

CLAIMS

1. A ~~combination~~composition comprising an antibody molecule that binds to CD70 and at least one antibody molecule that binds to a leukemic stem cell target.

~~2. The combination of claim 1, wherein the leukemic stem cell target is selected from the group consisting of: TIM-3; Galectin-9; CD47; and IL1RAP; LILRB2; CLL-1; CD123; CD33; SAIL; GPR56; CD44; E-selectin; CXCR4; CD25; CD32; PR1; WT1; ADGRE2; CCR1; TNFRSF1B and CD96.~~

~~3. The combination of claim 1 or claim 2, wherein the antibody molecule that binds to CD70 comprises a variable heavy chain domain (VH) and a variable light chain domain (VL) wherein the VH and VL domains comprise the CDR sequences:~~

HCDR3 comprising or consisting of SEQ ID NO: 3;

HCDR2 comprising or consisting of SEQ ID NO: 2;

HCDR1 comprising or consisting of SEQ ID NO: 1;

LCDR3 comprising or consisting of SEQ ID NO: 7;

LCDR2 comprising or consisting of SEQ ID NO: 6; and

LCDR1 comprising or consisting of SEQ ID NO: 5.

~~4. The combination of claim 3, wherein the antibody molecule that binds to CD70 comprises a VH domain comprising an amino acid sequence at least 70% identical to SEQ ID NO: 4 and a VL domain comprising an amino acid sequence at least 70% identical to SEQ ID NO: 8.~~

~~5. The combination of claim 4, wherein the antibody molecule that binds to CD70 is ARGX-110.~~

~~6. The combination of any of claims 1-5, wherein the leukemic stem cell target is selected from the group consisting of TIM-3 and Galectin-9.~~

~~7. The combination of claim 6, wherein the leukemic stem cell target is TIM-3.~~

~~8. The combination of any of claims 1-5, wherein the leukemic stem cell target is CD47.~~

~~9. The combination of any of claims 1-5, wherein the leukemic stem cell target is IL1RAP.~~

10. ~~The combination of any of claims 1-5, wherein the leukemic stem cell target is LILRB2.~~
11. ~~The combination of any of claims 1-5, wherein the combination comprises an antibody molecule that binds to a first leukemic stem cell target and an antibody molecule that binds to a second leukemic stem cell target, wherein the first and second leukemic stem cell targets are different.~~
12. ~~The combination of claim 11, wherein the first and/or second leukemic stem cell targets are selected from the group consisting of: TIM-3; Galectin-9; CD47; IL1RAP; LILRB2; CLL-1; CD123; CD33; SAIL; GPR56; CD44; E-selectin; CXCR4; CD25; CD32; PR1; WT1; ADGRE2; CCR1; TNFRSF1B and CD96.~~
13. ~~The combination of claim 11, wherein the first leukemic stem cell target is selected from the group consisting of: TIM-3; Galectin-9; CD47; IL1RAP and LILRB2.~~
14. ~~The combination of claim 11 or claim 13, wherein the second leukemic stem cell target is selected from the group consisting of: TIM-3; Galectin-9; CD47; IL1RAP and LILRB2.~~
15. ~~The combination of claim 11, wherein the first leukemic stem cell target is TIM-3 and the second leukemic stem cell target is CD47.~~
16. ~~The combination of claim 11, wherein the first leukemic stem cell target is TIM-3 and the second leukemic stem cell target is IL1RAP.~~
17. ~~The combination of any of the preceding claim comprising an antibody molecule that binds IL1RAP, wherein said antibody molecule, when present, results in reduced NF-κB signaling; reduced Wnt signaling/β-catenin signalling; reduced stemness of AML cells; or a combination thereof; and~~
18. ~~The combination of any of wherein the preceding claims comprising an antibody molecule that binds TIM-3, wherein said antibody molecule to IL1RAP, when present, results in reduced NF-κB signaling; reduced Wnt signaling/β-catenin signalling; reduced stemness of AML cells; or a combination thereof.~~
19. ~~The combination composition of any of claim 1, wherein the preceding claims comprising an antibody molecule that binds TIM-3 to CD70 comprises a VH domain comprising an amino~~

acid sequence at least 70% identical to SEQ ID NO: 4 and a VL domain comprising an amino acid sequence at least 70% identical to SEQ ID NO: 8.

3. The composition of claim 1 or claim 2, wherein said antibody molecule inhibits the interaction of leukemic stem cell target is TIM-3 with one or more TIM-3 interacting proteins.

20. ~~The combination of claim 19, wherein the TIM-3 interacting proteins are selected from: CEACAM-1; HMGB-1; phosphatidylserine; Galectin-9; LILRB2; or combinations thereof.~~

214. ~~The combination composition of claim 201 or claim 2, wherein the antibody molecule that binds TIM-3 inhibits the interaction of TIM-3 with Galectin-9.~~

22. ~~The combination of claim 20, wherein the antibody molecule that binds TIM-3 inhibits the interaction of TIM-3 with LILRB2.~~

23. ~~The combination of any of the preceding claims, wherein the antibody molecule or molecules that bind to leukemic stem cell targets is/are selected from one or more immune libraries obtained by a method comprising the step of immunizing a camelid with the leukemic stem cell target(s). is IL1RAP.~~

245. ~~The combination of claim 23, wherein the camelid is a llama.~~

25. ~~The combination of claim 23 or 24, wherein the camelid is immunized with the LSC target protein or a polypeptide fragment thereof, or with an mRNA molecule or a cDNA molecule expressing the LSC target protein or a polypeptide fragment thereof.~~

26. ~~The combination composition of any of the preceding claims 1-3 comprising an antibody molecule that binds TIM-3, wherein said antibody molecule is selected from the group consisting of antibody molecules comprising a combination of variable heavy chain CDR3 (HCDR3), variable heavy chain CDR2 (HCDR2) and variable heavy chain CDR1 (HCDR1), variable light chain CDR3 (LCDR3), variable light chain CDR2 (LCDR2) and variable light chain CDR1 (LCDR1) selected from the following:~~

- (i) HCDR3 comprising SEQ ID NO: 41; HCDR2 comprising SEQ ID NO: 40; HCDR1 comprising SEQ ID NO: 39; LCDR3 comprising SEQ ID NO: 80; LCDR2 comprising SEQ ID NO: 79; and LCDR1 comprising SEQ ID NO: 78;

- (ii) HCDR3 comprising SEQ ID NO: 43; HCDR2 comprising SEQ ID NO: 42; HCDR1 comprising SEQ ID NO: 39; LCDR3 comprising SEQ ID NO: 83; LCDR2 comprising SEQ ID NO: 82; and LCDR1 comprising SEQ ID NO: 81;
- (iii) HCDR3 comprising SEQ ID NO: 46; HCDR2 comprising SEQ ID NO: 45; HCDR1 comprising SEQ ID NO: 44; LCDR3 comprising SEQ ID NO: 86; LCDR2 comprising SEQ ID NO: 85; and LCDR1 comprising SEQ ID NO: 84;
- (iv) HCDR3 comprising SEQ ID NO: 49; HCDR2 comprising SEQ ID NO: 48; HCDR1 comprising SEQ ID NO: 47; LCDR3 comprising SEQ ID NO: 88; LCDR2 comprising SEQ ID NO: 82; and LCDR1 comprising SEQ ID NO: 87;
- (v) HCDR3 comprising SEQ ID NO: 52; HCDR2 comprising SEQ ID NO: 51; HCDR1 comprising SEQ ID NO: 50; LCDR3 comprising SEQ ID NO: 91; LCDR2 comprising SEQ ID NO: 90; and LCDR1 comprising SEQ ID NO: 89;
- (vi) HCDR3 comprising SEQ ID NO: 55; HCDR2 comprising SEQ ID NO: 54; HCDR1 comprising SEQ ID NO: 53; LCDR3 comprising SEQ ID NO: 94; LCDR2 comprising SEQ ID NO: 93; and LCDR1 comprising SEQ ID NO: 92;
- (vii) HCDR3 comprising SEQ ID NO: 58; HCDR2 comprising SEQ ID NO: 57; HCDR1 comprising SEQ ID NO: 56; LCDR3 comprising SEQ ID NO: 97; LCDR2 comprising SEQ ID NO: 96; and LCDR1 comprising SEQ ID NO: 95;
- (viii) HCDR3 comprising SEQ ID NO: 60; HCDR2 comprising SEQ ID NO: 59; HCDR1 comprising SEQ ID NO: 50; LCDR3 comprising SEQ ID NO: 100; LCDR2 comprising SEQ ID NO: 99; and LCDR1 comprising SEQ ID NO: 98;
- (ix) HCDR3 comprising SEQ ID NO: 63; HCDR2 comprising SEQ ID NO: 62; HCDR1 comprising SEQ ID NO: 61; LCDR3 comprising SEQ ID NO: 103; LCDR2 comprising SEQ ID NO: 102; and LCDR1 comprising SEQ ID NO: 101;
- (x) HCDR3 comprising SEQ ID NO: 65; HCDR2 comprising SEQ ID NO: 64; HCDR1 comprising SEQ ID NO: 39; LCDR3 comprising SEQ ID NO: 106; LCDR2 comprising SEQ ID NO: 105; and LCDR1 comprising SEQ ID NO: 104;
- (xi) HCDR3 comprising SEQ ID NO: 67; HCDR2 comprising SEQ ID NO: 66; HCDR1 comprising SEQ ID NO: 50; LCDR3 comprising SEQ ID NO: 109; LCDR2 comprising SEQ ID NO: 108; and LCDR1 comprising SEQ ID NO: 107;
- (xii) HCDR3 comprising SEQ ID NO: 69; HCDR2 comprising SEQ ID NO: 68; HCDR1 comprising SEQ ID NO: 50; LCDR3 comprising SEQ ID NO: 112; LCDR2 comprising SEQ ID NO: 111; and LCDR1 comprising SEQ ID NO: 110;
- (xiii) HCDR3 comprising SEQ ID NO: 72; HCDR2 comprising SEQ ID NO: 71; HCDR1 comprising SEQ ID NO: 70; LCDR3 comprising SEQ ID NO: 115; LCDR2 comprising SEQ ID NO: 114; and LCDR1 comprising SEQ ID NO: 113;

- (xiv) HCDR3 comprising SEQ ID NO: 74; HCDR2 comprising SEQ ID NO: 73; HCDR1 comprising SEQ ID NO: 50; LCDR3 comprising SEQ ID NO: 117; LCDR2 comprising SEQ ID NO: 111; and LCDR1 comprising SEQ ID NO: 116; and
- (xv) HCDR3 comprising SEQ ID NO: 77; HCDR2 comprising SEQ ID NO: 76; HCDR1 comprising SEQ ID NO: 75; LCDR3 comprising SEQ ID NO: 120; LCDR2 comprising SEQ ID NO: 119; and LCDR1 comprising SEQ ID NO: 118.

~~276.~~ The ~~combination~~ composition of any of the ~~preceding~~ claims 1-3 or 5 comprising an antibody molecule that binds TIM-3, wherein said antibody molecule is selected from an antibody molecule comprising or consisting of a variable heavy chain domain (VH) and a variable light chain domain (VL) selected from the following:

- (i) a VH domain comprising or consisting of the amino acid sequence of SEQ ID NO: 9 or an amino acid sequence having at least 80%, 90%, 95%, 98% 99% identity thereto, and a VL domain comprising or consisting of the amino acid sequence of SEQ ID NO: 10 or an amino acid sequence having at least 80%, 90%, 95%, 98% 99% identity thereto;
- (ii) a VH domain comprising or consisting of the amino acid sequence of SEQ ID NO: 11 or an amino acid sequence having at least 80%, 90%, 95%, 98% 99% identity thereto, and a VL domain comprising or consisting of the amino acid sequence of SEQ ID NO: 12 or an amino acid sequence having at least 80%, 90%, 95%, 98% 99% identity thereto;
- (iii) a VH domain comprising or consisting of the amino acid sequence of SEQ ID NO: 13 or an amino acid sequence having at least 80%, 90%, 95%, 98% 99% identity thereto, and a VL domain comprising or consisting of the amino acid sequence of SEQ ID NO: 14 or an amino acid sequence having at least 80%, 90%, 95%, 98% 99% identity thereto;
- (iv) a VH domain comprising or consisting of the amino acid sequence of SEQ ID NO: 15 or an amino acid sequence having at least 80%, 90%, 95%, 98% 99% identity thereto, and a VL domain comprising or consisting of the amino acid sequence of SEQ ID NO: 16 or an amino acid sequence having at least 80%, 90%, 95%, 98% 99% identity thereto;
- (v) a VH domain comprising or consisting of the amino acid sequence of SEQ ID NO: 17 or an amino acid sequence having at least 80%, 90%, 95%, 98% 99% identity thereto, and a VL domain comprising or consisting of the amino acid sequence of SEQ ID NO: 18 or an amino acid sequence having at least 80%, 90%, 95%, 98% 99% identity thereto;

- 5 (vi) a VH domain comprising or consisting of the amino acid sequence of SEQ ID NO: 19 or an amino acid sequence having at least 80%, 90%, 95%, 98% 99% identity thereto, and a VL domain comprising or consisting of the amino acid sequence of SEQ ID NO: 20 or an amino acid sequence having at least 80%, 90%, 95%, 98% 99% identity thereto;
- 10 (vii) a VH domain comprising or consisting of the amino acid sequence of SEQ ID NO: 21 or an amino acid sequence having at least 80%, 90%, 95%, 98% 99% identity thereto, and a VL domain comprising or consisting of the amino acid sequence of SEQ ID NO: 22 or an amino acid sequence having at least 80%, 90%, 95%, 98% 99% identity thereto;
- 15 (viii) a VH domain comprising or consisting of the amino acid sequence of SEQ ID NO: 23 or an amino acid sequence having at least 80%, 90%, 95%, 98% 99% identity thereto, and a VL domain comprising or consisting of the amino acid sequence of SEQ ID NO: 24 or an amino acid sequence having at least 80%, 90%, 95%, 98% 99% identity thereto;
- 20 (ix) a VH domain comprising or consisting of the amino acid sequence of SEQ ID NO: 25 or an amino acid sequence having at least 80%, 90%, 95%, 98% 99% identity thereto, and a VL domain comprising or consisting of the amino acid sequence of SEQ ID NO: 26 or an amino acid sequence having at least 80%, 90%, 95%, 98% 99% identity thereto;
- 25 (x) a VH domain comprising or consisting of the amino acid sequence of SEQ ID NO: 27 or an amino acid sequence having at least 80%, 90%, 95%, 98% 99% identity thereto, and a VL domain comprising or consisting of the amino acid sequence of SEQ ID NO: 28 or an amino acid sequence having at least 80%, 90%, 95%, 98% 99% identity thereto;
- 30 (xi) a VH domain comprising or consisting of the amino acid sequence of SEQ ID NO: 29 or an amino acid sequence having at least 80%, 90%, 95%, 98% 99% identity thereto, and a VL domain comprising or consisting of the amino acid sequence of SEQ ID NO: 30 or an amino acid sequence having at least 80%, 90%, 95%, 98% 99% identity thereto;
- 35 (xii) a VH domain comprising or consisting of the amino acid sequence of SEQ ID NO: 31 or an amino acid sequence having at least 80%, 90%, 95%, 98% 99% identity thereto, and a VL domain comprising or consisting of the amino acid sequence of SEQ ID NO: 32 or an amino acid sequence having at least 80%, 90%, 95%, 98% 99% identity thereto;
- (xiii) a VH domain comprising or consisting of the amino acid sequence of SEQ ID NO: 33 or an amino acid sequence having at least 80%, 90%, 95%, 98% 99%

identity thereto, and a VL domain comprising or consisting of the amino acid sequence of SEQ ID NO: 34 or an amino acid sequence having at least 80%, 90%, 95%, 98% 99% identity thereto;

(xiv) a VH domain comprising or consisting of the amino acid sequence of SEQ ID NO: 35 or an amino acid sequence having at least 80%, 90%, 95%, 98% 99% identity thereto, and a VL domain comprising or consisting of the amino acid sequence of SEQ ID NO: 36 or an amino acid sequence having at least 80%, 90%, 95%, 98% 99% identity thereto;

(xv) a VH domain comprising or consisting of the amino acid sequence of SEQ ID NO: 37 or an amino acid sequence having at least 80%, 90%, 95%, 98% 99% identity thereto, and a VL domain comprising or consisting of the amino acid sequence of SEQ ID NO: 38 or an amino acid sequence having at least 80%, 90%, 95%, 98% 99% identity thereto.

~~287.~~ The ~~combination~~composition of any of the ~~preceding~~ claims 1, 2 or 4 comprising an antibody molecule that binds IL1RAP, wherein said antibody molecule is selected from the group consisting of antibody molecules comprising a combination of variable heavy chain CDR3 (HCDR3), variable heavy chain CDR2 (HCDR2) and variable heavy chain CDR1 (HCDR1), variable light chain CDR3 (LCDR3), variable light chain CDR2 (LCDR2) and variable light chain CDR1 (LCDR1) selected from the following:

(i) HCDR3 comprising SEQ ID NO: 127; HCDR2 comprising SEQ ID NO: 126; HCDR1 comprising SEQ ID NO: 125; LCDR3 comprising SEQ ID NO: 133; LCDR2 comprising SEQ ID NO: 132; and LCDR1 comprising SEQ ID NO: 131; and

(ii) HCDR3 comprising SEQ ID NO: 130; HCDR2 comprising SEQ ID NO: 129; HCDR1 comprising SEQ ID NO: 128; LCDR3 comprising SEQ ID NO: 136; LCDR2 comprising SEQ ID NO: 135; and LCDR1 comprising SEQ ID NO: 134.

~~298.~~ The ~~combination~~composition of any of the ~~preceding~~ claims 1, 2, 4 or 7 comprising an antibody molecule that binds IL1RAP, wherein said antibody molecule is selected from an antibody molecule comprising or consisting of a variable heavy chain domain (VH) and a variable light chain domain (VL) selected from the following:

(i) a VH domain comprising or consisting of the amino acid sequence of SEQ ID NO: 121 or an amino acid sequence having at least 80%, 90%, 95%, 98% 99% identity thereto, and a VL domain comprising or consisting of the amino acid sequence of SEQ ID NO: 122 or an amino acid sequence having at least 80%, 90%, 95%, 98% 99% identity thereto; and

- (ii) a VH domain comprising or consisting of the amino acid sequence of SEQ ID NO: 123 or an amino acid sequence having at least 80%, 90%, 95%, 98% 99% identity thereto, and a VL domain comprising or consisting of the amino acid sequence of SEQ ID NO: 124 or an amino acid sequence having at least 80%, 90%, 95%, 98% 99% identity thereto.

~~30. The combination of any of the preceding claims comprising an antibody molecule that binds CD47, wherein said antibody molecule inhibits the interaction between CD47 and SIRP α .~~

~~31. The combination of any of the preceding claims comprising an antibody molecule that binds CD47, wherein said antibody molecule increases phagocytosis of tumour cells.~~

~~32. The combination of any of the preceding claims comprising an antibody molecule that binds CD47, wherein said antibody molecule is selected from: Hu5F9-G4; CC-90002; and ALX148.~~

~~33. The combination of any of the preceding claims, wherein the antibody molecules of the combination are independently selected from the group consisting of: an IgG antibody; an antibody light chain variable domain (VL); an antibody heavy chain variable domain (VH); a single chain antibody (scFv); a F(ab')₂ fragment; a Fab fragment; an Fd fragment; an Fv fragment; a one-armed (monovalent) antibody; diabodies, triabodies, tetrabodies or any antigen-binding molecule formed by combination, assembly or conjugation of such antigen binding fragments.~~

~~34. The combination of any of the preceding claims, wherein the antibody molecules of the combination are combined in a multispecific antibody.~~

~~35. The combination of claim 34, wherein the combination comprises a first antibody molecule that binds to CD70 and a second antibody molecule that binds to a leukemic stem cell target combined in a bispecific antibody.~~

~~36. The combination of any of claims 1-33, wherein the antibody molecules of the combination are co-formulated.~~

~~37. The combination of claim 36, wherein the combination comprises a first antibody molecule that binds to CD70 and a second antibody molecule that binds to a leukemic stem~~

cell target, and wherein the first and second antibody molecules are formulated according to a ratio of 1:1 or 1:2 or 2:1.

~~38. The combination of any of claims 1-33, wherein the antibody molecules are provided separately.~~

~~39. The combination of any of the preceding claims, wherein at least one of the antibody molecules blocks its target's function completely or partially.~~

~~40. The combination~~9. The composition of any of the preceding claims, wherein at least one of the antibody molecules has ADCC activity-, and/or wherein at least one of the antibody molecules has CDC activity, and/or wherein at least one of the antibody molecules has ADCP activity.

~~41. The combination of claim 40, wherein at least one~~10. Use of the antibody molecules comprises a defucosylated antibody domain.

~~42. The combination~~composition of any of the preceding claims, wherein at least one of the antibody molecules has CDC activity in the manufacture of a medicament for the treatment of malignancy in a human subject.

~~43. The combination of any of the preceding claims, where at least one of the antibody molecules has ADCP activity.~~

~~44. The combination of any of the preceding claims, wherein the combination additionally comprises an agent that inhibits SIRPα signalling.~~

~~45. The combination of claim 44, wherein the agent that inhibits SIRPα signalling is an antibody molecule that binds to SIRPα and inhibits the interaction between CD47 and SIRPα.~~

~~46. The combination of claim 45, wherein the agent that inhibits SIRPα signalling is a SIRPα-antibody molecule fusion protein.~~

~~47. The combination of claim 46, wherein the SIRPα-antibody molecule is a SIRPα-Fc fusion.~~

48. The combination of claim 46 or claim 47, wherein the SIRP α -antibody molecule fusion protein comprises at least one of the antibody molecules of the combination.

49. The combination of claim 48, wherein the SIRP α -antibody molecule fusion protein comprises the antibody molecule of the combination that binds CD70.

50. A combination kit comprising an antibody molecule that binds to CD70 and an agent that inhibits SIRP α signalling.

51. The combination of claim 50, wherein the agent that inhibits SIRP α signalling is an antibody molecule that binds CD47 and inhibits the interaction between CD47 and SIRP α .

52. The combination of claim 50, wherein the agent that inhibits SIRP α signalling is an antibody molecule that binds SIRP α and inhibits the interaction between CD47 and SIRP α .

53. The combination of claim 50, wherein the agent that inhibits SIRP α signalling is a SIRP α -antibody molecule fusion protein.

54. The combination of claim 53, wherein the SIRP α -antibody molecule fusion protein is a SIRP α -Fc fusion.

55. The combination of claim 53, wherein the SIRP α -antibody molecule fusion protein comprises at least one SIRP α V-like domain covalently linked to the antibody molecule that binds to CD70.

56. The combination of claim 55, wherein the at least one SIRP α V-like domain is covalently linked to the antibody molecule via a linker.

57. The combination of any of the preceding claims, wherein the combination comprises at least one additional anti-cancer agent, preferably an agent for the treatment of a myeloid malignancy.

58. The combination of claim 57, wherein the anti-cancer agent is an agent for the treatment of AML.

59. The combination of any of the preceding claims, wherein the combination additionally comprises a hypomethylating agent.

60. ~~The combination of claim 59, wherein the hypomethylating agent is azacitidine.~~

61. ~~The combination of any of the preceding claims, wherein the combination additionally comprises a PD-1 inhibitor and/or a PD-L1 inhibitor, optionally wherein the inhibitor is an antibody.~~

62. ~~The combination of claim 61, wherein the PD-1 and/or PD-L1 inhibitor is selected from: nivolumab; pembrolizumab; pidilizumab, REGN2810; AMP-224; MEDI0680; PDR001; atezolizumab; or avolumab.~~

63. ~~The combination of any of the preceding claims for use in the treatment of malignancy in a human subject.~~

64. ~~An antibody molecule that binds to CD70 for use in the treatment of malignancy in a human subject, wherein the antibody molecule is administered in combination with an at least one antibody molecule that binds to a leukemic stem cell target.~~

65. ~~An antibody molecule that binds to a , wherein the leukemic stem cell target for use in the treatment of malignancy in a human subject, wherein the antibody molecule is administered in combination with an antibody molecule that binds to CD70.~~

66. ~~The antibody molecule for use according to claim 64 or claim 65, wherein the leukemic stem cell target is is selected from the group consisting of: TIM-3.~~

67. ~~The antibody molecule for use according to claim 64 or claim 65, wherein the leukemic stem cell target is CD47.~~

68. ~~The antibody molecule for use according to claim 64 or claim 65, wherein the leukemic stem cell target is ; and IL1RAP₊, and wherein the antibody molecule that binds to CD70 comprises a variable heavy chain domain (VH) and a variable light chain domain (VL) wherein the VH and VL domains comprise the CDR sequences:~~

69. ~~The antibody molecule for use according to claim 64 or claim 65, wherein the leukemic stem cell target is LILRB2.~~

70. ~~An HCDR3 comprising or consisting of SEQ ID NO: 3;~~

HCDR2 comprising or consisting of SEQ ID NO: 2;
HCDR1 comprising or consisting of SEQ ID NO: 1;
LCDR3 comprising or consisting of SEQ ID NO: 7;
LCDR2 comprising or consisting of SEQ ID NO: 6; and
LCDR1 comprising or consisting of SEQ ID NO: 5,

wherein the antibody molecule that binds to CD70 for use in the treatment of malignancy in a human subject
TIM-3, when present, results in reduced NF- κ B signaling; reduced Wnt signaling/ β -catenin signalling; reduced stemness of AML cells; or a combination thereof, and
wherein the antibody molecule that binds to IL1RAP, when present, results in reduced NF- κ B signaling; reduced Wnt signaling/ β -catenin signalling; reduced stemness of AML cells; or a combination thereof.

12. The kit of claim 11, wherein the antibody molecule is administered in combination with an agent that inhibits SIRP α signaling.

71. An agent that inhibits SIRP α signaling for use in the treatment of malignancy in a human subject, wherein the agent is administered in combination with an antibody molecule that binds CD70.

72. A method for treating a malignancy in a human subject, said method comprising administering to the subject an effective amount of a combination molecules are as defined in any of claims 1-62.

73. The method of claim 72, wherein the malignancy is a malignancy comprising the production of cancer progenitor or stem cells expressing CD70, CD27, or both.

74. The method of claim 72 or claim 73, wherein the malignancy is a malignancy comprising the production of cancer progenitor or stem cells expressing the LSC target to which at least one of the antibody molecules of the combination bind.

75. The method of any of claims 72-74, wherein the malignancy is a myeloid malignancy.

76. The method of claim 75, wherein the myeloid malignancy is selected from newly diagnosed or relapsed/refractory myeloid malignancies.

77. The method of claim 75 or claim 76, wherein the myeloid malignancy is selected from: acute myeloid leukemia (AML); myelodysplastic syndromes (MDS); myeloproliferative neoplasms (MPN); chronic myeloid leukemia (CML); and myelomonocytic leukemia (CMML).

5 78. The method of claim 77, wherein the myeloid malignancy is acute myeloid leukemia (AML).

79. The method of claim 77 or claim 78, further comprising monitoring of the patient's blast count.

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80. The method of claim 79, wherein the patient's bone marrow blast count is reduced to less than 5%.

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81. The method of claim 79, wherein the patient's bone marrow blast count is reduced to between 5% and 25% and the bone marrow blast percentage is reduced by more than 50% as compared to pretreatment.

82. The method of any of claims 72-79, which induces a partial response or a complete response.

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83. The method of claim 82, which induces a complete response with platelet recovery.

84. The method of claim 82 or 83, which induces a complete response with neutrophil recovery.

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85. The method of any of claims 72-84, which induces transfusion independence of red blood cells or platelets, or both, for 8 weeks or longer.

86. The method of any of claims 72-85, which increases survival.

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87. The method of any of claims 72-86, which increases survival versus standard of care agents used for treatment of myeloid malignancies.

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88. The method of any of claims 72-87, which induces a minimal residual disease status that is negative.

~~89. The method of any of claims 72-88, further comprising subjecting the subject to a bone marrow transplantation.~~

5 ~~90. The method of any of claims 72-89, further comprising administering one or more additional anti-cancer agents.~~

~~91. The method of claim 90, wherein the one or more additional anti-cancer agents are selected from agents suitable for the treatment of myeloid malignancies.~~

10 ~~92. The method of claim 90, wherein the one or more additional anti-cancer agents are selected from agents suitable for the treatment of AML.~~

~~93. The method of claim 92, wherein the one or more additional anti-cancer agents are selected from: Venetoclax; Vyxeos; Idhifa (Enasidenib); and Rydapt (midostaurin).~~

15 ~~2-9.~~