

CLAIMS

1. A binding protein comprising a first and a second antigen binding domain (ABD) and all or part of an immunoglobulin Fc region or variant thereof, wherein each of said ABD comprises an immunoglobulin heavy chain variable domain (VH) and an immunoglobulin light chain variable domain (VL), wherein each VH and VL comprises three complementary determining regions (CDR-1 to CDR-3); and wherein:

(i) the first ABD binds specifically to human CD123 and comprises:

- a VH1 comprising a CDR-H1, H2 and H3 ~~corresponding to~~comprising the amino acid sequences of SEQ ID NO: 1 to 3 respectively or ~~corresponding to~~comprising the amino acid sequences of SEQ ID NO: 4 to 6 respectively, and

- a VL1 comprising a CDR-L1, L2 and L3 ~~corresponding to~~comprising the amino acid sequences of SEQ ID NO: 7 to 9 respectively or ~~corresponding to~~comprising the amino acid sequences of SEQ ID NO: 10 to 12 respectively;

(ii) the second ABD binds specifically to human NKp46 and comprises:

- a VH2 comprising a CDR-H1, 2 and 3 ~~corresponding to~~comprising:

the amino acid sequences of SEQ ID NO: 13 to 15 respectively;

the amino acid sequences of SEQ ID NO: 16 to 18 respectively;

the amino acid sequences of SEQ ID NO: 19 to 21 respectively;

the amino acid sequences of SEQ ID NO: 22 to 24 respectively; or

the amino acid sequences of SEQ ID NO: 16, 25 and 26 respectively;

and

- a VL2 comprising a CDR-L1, 2 and 3 ~~corresponding to~~comprising:

the amino acid sequences of SEQ ID NO: 27 to 29 respectively;

the amino acid sequences of SEQ ID NO: 30 to 32 respectively;

the amino acid sequences of SEQ ID NO: 33 to 35 respectively;

the amino acid sequences of SEQ ID NO: 36 to 38 respectively; or

the amino acid sequences SEQ ID NO: 39, 31 and 40 respectively;

and wherein all or part of the immunoglobulin Fc region or variant thereof binds to a human Fc- γ receptor.

2. The binding protein according to claim 1, comprising three polypeptide chains (I), (II) and (III) that form two ABDs, as defined below:

light chain variable domain 1A (V_{1A}—) – light chain constant domain 1A (C_{1A}) –
Hinge₁ – (C_{H2}-C_{H3})_A (I)

heavy chain variable domain 1B (V_{1B}—) – heavy chain constant domain 1B (C_{1B}) –
Hinge₂ – (C_{H2}-C_{H3})_B – L₁ – heavy chain variable domain 2A (V_{2A}—) – heavy chain
constant domain 2A (C_{2A}) – Hinge₃ (II)

light chain variable domain 2B (V_{2B}—)
– light chain constant domain 2B (C_{2B})
(III)

wherein :

V_{1A} and V_{1B} form a binding pair V₁ (V_{H1}/V_{L1});

V_{2A} and V_{2B} form a binding pair V₂ (V_{H2}/V_{L2});

C_{1A} and C_{1B} form a pair C₁ (C_{H1}/C_L) and C_{2A} and C_{2B} form a pair C₂ (C_{H1}/C_L) wherein C_{H1} is an immunoglobulin heavy chain constant domain 1 and C_L is an immunoglobulin light chain constant domain;

Hinge₁, Hinge₂ and Hinge₃ are identical or different and ~~correspond to~~comprise all or part of an immunoglobulin hinge region;

(C_{H2}-C_{H3})_A and (C_{H2}-C_{H3})_B are identical or different, and comprise an immunoglobulin heavy chain constant domain 2 (C_{H2}) and an immunoglobulin heavy chain constant domain 3 (C_{H3});

L₁ is an amino acid linker.

3. The binding protein according to claim 2 wherein:

C_{1B} is an immunoglobulin heavy chain constant domain 1 (C_{H1});

C_{2A} is an immunoglobulin heavy chain constant domain 1 (C_{H1});

C_L ~~corresponds to~~comprises an immunoglobulin kappa light chain constant domain (C_K);

(C_{H2}-C_{H3})_A ~~corresponds to~~comprises the amino acid sequence of SEQ ID NO: 69 ;

(C_{H2}-C_{H3})_B ~~corresponds to~~comprises the amino acid sequence of SEQ ID NO: 70;

Hinge₁ ~~corresponds to~~comprises the amino acid sequence of SEQ ID NO:74;

Hinge₂ ~~corresponds to~~comprises the amino acid sequence of SEQ ID NO:75;

Hinge₃ ~~corresponds to~~comprises the amino acid sequence of SEQ ID NO: 77;

L₁ ~~corresponds to~~comprises the amino acid sequence of SEQ ID NO: 76.

4. The binding protein according to ~~any one of the preceding claims~~claim 1, wherein the residue N297 of the Fc region or variant thereof according to EU numbering comprises a N-linked glycosylation, wherein the Fc region or variant thereof is a human Fc region or variant thereof of an IgG1, IgG2, IgG3, or IgG4 isotype.

5. The binding protein according to ~~any one of the preceding claims~~claim 1, wherein the all or part of the Fc region or variant thereof binds to a human CD16A (FcγRIII) polypeptide.

6. The binding protein according to ~~anyone of claims 2 to 5~~claim 2, comprising at least two polypeptide chains linked by at least one disulfide bridge.

7. The binding protein according to claim 6, wherein the polypeptide chains (I) and (II) are linked by at least one disulfide bridge between C_{1A} and Hinge₂ and/or wherein the polypeptide chains (II) and (III) are linked by at least one disulfide bridge between Hinge₃ and C_{2B}.

8. The binding protein according to ~~anyone of claims 2 to 7~~claim 2, wherein V_{1A} is V_{L1} and V_{1B} is V_{H1}.

9. The binding protein according to ~~anyone of claims~~claim 2 to 8, wherein V_{2A} is V_{H2} and V_{2B} is V_{L2}.

10. The binding protein according to ~~any one of the preceding claims~~claim 1, wherein:

(a) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 1; a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 2; a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 3; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 7; a CDR-L2 comprising the amino acid sequence of SEQ ID

NO: 8; a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 9; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 13; a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 14; a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 15; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 27; a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 28; a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 29;

(b) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 1; a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 2; a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 3; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 7; a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 8; a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 9; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 16; a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 17; a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 18; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 30; a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 31; a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 32;

(c) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 1; a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 2; a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 3; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 7; a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 8; a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 9; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 19; a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 20; a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 21; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 33; a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 34; a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 35;

(d) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 1; a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 2; a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 3; V_{L1} comprises a CDR-L1 comprising the amino

acid sequence of SEQ ID NO: 7; a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 8; a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 9; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 22; a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 23; a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 24; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 36; a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 37; a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 38;

(e) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 1; a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 2; a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 3; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 7; a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 8; a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 9; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 16; a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 25; a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 26; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 39; a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 31; a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 40;

(f) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 4; a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 5; a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 6; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 10; a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 11; a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 12; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 13; a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 14; a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 15; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 27; a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 28; a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 29;

(g) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 4; a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 5; a CDR-H3 comprising

the amino acid sequence of SEQ ID NO: 6; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 10; a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 11; a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 12; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 16; a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 17; a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 18; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 30; a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 31; a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 32;

(h) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 4; a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 5; a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 6; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 10; a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 11; a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 12; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 19; a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 20; a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 21; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 33; a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 34; a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 35;

(i) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 4; a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 5; a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 6; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 10; a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 11; a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 12; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 22; a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 23; a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 24; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 36; a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 37; a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 38; or

____(j) V_{H1} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 4; a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 5; a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 6; V_{L1} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 10; a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 11; a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 12; V_{H2} comprises a CDR-H1 comprising the amino acid sequence of SEQ ID NO: 16; a CDR-H2 comprising the amino acid sequence of SEQ ID NO: 25; a CDR-H3 comprising the amino acid sequence of SEQ ID NO: 26; V_{L2} comprises a CDR-L1 comprising the amino acid sequence of SEQ ID NO: 39; a CDR-L2 comprising the amino acid sequence of SEQ ID NO: 31; a CDR-L3 comprising the amino acid sequence of SEQ ID NO: 40.

11. The binding protein according to ~~any one of the preceding claims~~claim 1, wherein:

(a) V_{H1} and V_{L1} ~~corresponds to comprise~~ the amino acid sequences of SEQ ID NO: 41 and 43 respectively or ~~corresponds to comprise~~ the amino acid sequences of SEQ ID NO: 42 and 44 respectively;
and/or

(b) V_{H2} and V_{L2} ~~corresponds to comprise~~
the amino acid sequences of SEQ ID NO: 45 and 53 respectively;
the amino acid sequences of SEQ ID NO: 46 and 54 respectively;
the amino acid sequences of SEQ ID NO: 47 and 55 respectively;
the amino acid sequences of SEQ ID NO: 48 and 56 respectively;
the amino acid sequences of SEQ ID NO: 49 and 57 respectively;
the amino acid sequences of SEQ ID NO: 50 and 58 respectively;
the amino acid sequences of SEQ ID NO: 51 and 59 respectively; or
the amino acid sequences of SEQ ID NO: 52 and 60 respectively.

12. The binding protein according to claim 11, wherein:

(a) V_{H1} comprises the amino acid sequence of SEQ ID NO: 41; V_{L1} comprises the amino acid sequence of SEQ ID NO: 43; V_{H2} comprises the amino acid sequence of SEQ ID NO: 45; V_{L2} comprises the amino acid sequence of SEQ ID NO: 53;

(b) V_{H1} comprises the amino acid sequence of SEQ ID NO: 41; V_{L1} comprises the amino acid sequence of SEQ ID NO: 43; V_{H2} comprises the amino acid sequence of SEQ ID NO: 46; V_{L2} comprises the amino acid sequence of SEQ ID NO: 54;

(c) V_{H1} comprises the amino acid sequence of SEQ ID NO: 41; V_{L1} comprises the amino acid sequence of SEQ ID NO: 43; V_{H2} comprises the amino acid sequence of SEQ ID NO: 47; V_{L2} comprises the amino acid sequence of SEQ ID NO: 55;

(d) V_{H1} comprises the amino acid sequence of SEQ ID NO: 41; V_{L1} comprises the amino acid sequence of SEQ ID NO: 43; V_{H2} comprises the amino acid sequence of SEQ ID NO: 48; V_{L2} comprises the amino acid sequence of SEQ ID NO: 56;

(e) V_{H1} comprises the amino acid sequence of SEQ ID NO: 41; V_{L1} comprises the amino acid sequence of SEQ ID NO: 43; V_{H2} comprises the amino acid sequence of SEQ ID NO: 49; V_{L2} comprises the amino acid sequence of SEQ ID NO: 57;

(f) V_{H1} comprises the amino acid sequence of SEQ ID NO: 41; V_{L1} comprises the amino acid sequence of SEQ ID NO: 43; V_{H2} comprises the amino acid sequence of SEQ ID NO: 50; V_{L2} comprises the amino acid sequence of SEQ ID NO: 58;

(g) V_{H1} comprises the amino acid sequence of SEQ ID NO: 41; V_{L1} comprises the amino acid sequence of SEQ ID NO: 43; V_{H2} comprises the amino acid sequence of SEQ ID NO: 51; V_{L2} comprises the amino acid sequence of SEQ ID NO: 59;

(h) V_{H1} comprises the amino acid sequence of SEQ ID NO: 41; V_{L1} comprises the amino acid sequence of SEQ ID NO: 43; V_{H2} comprises the amino acid sequence of SEQ ID NO: 52; V_{L2} comprises the amino acid sequence of SEQ ID NO: 60;

(i) V_{H1} comprises the amino acid sequence of SEQ ID NO: 42; V_{L1} comprises the amino acid sequence of SEQ ID NO: 44; V_{H2} comprises the amino acid sequence of SEQ ID NO: 45; V_{L2} comprises the amino acid sequence of SEQ ID NO: 53;

(j) V_{H1} comprises the amino acid sequence of SEQ ID NO: 42; V_{L1} comprises the amino acid sequence of SEQ ID NO: 44; V_{H2} comprises the amino acid sequence of SEQ ID NO: 46; V_{L2} comprises the amino acid sequence of SEQ ID NO: 54;

(k) V_{H1} comprises the amino acid sequence of SEQ ID NO: 42; V_{L1} comprises the amino acid sequence of SEQ ID NO: 44; V_{H2} comprises the amino acid sequence of SEQ ID NO: 47; V_{L2} comprises the amino acid sequence of SEQ ID NO: 55;

(l) V_{H1} comprises the amino acid sequence of SEQ ID NO: 42; V_{L1} comprises the amino acid sequence of SEQ ID NO: 44; V_{H2} comprises the amino acid sequence of SEQ ID NO: 48; V_{L2} comprises the amino acid sequence of SEQ ID NO: 56;

(m) V_{H1} comprises the amino acid sequence of SEQ ID NO: 42; V_{L1} comprises the amino acid sequence of SEQ ID NO: 44; V_{H2} comprises the amino acid sequence of SEQ ID NO: 49; V_{L2} comprises the amino acid sequence of SEQ ID NO: 57;

(n) V_{H1} comprises the amino acid sequence of SEQ ID NO: 42; V_{L1} comprises the amino acid sequence of SEQ ID NO: 44; V_{H2} comprises the amino acid sequence of SEQ ID NO: 50; V_{L2} comprises the amino acid sequence of SEQ ID NO: 58.

(o) V_{H1} comprises the amino acid sequence of SEQ ID NO: 42; V_{L1} comprises the amino acid sequence of SEQ ID NO: 44; V_{H2} comprises the amino acid sequence of SEQ ID NO: 51; V_{L2} comprises the amino acid sequence of SEQ ID NO: 59;

(p) V_{H1} comprises the amino acid sequence of SEQ ID NO: 42; V_{L1} comprises the amino acid sequence of SEQ ID NO: 44; V_{H2} comprises the amino acid sequence of SEQ ID NO: 52; V_{L2} comprises the amino acid sequence of SEQ ID NO: 60.

13. The binding protein according to ~~any one of claims 2 to 12~~claim 2, wherein:

- polypeptide (I) consists of ~~anthe~~anthe amino acid sequence of SEQ ID NO: 64;
- polypeptide (II) consists of ~~anthe~~anthe amino acid sequence of SEQ ID NO: 65; and
- polypeptide (III) consists of ~~anthe~~anthe amino acid sequence of SEQ ID NO: 66.

~~14. The binding protein according to any one of the preceding claims, for use as a medicament.~~

~~15. The binding protein according to any one of the preceding claims, for use in a method for the treatment or prevention of blood cancer.~~

~~16. The binding protein according to any one of the preceding claims, for use in a method for the treatment or prevention of a myelodysplastic syndrome (MDS) or of a lymphoproliferative disorder.~~

~~17. The binding protein according to any one of the preceding claims, for use in a method for the treatment or prevention of Acute Myeloid Leukemia (AML).~~

~~18. The binding protein according to any one of the preceding claims, for use in a method for the treatment or prevention of CD64 positive and CD64 negative Acute Myeloid Leukemia (AML).~~

~~19.~~14. A pharmaceutical composition comprising the binding protein according to ~~any one of claims 1 to 13~~claim 1 and a pharmaceutically acceptable carrier.

~~20. An isolated nucleic acid molecule comprising a nucleotide sequence that encodes the binding protein according to any one of claims 1 to 13.~~

~~21. An expression vector comprising the nucleic acid molecule of claim 20.~~

~~22. An isolated cell comprising the nucleic acid molecule of claim 20.~~

~~23. An isolated cell comprising the expression vector of claim 21.~~

~~24. The isolated cell of claim 23, wherein the host cell is a mammalian cell.~~

~~25. A method for making the binding protein according to any one of claims 1 to 13, comprising a step of:~~

~~(a) culturing host cell(s) under conditions suitable for expressing a plurality of recombinant polypeptides, said plurality comprising (i) a polypeptide comprising an amino acid sequence of SEQ ID NO: 64, and (ii) a polypeptide comprising an amino acid sequence of SEQ ID NO: 65, and (iii) a polypeptide comprising an amino acid sequence of SEQ ID NO: 66;~~

~~(b) optionally recovering the expressed recombinant polypeptides.~~

~~26. A method of treating or preventing a blood cancer, the method comprising administering to a subject in need of said treatment or prevention the pharmaceutical composition of claim 19.~~

~~27. A method of treating or preventing a myelodysplastic syndrome (MDS) or a lymphoproliferative disorder, the method comprising administering to a subject in need of said treatment or prevention the pharmaceutical composition of claim 19.~~

~~28. A method of treating or preventing an Acute Myeloid Leukemia (AML), the method comprising administering to a subject in need of said treatment or prevention the pharmaceutical composition of claim 19.~~

~~29. A method of treating or preventing a CD64 positive and CD64 negative Acute Myeloid Leukemia (AML), the method comprising administering to a subject in need of said treatment or prevention the pharmaceutical composition of claim 19.~~

15. A method of treating or preventing a CD64 positive Acute Myeloid Leukemia (AML), the method comprising administering to a subject in need of said treatment or prevention a binding protein comprising a first and a second antigen binding domain (ABD) and all or part of an immunoglobulin Fc region or variant thereof, wherein each of said ABD comprises an immunoglobulin heavy chain variable domain (VH) and an immunoglobulin light chain variable domain (VL), wherein each VH and VL comprises three complementary determining regions (CDR-1 to CDR-3); and wherein:

(i) the first ABD binds specifically to human CD123, and comprises a V_{H1} comprising the amino acid sequence of SEQ ID NO: 41 and a V_{L1} comprising the amino acid sequence of SEQ ID NO: 43; and

(ii) the second ABD binds specifically to human NKp46, and wherein and comprises a V_{H2} comprising the amino acid sequence of SEQ ID NO: 45 and a V_{L2} comprising the amino acid sequence of SEQ ID NO: 53.

16. The binding protein according to claim 15, wherein the residue N297 of the Fc region or variant thereof according to EU numbering comprises a N-linked glycosylation, wherein the Fc region or variant thereof is a human Fc region or variant thereof of an IgG1, IgG2, IgG3, or IgG4 isotype.

~~30.~~17. The binding protein according to claim 15, wherein the all or part of the immunoglobulin-Fc region or variant thereof binds to a human ~~Fe-γ receptor~~. CD16A (FcγRIII) polypeptide.

18. A pharmaceutical composition comprising the binding protein according to claim 15 and a pharmaceutically acceptable carrier.

19. A binding protein comprising three polypeptide chains (I), (II) and (III) that form a first and a second antigen binding domain (ABD), wherein:
polypeptide (I) consists of the amino acid sequence of SEQ ID NO: 64;
polypeptide (II) consists of the amino acid sequence of SEQ ID NO: 65; and
polypeptide (III) consists of the amino acid sequence of SEQ ID NO: 66.

20. A pharmaceutical composition comprising the binding protein according to claim 19 and a pharmaceutically acceptable carrier.

21. A binding protein comprising three polypeptide chains (I), (II) and (III) that form a first and a second antigen binding domain (ABD), wherein:
polypeptide (I) comprises the amino acid sequence of SEQ ID NO: 64;
polypeptide (II) comprises the amino acid sequence of SEQ ID NO: 65; and
polypeptide (III) comprises the amino acid sequence of SEQ ID NO: 66.

22. A pharmaceutical composition comprising the binding protein according to claim 21 and a pharmaceutically acceptable carrier.