WHAT IS CLAIMED IS:

1. A method of identifying a subject having acute myeloid leukemia (AML) who is likely to be responsive to a treatment comprising a compound or predicting the responsiveness of a subject having or suspected of having AML to a treatment comprising the compound, comprising:

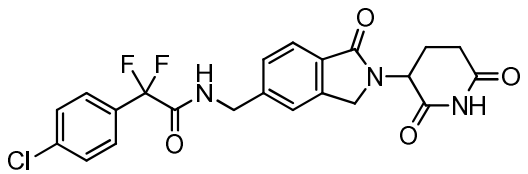
i. providing a sample from the subject;

ii. measuring gene expression level of one or more genes in the sample;

iii. calculating a leukemic stem cell (LSC) signature score for the sample based on the gene expression level of the one or more genes; and

iv. identifying the subject as being likely to be responsive to the treatment comprising the compound if the level of the LSC signature score is higher than a reference level thereof,

wherein the compound is 2-(4-chlorophenyl)-N-((2-(2,6-dioxopiperidin-3-yl)-1-oxoisoindolin-5-yl)methyl)-2,2-difluoroacetamide (Compound D), which has the following structure:



or a stereoisomer or mixture of stereoisomers, isotopologue, pharmaceutically acceptable salt, tautomer, solvate, hydrate, co-crystal, clathrate, or polymorph thereof.

2. Use of a compound in the manufacture of a medicament for treating a subject having AML, wherein:

(a) the subject having AML that may be responsive to the treatment comprising the compound is to be identified, wherein:

i. a sample from the subject is to be provided;

ii. gene expression level of one or more genes in the sample is to be measured;

iii. a leukemic stem cell (LSC) signature score for the sample based on the gene expression level of the one or more genes is to be calculated; and

iv. the subject as being likely to be responsive to the treatment comprising the compound is to be identified if the level of the LSC signature score is higher than a reference level thereof, and

(b) a therapeutically effective amount of the compound is to be administered to the subject if the subject is identified as being likely to be responsive to the treatment comprising the compound,

wherein the compound is Compound D, or a stereoisomer or mixture of stereoisomers, isotopologue, pharmaceutically acceptable salt, tautomer, solvate, hydrate, co-crystal, clathrate, or polymorph thereof.

3. The method of claim 1 or use of claim 2, wherein the LSC signature score is calculated as the weighted sum of the expression level of the one or more genes.

4. The method or use of any one of claims 1 to 3, wherein the reference level is the median LSC signature score in a population.

5. The method or use of any one of claims 1 to 3, wherein the reference level is a pre-determined LSC signature score level.

6. The method or use of any one of claims 1 to 5, wherein the LSC signature score that is higher than the reference level thereof suggests that the subject has resistant and/or refractory AML.

7. The method or use of any one of claims 1 to 6, wherein the one or more genes are selected from the group consisting of

(a) CD34, SPINK2, LAPTM48, HOXA5, GUCY1A3, SHANK3, ANGPT1, ARHGAP22, LOC284422, MYCN, MAMDC2, PRSSL1, KIAA0125, GPSM1, HOXA9, MMRN1, FSCN1, DNMT38, HOXA6, AIF1L, SOCS2, CDK6, FAM69B, NGFRAP1, C3orf54, CPXM1, TNFRSF4, ZBTB46, DPYSL3, NYNRIN, COL24A1, FAM30A, C10orf140, SPNS2, GPR56, AKR1C3, FLT3, TFPI, KCNK17, EPDR1, C1orf150, BIVM, H2AFY2, VWF, EMP1, RAGE, ATP8B4, GATA2, SLC25A37, SGK, LOC652694, ITPR3, LOC654103, CXCR4,

FCRL3, RBM38, LILRA5, IL18RAP, CCDC109B, ISG20, MTSS1, CECR1, ADAM19, FCGR2A, AIM2, NPL, IL10RA, CTSL1, GNLY, CKAP4, ADM, KLRB1, SLC15A3, FGR, FCRLA, IL2RB, CXCL16, SLC4A1, GZMH, FLJ22662, LOC647506, GIMAP4, JAZF1, CTSH, GZMA, CHST15, AQP9, CD247, BCL6, SLC7A7, E2F2, LOC647450, GZMB, LOC652493, HBM, CD14, ALAS2, HBB, LOC642113, AHSP, FCN1, CD48, HBA2, and HBA1, or

(b) CD34, SPINK2, LAPTM48, HOXA5, GUCY1A3, SHANK3, ANGPT1, ARHGAP22, LOC284422, MYCN, MAMDC2, PRSSL1, KIAA0125, GPSM1, HOXA9, MMRN1, FSCN1, DNMT38, HOXA6, AIF1L, SOCS2, CDK6, FAM69B, NGFRAP1, C3orf54, CPXM1, TNFRSF4, ZBTB46, DPYSL3, NYNRIN, COL24A1, FAM30A, C10orf140, SPNS2, GPR56, AKR1C3, FLT3, TFPI, KCNK17, EPDR1, C1orf150, BIVM, H2AFY2, VWF, EMP1, RAGE, ATP8B4, and GATA2.

8. The method or use of any one of claims 1 to 6, wherein the one or more genes are selected from the group consisting of AKR1C3, ARHGAP22, CD34, CDK6, CPXM1, DNMT3B, DPYSL3, EMP1, GPR56, KIAA0125, LAPTM4B, MMRN1, NGFRAP1, NYNRIN, SMIM24, SOCS2, and ZBTB46.

9. The method or use of any one of claims 1 to 6, wherein the LSC signature score is based on the gene expression levels of AKR1C3, ARHGAP22, CD34, CDK6, CPXM1, DNMT3B, DPYSL3, EMP1, GPR56, KIAA0125, LAPTM4B, MMRN1, NGFRAP1, NYNRIN, SMIM24, SOCS2, and ZBTB46.

10. The method or use of any one of claims 1 to 6, wherein the LSC signature score is calculated as follows: (expression level of DNMT3B × weight of DNMTT3B) + (expression level of ZBTB46 × weight of ZBTB46) + (expression level of NYNRIN × weight of NYNRIN) + (expression level of ARHGAP22 × weight of ARHGAP22) + (expression level of LAPTM4B × weight of LAPTM4B) + (expression level of MMRN1 × weight of MMRN1) + (expression level of DPYSL3 × weight of DPYSL3) + (expression level of KIAA0125 × weight of KIAA0125) + (expression level of CDK6 × weight of CDK6) + (expression level of CPXM1 × weight of CPXM1) + (expression level of SOCS2 × weight of SOCS2) + (expression level of

SMIM24 × weight of SMIM24) + (expression level of EMP1 × weight of EMP1) + (expression level of NGFRAP1 × weight of NGFRAP1) + (expression level of CD34 × weight of CD34) + (expression level of AKR1C3 × weight of AKR1C3) + (expression level of GPR56 × weight of GPR56); and

wherein the weight of DNMTT3B is in a range from 0.08 to 0.09, the weight of ZBTB46 is in a range from − 0.03 to − 0.04, the weight of NYNRIN is in a range from − 0.008 to 0.009, the weight of ARHGAP22 is in a range from -0.015 to 0.01, the weight of LAPTM4B is in a range from -0.006 to 0.005, the weight of MMRN1 is in a range from 0.02 to 0.03, the weight of DPYSL3 is in a range from 0.02 to 0.03, the weight of KIAA0125 is in a range from 0.01 to 0.02, the weight of CDK6 is in a range from − 0.08 to – 0.07, the weight of CPXM1 is in a range from – 0.02 to – 0.03, the weight of SOCS2 is in a range from 0.02 to 0.03, the weight of SMIM24 is in a range from – 0.02 to – 0.03, the weight of EMP1 is in a range from 0.014 to 0.02, the weight of NGFRAP1 is in a range from 0.04 to 0.05, the weight of CD34 is in a range from 0.03 to 0.04, the weight of AKR1C3 is in a range from – 0.04 to – 0.05, and the weight of GPR56 is in a range from 0.04 to 0.055.

11. The method or use of any one of claims 1 to 6, wherein the LSC signature score is calculated as follows: (expression level of DNMT3B × 0.0874) + (expression level of ZBTB46 × − 0.0347) + (expression level of NYNRIN × 0.00865) + (expression level of ARHGAP22 × − 0.0138) + (expression level of LAPTM4B × 0.00582) + (expression level of MMRN1 × 0.0258) + (expression level of DPYSL3 × 0.0284) + (expression level of KIAA0125 × 0.0196) + (expression level of CDK6 × − 0.0704) + (expression level of CPXM1 × − 0.0258) + (expression level of SOCS2 × 0.0271) + (expression level of SMIM24 × − 0.0226) + (expression level of EMP1 × 0.0146) + (expression level of NGFRAP1 × 0.0465) + (expression level of CD34 × 0.0338) + (expression level of AKR1C3 × − 0.0402) + (expression level of GPR56 × 0.0501).

12. The method or use of claim 11, wherein the reference level is 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8. 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, or 2.

13. The method or use of any one of claims 1 to 6, wherein the LSC signature score is based on the gene expression levels of TNFRSF4, SLC4A1, SLC7A7, and AIM2.

14. The method or use of claim 13, wherein the LSC signature score is calculated as follows: (expression level of TNFRSF4 × weight of TNFRSF4) + (expression level of SLC4A1 × weight of SLC4A1) + (expression level of SLC7A7 × weight of SLC7A7) + (expression level of AIM2 × weight of AIM2); and wherein the weight of TNFRSF4 is in a range from – 1.5 to -1, the weight of SLC4A1 is in a range from 13 to 14, the weight of SLC7A7 is in a range from – 4 to – 3, the weight of AIM2 is in a range from − 3 to −4.

15. The method or use of claim 13, wherein the LSC signature score is calculated as follows: (expression level of TNFRSF4 × − 1.13) + (expression level of SLC4A1 × 13.59) + (expression level of SLC7A7 × − 3.57) + (expression level of AIM2 × − 3.04).

16. The method or use of claim 15, wherein the reference level is in a range from − 50 to 115, from − 45 to 110, from – 40 to 105, from – 37 to 100, from – 30 to 95, from – 25 to 90, from – 20 to 85, from – 15 to 80, from – 10 to 75, from – 5 to 70, from 0 to 65, from 5 to 60, from 10 to 55, from 15 to 50, from 20 to 45, from 25 to 40, or from 30 to 35.

17. The method or use of any one of claims 1 to 6, wherein the LSC signature score is based on the gene expression levels of SLC4A1, SLC7A7, and AIM2.

18. The method or use of claim 17, wherein the LSC signature score is calculated as follows: (expression level of SLC4A1 × weight of SLC4A1) + (expression level of SLC7A7 × weight of SLC7A7) + (expression level of AIM2 × weight of AIM2); and wherein the weight of SLC4A1 is in a range from 11 to 15, the weight of SLC7A7 is in a range from – 5.5 to – 1.5, the weight of AIM2 is in a range from − 5 to − 1.

19. The method or use of claim17, wherein the LSC signature score is calculated as follows: is calculated as follows: (expression level of SLC4A1 × 13.59) + (expression level of SLC7A7 × − 3.57) + (expression level of AIM2 × − 3.04).

20. The method or use of claim 19, wherein the reference level is in a range from − 65 to 110, from − 60 to 105, from – 55 to 100, from – 49 to 93, from – 45 to 90, from – 40 to 85, from – 35 to 80, from – 30 to 75, from – 25 to 70, from – 20 to 65, from – 15 to 60, from – 10 to 55, from – 5 to 50, from 0 to 45, from 5 to 40, from 10 to 35, from 15 to 30, from 20 to 35, or from 25 to 30.

21. A method of identifying a subject having AML who is likely to be responsive to a treatment comprising a compound or predicting the responsiveness of a subject having or suspected of having AML to a treatment comprising the compound, comprising:

i. providing a sample from the subject;

ii. administering the compound to the sample;

iii. measuring the proportion of one or more types of cells;

iv. identifying the subject as being likely to be responsive to the treatment comprising the compound if the proportion of the one or more types of cells differentiates from a reference proportion of the cells,

wherein the compound is Compound D, or a stereoisomer or mixture of stereoisomers, isotopologue, pharmaceutically acceptable salt, tautomer, solvate, hydrate, co-crystal, clathrate, or polymorph thereof.

22. Use of a compound in the manufacture of a medicament for treating a subject having AML, wherein:

(a) the subject having AML that may be responsive to the treatment comprising the compound is to be identified, wherein:

i. a sample from the subject is to be provided;

ii. the compound is to be administered to the sample;

iii. the proportion of one or more types of cells is to be measured;

iv. the subject as being likely to be responsive to the treatment comprising the compound is to be identified if the proportion of the one or more types of cells differentiates from a reference proportion of the cells, and

(b) a therapeutically effective amount of the compound is to be administered to the subject if the subject is identified as being likely to be responsive to the treatment comprising the compound,

wherein the compound is Compound D, or a stereoisomer or mixture of stereoisomers, isotopologue, pharmaceutically acceptable salt, tautomer, solvate, hydrate, co-crystal, clathrate, or polymorph thereof.

23. The method of claim 21 or the use of claim 22, wherein the reference proportion of a type of cells is the proportion of the type of cells in the sample prior to the administration of the compound.

24. The method of claim 21 or the use of claim 22, wherein the reference proportion of a type of cells is a pre-determined proportion.

25. The method or use of any one of claims 21 to 24, wherein the proportion of primitive cells and/or the proportion differentiated leukemia cells is to be measured.

26. The method or use of claim 25, wherein a reduction of the proportion of primitive cells and/or an increase of the proportion of differentiated leukemia cells as compared to their respective proportions prior to the administration of the compound indicates that the subject is likely to be responsive to the treatment comprising the compound.

27. The method or use of any one of claims 21 to 26, wherein the proportion of CD34+, CD15+ cells, CD14+ cells, and/or CD11b+ cells is to be measured.

28. The method or use of any one of claims 21 to 27, wherein the proportion of CD34+ cells is to be measured, and wherein a reduction of the proportion of CD34+ cells as compared to the proportion of CD34+ cells prior to the administration of the compound indicates the subject is likely to be responsive to the treatment comprising the compound.

29. The method or use of any one of claims 21 to 27, wherein the proportion of CD15+ cells and/or CD14+ cells is to be measured, and wherein an increase of the proportion of CD15+ cells and/or CD14+ cells as compared to the proportion of CD15+ cells and/or CD14+ cells prior to the administration of the compound indicates the subject is likely to be responsive to the treatment comprising the compound.

30. The method or use of any one of claims 1 to 29, wherein the AML is refractory or resistant.

31. The method or use of any one of claims 1 to 29, wherein the AML is resistant to treatment using one or more agents selected from the group consisting of daunorubicin, cytarabine (ara-C), and gemtuzumab ozogamicin, or resistant to chemotherapies.