a second polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:39.

48. The protein of claim 1, wherein the first moiety binds specifically to human Her2, wherein the second moiety binds specifically to human CD3, and wherein the protein comprises a first polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:40 and a second polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:41.

49. The protein of claim 1, wherein the first moiety binds specifically to human Her2, wherein the second moiety binds specifically to human CD47, and wherein the protein comprises a first polypeptide chain and a second polypeptide chain, wherein:

(a) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:42, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:43; or

(b) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:44, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:45; or

(c) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:46, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:47; or

(d) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:48, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:49; or

(e) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:50, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:51; or

(f) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:52, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:53; or

(g) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:54, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:55; or

(h) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:88, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:89; or

(i) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:90, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:91; or

(j) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:44, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:92; or

(k) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:44, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:93; or

(l) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:44, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:94; or

(m) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:44, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:95; or

(n) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:44, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:96; or

(o) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:44, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:97.

50. The protein of claim 1, wherein the first moiety binds specifically to human Her2, wherein the second moiety binds specifically to human CD3, and wherein the protein comprises a first polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:73 and a second polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:74.

51. The protein of claim 1, wherein the first moiety binds specifically to human cMET, wherein the second moiety binds specifically to human cMET, and wherein the protein comprises a first

polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:75 and a second polypeptide chain comprising or consisting of the amino acid sequence of SEQ ID NO:76.

52. The protein of claim 1, wherein the first moiety binds specifically to human Her2, wherein the second moiety binds specifically to human CD3, and wherein the protein comprises a first polypeptide chain and a second polypeptide chain, wherein:

(a) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:98, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:99; or

(b) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:100, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:101; or

(c) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:102, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:103; or

(d) the first polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:104, and the second polypeptide chain comprises or consists of the amino acid sequence of SEQ ID NO:105.

53. An immunoconjugate comprising the protein of any one of claims 1-52 linked to a therapeutic agent.

54. The immunoconjugate of claim 53, wherein the therapeutic agent is a cytotoxin, a radioisotope, a chemotherapeutic agent, an immunomodulatory agent, a cytostatic enzyme, a cytolytic enzyme, a therapeutic nucleic acid, an anti-angiogenic agent, an anti-proliferative agent, or a pro-apoptotic agent.

55. A pharmaceutical composition comprising the protein of any one of claims 1-52 or the immunoconjugate of claim 53 or 54, and a pharmaceutically acceptable carrier, diluent or excipient.

56. A nucleic acid molecule encoding the protein or a portion of the protein of any one of claims 1-52.

57. A nucleic acid molecule encoding the first polypeptide chain, the second polypeptide chain, or both the first polypeptide chain and the second polypeptide chain of the protein of any one of claims 43-52.

58. An expression vector comprising the nucleic acid molecule of claim 56 or 57.
59. A recombinant host cell comprising the nucleic acid molecule of claim 56 or 57 or the expression vector of claim 58.
60. A method of producing a protein, the method comprising:  
culturing a recombinant host cell comprising the expression vector of claim 57 under conditions whereby the nucleic acid molecule is expressed, thereby producing the protein; and  
isolating the protein from the host cell or culture.
61. The protein of any one of claims 1-52, the immunoconjugate of claim 53 or 54, or the pharmaceutical composition of claim 55 for use in therapy.
62. Use of the protein of any one of claims 1-52, the immunoconjugate of claim 53 or 54, or the pharmaceutical composition of claim 55, in the manufacture of a medicament for the treatment of cancer, an autoimmune disease, an inflammatory disease, a cardiovascular disease or a fibrotic disease in a subject, wherein the medicament is to be administered to the subject.
63. The use of claim 62, wherein the cancer is Gastrointestinal Stromal cancer (GIST), pancreatic cancer, skin cancer, melanoma, breast cancer, lung cancer, bronchial cancer, colorectal cancer, prostate cancer, stomach cancer, ovarian cancer, urinary bladder cancer, brain or central nervous system cancer, peripheral nervous system cancer, esophageal cancer, cervical cancer, uterine or endometrial cancer, cancer of the oral cavity or pharynx, liver cancer, kidney cancer, testicular cancer, biliary tract cancer, small bowel or appendix cancer, salivary gland cancer, thyroid gland cancer, adrenal gland cancer, osteosarcoma, chondrosarcoma or cancer of hematological tissues.
64. The use of claim 62, wherein the autoimmune disease or the inflammatory disease is arthritis, asthma, multiple sclerosis, psoriasis, Crohn's disease, inflammatory bowel disease, lupus, Grave's disease, Hashimoto's thyroiditis or ankylosing spondylitis.
65. The use of claim 62, wherein the cardiovascular disease is coronary heart disease, atherosclerosis, or stroke.

66. The use of claim 62, wherein the fibrotic disease is myocardial infarction, angina, osteoarthritis, pulmonary fibrosis, cystic fibrosis, bronchitis or asthma.