

CLAIMS

1. A method of treating a tumor or cancer in a subject in need thereof, comprising administering to the subject an effective amount of a CD93/IGFBP7 blocking agent that specifically inhibits the IGFBP7/CD93 signaling pathway.
2. The method of claim 1, wherein the CD93/IGFBP7 blocking agent blocks interaction between CD93 and IGFBP7.
3. The method of claim 2, wherein the CD93/IGFBP7 blocking agent comprises an anti-CD93 antibody specifically recognizing CD93.
4. The method of claim 3, wherein the anti-CD93 antibody binds to CD93 competitively with mAb MM01 or mAb 7C10.
5. The method of claim 3 or claim 4, wherein the anti-CD93 antibody binds to an epitope that overlaps or substantially overlaps with that of mAb MM01 or mAb 7C10.
6. The method of any one of claim 3-5, wherein the anti-CD93 antibody also blocks interaction between CD93 and MMRN2.
7. The method of any one of claim 3-5, wherein the anti-CD93 antibody does not block interaction between CD93 and MMRN2.
8. The method of any one of claims 3-7, wherein the anti-CD93 antibody binds to the IGFBP7 binding site on CD93.
9. The method of any one of claim 3-7, wherein the anti-CD93 antibody binds to a region on CD93 that is outside of the IGFBP7 binding site.
10. The method of any one of claims 3-9, wherein the anti-CD93 antibody binds to an extracellular region of CD93.
11. The method of claim 10, wherein the extracellular region of CD93 comprises residues

22-580 of the amino acid sequence of SEQ ID NO: 1.

12. The method of any one of claims 3-9, wherein the anti-CD93 antibody binds to an EGF-like region of CD93.

13. The method of claim 12, wherein the EGF-like region of CD93 consists of residues 257-469 and/or 260-468 of the amino acid sequence of SEQ ID NO: 1.

14. The method of any one of claims 3-9, wherein the anti-CD93 antibody binds to a C-type lectin domain of CD93.

15. The method of claim 14, wherein the C-type lectin domain of CD93 comprises 22-174 of the amino acid sequence of SEQ ID NO: 1.

16. The method of any one of claims 3-9, wherein the anti-CD93 antibody binds to a long-loop region of CD93.

17. The method of claim 16, wherein the long-loop region of CD93 comprises residues 96-141 of the amino acid sequence of SEQ ID NO: 1.

18. The method of any one of claims 3-17, wherein the anti-CD93 antibody is an anti-human CD93 antibody.

19. The method of claim 18, wherein the anti-human CD93 antibody is mAb MM01 or a humanized version thereof.

20. The method of any one of claims 3-19, wherein the anti-CD93 antibody is a full length antibody, a single-chain Fv (scFv), a Fab, a Fab', a F(ab')₂, an Fv fragment, a disulfide stabilized Fv fragment (dsFv), a (dsFv)₂, a V_HH, a Fv-Fc fusion, a scFv-Fc fusion, a scFv-Fv fusion, a diabody, a tribody, or a tetrabody.

21. The method of any one of claims 3-20, wherein the anti-CD93 is comprised in a fusion protein.

22. The method of claim 1 or claim 2, wherein the CD93/IGFBP7 blocking agent is a polypeptide.
23. The method of claim 22, wherein the polypeptide is an inhibitory CD93 polypeptide comprising an extracellular domain of CD93 or a variant thereof.
24. The method of claim 22 or claim 23, wherein the polypeptide is a soluble polypeptide.
25. The method of claim 22 or claim 23, wherein the polypeptide is membrane bound.
26. The method of any one of claims 23-25, wherein the inhibitory CD93 polypeptide comprises a variant of the extracellular domain of CD93.
27. The method of any one of claims 22-26, wherein the polypeptide binds to IGFBP7 with a greater affinity than to MMNR2.
28. The method of any one of claims 22-27, wherein the polypeptide binds to IGFBP7 with a greater affinity than to CD93.
29. The method of any one of claims 23-28, wherein the inhibitory CD93 polypeptide comprises an F238 residue, wherein the amino acid numbering is based on SEQ ID NO: 1.
30. The method of any one of claims 23-29, wherein the inhibitory CD93 polypeptide further comprises a stabilizing domain.
31. The method of claim 30, wherein the stabilizing domain is an Fc domain.
32. The method of any one of claims 22-31, wherein the polypeptide is about 50 to about 200 amino acids long.
33. The method of claim 2, wherein the CD93/IGFBP7 blocking agent comprises an anti-IGFBP7 antibody specifically recognizing IGFBP7.
34. The method of claim 33, wherein the anti-IGFBP7 antibody binds to IGFBP7

competitively with mAb R003 or mAb 2C6.

35. The method of claim 33 or 34, wherein the anti-IGFBP7 antibody binds to an epitope that overlaps with that of mAb R003 or mAb 2C6.

36. The method of claim 33, wherein the anti-IGFBP7 antibody also blocks interaction between IGFBP7 and IGF-1, IGF-2, and/or IGF1R.

37. The method of claim 33, wherein the anti-IGFBP7 antibody does not block interaction between IGFBP7 and IGF-1, IGF-2, and/or IGF1R.

38. The method of claim 33, wherein the anti-IGFBP7 antibody binds to a CD93 binding site on IGFBP7.

39. The method of claim 33, wherein the anti-IGFBP7 antibody binds to a region on IGFBP7 that is outside of the CD93 binding site.

40. The method of claim 33, wherein the anti-IGFBP7 antibody binds to an N-terminal domain of IGFBP7 (residues 28-106).

41. The method of claim 40, wherein the N-terminal domain of IGFBP7 consists of residues 28-106 of the amino acid sequence of SEQ ID NO: 2.

42. The method of claim 33, wherein the anti-IGFBP7 antibody binds to a kazal-like domain of IGFBP7.

43. The method of claim 42, wherein the kazal-like domain of IGFBP7 consists of residues 105-158 of the amino acid sequence of SEQ ID NO: 2.

44. The method of claim 33, wherein the anti-IGFBP7 antibody binds to the Ig-like C2-type domain of IGFBP7.

45. The method of claim 44, wherein the Ig-like C2-type domain of IGFBP7 consists of residues 160-264 of the amino acid sequence of SEQ ID NO: 2.

46. The method of claim 33, wherein the anti-IGFBP7 antibody binds to the insulin binding (IB) domain of IGFBP7.
47. The method of any one of claims 33-46, wherein the anti-IGFBP7 antibody is an anti-human IGFBP7 antibody.
48. The method of claim 47, wherein the anti-human IGFBP7 antibody is mAb R003 or a humanized version thereof.
49. The method of any one of claims 33-48, wherein the anti-IGFBP7 antibody is a full length antibody, a single-chain Fv (scFv), a Fab, a Fab', a F(ab')₂, an Fv fragment, a disulfide stabilized Fv fragment (dsFv), a (dsFv)₂, a V_HH, a Fv-Fc fusion, a scFv-Fc fusion, a scFv-Fv fusion, a diabody, a tribody, or a tetrabody.
50. The method of any one of claims 33-49, wherein the anti-IGFBP7 antibody is comprised in a fusion protein.
51. The method of claim 22, wherein the polypeptide is an inhibitory IGFBP7 polypeptide comprising a variant of IGFBP7.
52. The method of claim 51, wherein the inhibitory IGFBP7 polypeptide binds to CD93 but does not activate CD93.
53. The method of any one of claims 51 or 52, wherein the inhibitory IGFBP7 polypeptide binds to CD93 with a greater affinity than for IGF-1, IGF-2, and/or IGF1R.
54. The method of any one of claims 22 or 51-53, wherein the polypeptide binds to CD93 with a greater affinity than IGFBP7.
55. The method of any one of claims 51-54, wherein the inhibitory IGFBP7 polypeptide comprises the IB domain of IGFBP7.
56. The method of any one of claims 51-55, wherein the inhibitory IGFBP7 polypeptide

further comprises a stabilizing domain.

57. The method of claim 56, wherein the stabilizing domain is an Fc domain.

58. The method of any one of claims 51-57, wherein the inhibitory IGFBP7 polypeptide is about 50 to about 200 amino acids long.

59. The method of claim 2, wherein the CD93/IGFBP7 blocking agent comprises a fusion protein, a peptide analog, an aptamer, avimer, anticalin, speigelmeyer, or a small molecule compound.

60. The method of claim 1, wherein the CD93/IGFBP7 blocking agent reduces the expression of CD93 or IGFBP7.

61. The method of claim 60, wherein the CD93/IGFBP7 blocking agent comprises a siRNA, a shRNA, a miRNA, an antisense RNA, or a gene editing system.

62. The method of any one of claims 1-61, further comprising administering to the subject a second agent.

63. The method of claim 62, wherein the second agent is an immune checkpoint inhibitor.

64. The method of claim 63, wherein the immune checkpoint inhibitor is an anti-PD1 antibody, an anti-PD-L1 antibody, an anti-CTLA4 antibody, or a combination thereof.

65. The method of claim 62, wherein the second agent is a chemotherapeutic agent.

66. The method of claim 62, wherein the second agent is an immune cell.

67. The method of claim 62, wherein the second agent is an anti-angiogenesis inhibitor.

68. The method of claim 67, wherein the anti-angiogenesis inhibitor is an anti-VEGF inhibitor.

69. The method of any one of claims 1-68, wherein the cancer is characterized by abnormal tumor vasculature.
70. The method of any one of claims 1-69, wherein the cancer is characterized by high expression of VEGF.
71. The method of any one of claims 1-70, wherein the cancer is characterized by high expression of CD93.
72. The method of any one of claims 1-71, wherein the cancer is characterized by high expression of IGFBP7.
73. The method of any one of claims 1-72, wherein the cancer is a solid tumor.
74. The method of claim 72, wherein the cancer is colorectal cancer, non-small cell lung cancer, glioblastoma, renal cell carcinoma, cervical cancer, ovarian cancer, fallopian tube cancer, peritoneal cancer, breast cancer, prostate cancer, bladder cancer, oral squamous cell carcinoma, head and neck squamous cell carcinoma, brain tumors, bone cancer, melanoma.
75. The method of any one of claims 71-74, wherein the cancer is triple-negative breast cancer (TNBC).
76. The method of claim 73, 74 or 75, wherein the cancer is enriched with blood vessels.
77. A method of determining whether a candidate agent is useful for treating cancer, comprising: determining whether the candidate agent disrupts the CD93/IGFBP7 interaction, wherein the candidate agent is useful for treating cancer if it is shown to specifically disrupt the CD93/IGFBP7 interaction.
78. The method of claim 77, wherein the method comprises determining whether the candidate agent disrupts the interaction of CD93 and IGFBP7 on a cell surface.
79. The method of claim 77, wherein the method comprises determining whether the candidate agent specifically disrupts interaction of CD93 and IGFBP7 in an *in vitro* assay

system.

- 80. The method of claim 79, wherein the *in vitro* system is a yeast two-hybrid system.
- 81. The method of claim 79, wherein the *in vitro* system is an ELISA-based assay.
- 82. The method of claim 81, wherein the *in vitro* system is an FACS-based assay.
- 83. The method of any one of claims 77-82, wherein the candidate agent is an antibody, a peptide, a fusion peptide, a peptide analog, a polypeptide, an aptamer, avimer, anticalin, speigimer, or a small molecule compound.
- 84. The method of any one of claims 77-83, wherein the method comprises contacting the candidate agent with a CD93/IGFBP7 complex.
- 85. An agent identified by the method of any one of claims 77-84.
- 86. A non-naturally occurring polypeptide which is a variant inhibitory CD93 polypeptide comprising the extracellular domain of CD93, wherein the polypeptide blocks interaction between CD93 and IGFBP7.
- 87. The non-naturally occurring polypeptide of claim 86, wherein the variant inhibitory CD93 polypeptide is membrane bound.
- 88. The non-naturally occurring polypeptide of claim 86, wherein the variant inhibitory CD93 polypeptide is soluble.
- 89. The non-naturally occurring polypeptide of any one of claims 86-88, wherein the variant inhibitory CD93 polypeptide binds to IGFBP7 with a greater affinity than for MMNR2.
- 90. The non-naturally occurring polypeptide of any one of claims 86-89, wherein the variant inhibitory CD93 polypeptide binds to IGFBP7 with a greater affinity than CD93.

91. The non-naturally occurring polypeptide of any one of claims 86-90, wherein the inhibitory CD93 polypeptide comprises an F238 residue, wherein the amino acid numbering is based on SEQ ID NO: 1.
92. The non-naturally occurring polypeptide of any one of claims 86-91, wherein inhibitory CD93 polypeptide further comprises a stabilizing domain.
93. The non-naturally occurring polypeptide of claim 92, wherein the stabilizing domain is an Fc domain.
94. The non-naturally occurring polypeptide of any one of claims 86-93, wherein the inhibitory polypeptide is about 50 to about 200 amino acids long.
95. A non-naturally occurring variant inhibitory IGFBP7 polypeptide comprising a variant of IGFBP7, wherein the polypeptide blocks interaction between CD93 and IGFBP7.
96. The non-naturally occurring variant inhibitory IGFBP7 polypeptide of claim 95, wherein the variant inhibitory IGFBP7 polypeptide binds to CD93 but does not activate CD93.
97. The non-naturally occurring variant inhibitory IGFBP7 polypeptide of claim 94 or claim 96, wherein the variant inhibitory IGFBP7 polypeptide binds to CD93 with a greater affinity than for IGF-1, IGF-2, and/or IGF1R.
98. The non-naturally occurring variant inhibitory IGFBP7 polypeptide of any one of claims 95-97, wherein the variant inhibitory IGFBP7 polypeptide binds to CD93 with a greater affinity than IGFBP7.
99. The non-naturally occurring variant inhibitory IGFBP7 polypeptide of any one of claims 95-98, wherein the variant inhibitory IGFBP7 polypeptide comprises the IB domain of IGFBP7.
100. The non-naturally occurring variant inhibitory IGFBP7 polypeptide of any one of claims 95-99, wherein the variant inhibitory IGFBP7 polypeptide further comprises a

stabilizing domain.

101. The non-naturally occurring variant inhibitory IGFBP7 polypeptide of claim 100, wherein the stabilizing domain is an Fc domain.

102. The non-naturally occurring variant inhibitory IGFBP7 polypeptide of any one of claims 95-101, wherein the variant inhibitory is about 50 to about 200 amino acids long.

103. A pharmaceutical composition comprising the agent of claim 85, the non-naturally occurring polypeptide of any one of claims 86-94, or the non-naturally occurring variant inhibitory IGFBP7 polypeptide of claims 95-102 and a pharmaceutically acceptable carrier and/or excipient.