Claims

1. A pharmaceutical composition comprising a CD33 targeting compound and at least one epigenetic factor, wherein
   (a) the CD33 targeting compound is a bispecific single chain antibody construct comprising a first binding domain specifically binding to CD33 and a second binding domain specifically binding to CD3; and
   (b) the at least one epigenetic factor is selected from the group consisting of histone deacetylase (HDAC) ~~inhibitors~~inhibitor panobinostat, DNA methyltransferase (DNMT) I ~~inhibitors~~inhibitor 5-azacitidine, hydroxyurea, and Granulocyte-Colony Stimulating Factor (G-CSF~~), histone methyltransferase (HMT) inhibitors and ATRA (All Trans retinoic acid~~).

2. The pharmaceutical composition of claim 1, wherein the ~~at least one epigenetic factor is selected from the group comprising~~

   ~~(a) a histone deacetylase (HDAC) inhibitor selected from the group consisting of panobinostat, vorinostat, romidepsin, N-acetyldinaline, belinostat, givinostat, entinostat, mocetinostat, EVP-0334, SRT501, CUDC-101, Quisinostat, abexinostat, LAQ824, and valproic acid;~~

   ~~(b) a DNA methyltransferase (DNMT) I inhibitor selected from the group consisting of 5-azacitidine, decitabine, hydralazine, zebularine, procainamide, (−)-epigallocatechin-3-gallate, MG98, RG108, and SGI-110; and~~

   ~~(c) a histone methyltransferase (HMT) inhibitor selected from the group consisting of LSD1 (KDM1A) demethylase inhibitor, and chaetocin.~~

~~3. The pharmaceutical composition of claim 1 or 2, wherein~~

(a) the epigenetic factor is administered prior to the administration of the CD33 targeting compound;

(b) the epigenetic factor is administered subsequent to the administration of the CD33 targeting compound; or

(c) the epigenetic factor and the CD33 targeting compound are administered simultaneously.

4. The pharmaceutical composition of any of claims 1 to 3, wherein a first dose of the epigenetic factor is administered prior to the start of the administration of the CD33 targeting compound.

5. The pharmaceutical composition of claim 4, wherein the administration of the epigenetic factor is continued during the administration of the CD33 targeting compound.

6. The pharmaceutical composition of any of claims 1 to 5, wherein the bispecific construct is a bispecific antibody construct.

7. The pharmaceutical composition of claim 6, wherein the bispecific antibody construct is a bispecific single chain antibody construct.

8. The pharmaceutical composition of claim 6 or 7, wherein the bispecific antibody construct binds to human and cynomolgous CD3 and human and cynomolgous CD33.

~~9~~3. The pharmaceutical composition of ~~any of claims 6 to 8~~claim 2, wherein the bispecific single chain antibody construct comprises

- a first binding domain specifically binding to CD33 and comprising a VL chain having an amino acid sequence ~~as depicted in~~selected from the group consisting of SEQ ID NO: 6, 24, 42, 60, 78, 96, 114 and ~~132and~~132 and a VH chain having an amino acid sequence ~~as depicted in~~selected from the group consisting of SEQ ID NO:1, 19, 37, 55, 73, 91, 109 and127; and
- a second binding domain specifically binding to CD3 and comprising a VL chain having an amino acid sequence ~~as depicted in~~selected from the group consisting SEQ ID NO: 154, 157, 160, 163, 166, 169 and 172 and a VH chain having an amino acid sequence ~~as depicted in~~selected from the group consisting of SEQ ID NO:155, 158, 161, 164, 167, 170 and 173.

~~10~~4. The pharmaceutical composition of claim ~~9~~3, wherein the bispecific single chain antibody construct comprises an amino acid sequence as depicted in any of SEQ ID NOs:13, 15, 17, 31, 33, 35, 49, 51, 53, 67, 69, 71, 85, 87, 89, 103, 105, 107, 121, 123, 125, 139, 141, 143, 148, 150, 152, 215, 217, 219, 221, 223, 225 and 227.

~~11~~

5. The pharmaceutical composition of any ~~of claims 1 to 10~~ preceding claim for use in the treatment of a myeloid leukemia.

~~12~~6. The pharmaceutical composition of claim ~~11~~5, wherein

(a) the epigenetic factor is to be administered prior to the administration of the CD33 targeting compound;

(b) the epigenetic factor is to be administered subsequent to the administration of the CD33 targeting compound; or

(c) the epigenetic factor and the CD33 targeting compound are to be administered simultaneously.

7. The pharmaceutical composition of claim 5 or 6, wherein a first dose of the epigenetic factor is to be administered prior to the start of the administration of the CD33 targeting compound.

8. The pharmaceutical composition of claim 7, wherein the administration of the epigenetic factor is to be continued during the administration of the CD33 targeting compound.

9. The pharmaceutical composition of claim 5, wherein the myeloid leukemia is selected from the group consisting of acute myeloblastic leukemia, chronic neutrophilic leukemia, myeloid dendritic cell leukemia, accelerated phase chronic myelogenous leukemia, acute myelomonocytic leukemia, juvenile myelomonocytic leukemia, chronic myelomonocytic leukemia, acute basophilic leukemia, acute eosinophilic leukemia, chronic eosinophilic leukemia, Acute megakaryoblastic leukemia, essential thrombocytosis, acute erythroid leukemia, polycythemia vera, myelodysplastic syndrome, acute panmyelosis, myeloid sarcoma, and acute biphenotypic leukaemia.

~~13. An~~10. Use of an epigenetic factor in the manufacture of an agent for ~~use in~~ the amelioration and/or treatment of a myeloid leukemia, wherein the epigenetic factor increases the responsiveness of a patient to a CD33 targeting compound, wherein

(a) the CD33 targeting compound is a bispecific single chain antibody construct comprising a first binding domain specifically binding to CD33 and a second binding domain specifically binding to CD3; and

(b) the at least one epigenetic factor is selected from the group consisting of histone deacetylase (HDAC) ~~inhibitors~~inhibitor panobinostat, , DNA methyltransferase (DNMT) I ~~inhibitors~~inhibitor 5-azacitidine, hydroxyurea, and Granulocyte-Colony Stimulating Factor (G-CSF~~), histone methyltransferase (HMT) inhibitors and ATRA (All Trans-retinoic acid).~~).

~~14. The epigenetic factor of claim 13, wherein the epigenetic factor is selected from the group comprising~~

~~(a) a histone deacetylase (HDAC) inhibitor selected from the group consisting of panobinostat, vorinostat, romidepsin, N-acetyldinaline, belinostat, givinostat, entinostat, mocetinostat, EVP-0334, SRT501, CUDC-101, Quisinostat, abexinostat, LAQ824, and valproic acid;~~

(b) a DNA methyltransferase (DNMT) I inhibitor selected from the group consisting of 5-azacitidine, decitabine, hydralazine, zebularine, procainamide, (−)-epigallocatechin-3-gallate, MG98, RG108, and SGI-110; and

(c) a histone methyltransferase (HMT) inhibitor selected from the group consisting of LSD1 (KDM1A) demethylase inhibitor, and chaetocin.

15. The epigenetic factor of claim 13 or 14, wherein

(a) the epigenetic factor is administered prior to the administration of the CD33 targeting compound;

(b) the epigenetic factor is administered subsequent to the administration of the CD33 targeting compound; or

(c) the epigenetic factor and the CD33 targeting compound are administered simultaneously.

16. The epigenetic factor of any of claims 13 to 15, wherein a first dose of the epigenetic factor is administered prior to the start of the administration of the CD33 targeting compound.

17. The epigenetic factor of claim 16, wherein the administration of the epigenetic factor is continued during the administration of the CD33 targeting compound.

18. The epigenetic factor of any of claim 13 to 17, wherein the bispecific construct is a bispecific antibody construct.

19. The epigenetic factor of claim 18, wherein the bispecific antibody construct is a bispecific single chain antibody construct.

20. The epigenetic factor of claim 18 or 19, wherein the bispecific antibody construct binds to human and cynomolgous CD3 and CD33.

21. The epigenetic factor of any of claim 18 to 20, wherein the bispecific antibody construct comprises

- a first binding domain specifically binding to CD33 and comprising a VL chain having an amino acid sequence as depicted in SEQ ID NO: 6, 24, 42, 60, 78, 96, 114 and 132and a VH chain having an amino acid sequence as depicted in SEQ ID NO:1, 19, 37, 55, 73, 91, 109 and127; and
- a second binding domain specifically binding to CD3 and comprising a VL chain having an amino acid sequence as depicted in SEQ ID NO: 154, 157, 160, 163, 166, 169 and 172 and a VH chain having an amino acid sequence as depicted in SEQ ID NO:155, 158, 161, 164, 167, 170 and 173.

22. The epigenetic factor of claim 21, wherein the bispecific antibody construct comprises an amino acid sequence as depicted in any of SEQ ID NOs: 13, 15, 17, 31, 33, 35, 49, 51, 53, 67, 69, 71, 85, 87, 89, 103, 105, 107, 121, 123, 125, 139, 141, 143, 148, 150, 152, 215, 217, 219, 221, 223, 225 and 227.

~~23. The epigenetic factor of any of claims 13 to 22, wherein the myeloid leukemia is selected from the group consisting of acute myeloblastic leukemia, chronic neutrophilic leukemia, myeloid dendritic cell leukemia, accelerated phase chronic myelogenous leukemia, acute myelomonocytic leukemia, juvenile myelomonocytic leukemia, chronic myelomonocytic leukemia, acute basophilic leukemia, acute eosinophilic leukemia, chronic eosinophilic leukemia, Acute megakaryoblastic leukemia, essential thrombocytosis, acute erythroid leukemia, polycythemia vera, myelodysplastic syndrome, acute panmyelosis, myeloid sarcoma, and acute biphenotypic leukaemia.~~

~~24. An use of at least one an epigenetic factor for increasing the responsiveness of a myeloid leukemia patient to a treatment with a CD33 targeting compound, wherein~~

~~(a) the CD33 targeting compound is a bispecific construct comprising a first binding domain specifically binding to CD33 and a second binding domain specifically binding to CD3; and~~

~~(b) the at least one epigenetic factor is selected from the group consisting of histone deacetylase (HDAC) inhibitors, DNA methyltransferase (DNMT) I inhibitors, hydroxyurea, Granulocyte-Colony Stimulating Factor (G-CSF), histone methyltransferase (HMT) inhibitors and ATRA (All Trans-retinoic acid).~~

~~25. The use of claim 24, wherein the at least one epigenetic factor is selected from the group comprising~~

(a) a histone deacetylase (HDAC) inhibitor selected from the group consisting of panobinostat, vorinostat, romidepsin, N-acetyldinaline, belinostat, givinostat, entinostat, mocetinostat, EVP-0334, SRT501, CUDC-101, Quisinostat, abexinostat, LAQ824, and valproic acid;

(b) a DNA methyltransferase (DNMT) I inhibitor selected from the group consisting of 5-azacitidine, decitabine, hydralazine, zebularine, procainamide, (−)-epigallocatechin-3-gallate, MG98, RG108, and SGI-110; and

(c) a histone methyltransferase (HMT) inhibitor selected from the group consisting of LSD1 (KDM1A) demethylase inhibitor, and chaetocin.

26. The use of claim 24 or 25, wherein

(a) the epigenetic factor is administered prior to the administration of the CD33 targeting compound;

(b) the epigenetic factor is administered subsequent to the administration of the CD33 targeting compound; or

(c) the epigenetic factor and the CD33 targeting compound are administered simultaneously.

27. The use of any of claims 24 to 26, wherein a first dose of the epigenetic factor is administered prior to the start of the administration of the CD33 targeting compound.

28. The use of claim 27, wherein the administration of the epigenetic factor is continued during the administration of the CD33 targeting compound.

29. The use of any of claim 24 to 28, wherein the bispecific construct is a bispecific antibody construct.

30. The use of claim 29, wherein the bispecific antibody construct is a bispecific single chain antibody construct.

31. The use of claim 29 or 30, wherein the bispecific antibody construct binds to human and cynomolgous CD3 and CD33.

32. The use of any of claim 29 to 31, wherein the bispecific antibody construct comprises

- a first binding domain specifically binding to CD33 and comprising a VL chain having an amino acid sequence as depicted in SEQ ID NO: 6, 24, 42, 60, 78, 96, 114 and 132and a VH chain having an amino acid sequence as depicted in SEQ ID NO:1, 19, 37, 55, 73, 91, 109 and127; and
- a second binding domain specifically binding to CD3 and comprising a VL chain having an amino acid sequence as depicted in SEQ ID NO: 154, 157, 160, 163, 166, 169 and 172 and a VH chain having an amino acid sequence as depicted in SEQ ID NO:155, 158, 161, 164, 167, 170 and 173.

33. The use of claim 32, wherein the bispecific antibody construct comprises an amino acid sequence as depicted in any of SEQ ID NOs: 13, 15, 17, 31, 33, 35, 49, 51, 53, 67, 69, 71, 85, 87, 89, 103, 105, 107, 121, 123, 125, 139, 141, 143, 148, 150, 152, 215, 217, 219, 221, 223, 225 and 227.

34. The use of any of claims 24 to 33, wherein the myeloid leukemia is selected from the group consisting of acute myeloblastic leukemia, chronic neutrophilic leukemia, myeloid dendritic cell leukemia, accelerated phase chronic myelogenous leukemia, acute myelomonocytic leukemia, juvenile myelomonocytic leukemia, chronic myelomonocytic leukemia, acute basophilic leukemia, acute eosinophilic leukemia, chronic eosinophilic leukemia, Acute megakaryoblastic leukemia, essential thrombocytosis, acute erythroid leukemia, polycythemia vera, myelodysplastic syndrome, acute panmyelosis, myeloid sarcoma, and acute biphenotypic leukaemia.

35. A method for the treatment of a myeloid leukemia, the method comprising the administration of at least one epigenetic factor and a CD33 targeting compound to a patient in the need thereof, wherein

(a) the CD33 targeting compound is a bispecific construct comprising a first binding domain specifically binding to CD33 and a second binding domain specifically binding to CD3; and

(b) the at least one epigenetic factor is selected from the group consisting of histone deacetylase (HDAC) inhibitors, DNA methyltransferase (DNMT) I inhibitors, hydroxyurea, Granulocyte-Colony Stimulating Factor

(G-CSF), histone methyltransferase (HMT) inhibitors and ATRA (All-Trans-retinoic acid).

36. The method of claim 35, wherein the at least one epigenetic factor is selected from the group comprising

(a) a histone deacetylase (HDAC) inhibitor selected from the group consisting of panobinostat, vorinostat, romidepsin, N-acetyldinaline, belinostat, givinostat, entinostat, mocetinostat, EVP-0334, SRT501, CUDC-101, Quisinostat, abexinostat, LAQ824, and valproic acid;

(b) a DNA methyltransferase (DNMT) I inhibitor selected from the group consisting of 5-azacitidine, decitabine, hydralazine, zebularine, procainamide, (−)-epigallocatechin-3-gallate, MG98, RG108, and SGI-110; and

(c) a histone methyltransferase (HMT) inhibitor selected from the group consisting of LSD1 (KDM1A) demethylase inhibitor, and chaetocin.

37. The method of claim 35 or 36, wherein

(a) the epigenetic factor is administered prior to the administration of the CD33 targeting compound;

(b) the epigenetic factor is administered subsequent to the administration of the CD33 targeting compound; or

(c) the epigenetic factor and the CD33 targeting compound are administered simultaneously.

38. The method of any of claims 35 to 37, wherein a first dose of the epigenetic factor is administered prior to the start of the administration of the CD33 targeting compound.

39. The method of claim 38, wherein the administration of the epigenetic factor is continued during the administration of the CD33 targeting compound.

40. The method of any of any of claims 35 to 39, wherein the bispecific construct is a bispecific antibody construct.

41. The method of claim 40, wherein the bispecific antibody construct is a bispecific single chain antibody construct.

42. The method of claim 40 or 41, wherein the bispecific antibody construct binds to human and cynomolgous CD3 and CD33.

43. The method of any of any of claims 40 to 42, wherein the bispecific antibody construct comprises

- a first binding domain specifically binding to CD33 and comprising a VL chain having an amino acid sequence as depicted in SEQ ID NO: 6, 24, 42, 60, 78, 96, 114 and 132and a VH chain having an amino acid sequence as depicted in SEQ ID NO:1, 19, 37, 55, 73, 91, 109 and127; and
- a second binding domain specifically binding to CD3 and comprising a VL chain having an amino acid sequence as depicted in SEQ ID NO: 154, 157, 160,

~~163, 166, 169 and 172 and a VH chain having an amino acid sequence as depicted in SEQ ID NO:155, 158, 161, 164, 167, 170 and 173.~~

~~44. The method of claim 43, wherein the bispecific antibody construct comprises an amino acid sequence as depicted in any of SEQ ID NOs: 13, 15, 17, 31, 33, 35, 49, 51, 53, 67, 69, 71, 85, 87, 89, 103, 105, 107, 121, 123, 125, 139, 141, 143, 148, 150, 152, 215, 217, 219, 221, 223, 225 and 227.~~

~~45. The method of any of claims 35 to 44, wherein the myeloid leukemia is selected from the group consisting of acute myeloblastic leukemia, chronic neutrophilic leukemia, myeloid dendritic cell leukemia, accelerated phase chronic myelogenous leukemia, acute myelomonocytic leukemia, juvenile myelomonocytic leukemia, chronic myelomonocytic leukemia, acute basophilic leukemia, acute eosinophilic leukemia, chronic eosinophilic leukemia, Acute megakaryoblastic leukemia, essential thrombocytosis, acute erythroid leukemia, polycythemia vera, myelodysplastic syndrome, acute panmyelosis, myeloid sarcoma, and acute biphenotypic leukaemia.~~

~~46~~11. A kit comprising a pharmaceutical composition of any of claims 1 to ~~12~~9 or an epigenetic factor ~~of any of claims 13 to 23~~defined in claim 10 and a bispecific CD33 targeting compound comprising a first binding domain specifically binding to CD33 and a second binding domain specifically binding to CD3, to be employed in the amelioration and/or treatment of a myeloid leukemia.