

WHAT IS CLAIMED IS:

- Claim 1. A method of determining whether a patient would be a suitable responder to the use of a **CD123 x CD3** bispecific molecule to treat a hematologic malignancy, wherein said method comprises:
- (a) evaluating the expression of one or more target genes in a cellular sample from said patient prior to the administration of said **CD123 x CD3** bispecific molecule, relative to the expression of one or more target and/or reference genes; and
 - (b) identifying the patient as a suitable responder for treatment with a **CD123 x CD3** bispecific molecule if the expression of said one or more target genes is found to be increased relative to said expression of said one or more target and/or reference genes, wherein said one or more target genes are selected from the group consisting of: SERPHINH1, NOTCH2, FCGR3A/B, FPR1, FBP1, PDGFA, CRABP2, THBS1, ICOS and CD8B.
- Claim 2. The method of claim 1, wherein said method evaluates:
- (i) the expression of one or more target genes; and
 - (ii) one or more reference genes whose expression is not characteristically associated with said hematologic malignancy.
- Claim 3. The method of any one of claims 1-2, wherein said method comprises evaluating the expression of said one or more target genes relative to the baseline expression of said one or more reference genes of said patient.
- Claim 4. The method of any one of claims 1-3, wherein said method comprises evaluating the expression of said one or more target genes of said patient relative to the expression of said one or more target genes of:
- (a) an individual who is suffering from said hematologic malignancy, or of a population of such individuals; or
 - (b) an individual who did not successfully respond to the use of a **CD123 x CD3** bispecific molecule to treat said hematologic malignancy, or of a population of such individuals; or

- (c) an individual who successfully responded to the use of a **CD123 x CD3** bispecific molecule to treat said hematologic malignancy, or of a population of such individuals.

Claim 5. The method of any one of claims 1-4, wherein the relative expression level of said one or more target genes in said population is established by averaging the gene expression level in cellular samples obtained from said population of individuals.

Claim 6. The method of any one of claims 1-5, wherein said patient exhibits an expression level of at least one of said target genes:

- (a) that is greater than the first quartile of the expression levels of said target gene in a population of individuals who are suffering from said hematologic malignancy; or
- (b) that is greater than the first quartile of the expression levels of said target gene in a population of individuals who did not successfully respond to a treatment for said hematologic malignancy that used a **CD123 x CD3** bispecific molecule; or
- (c) that is within at least the first quartile of the expression levels of said target gene in a population of individuals who successfully responded to a treatment for said hematologic malignancy that used a **CD123 x CD3** bispecific molecule.

Claim 7. The method of any one of claims 1-6, wherein said method further comprises administering a treatment dosage of said **CD123 x CD3** bispecific molecule to said patient if said patient is determined to be a suitable responder to such treatment, and wherein said administration of said **CD123 x CD3** bispecific molecule stimulates the killing of cells of said hematologic malignancy in said patient.

- Claim 8. A method of treating a hematologic malignancy, wherein said method comprises:
- (a) employing the method of any one of claims 1-6 to determine whether a patient would be a suitable responder to the use of a **CD123 x CD3** bispecific molecule to treat said hematologic malignancy;
 - (b) administering a treatment dosage of said **CD123 x CD3** bispecific molecule to said patient if said patient is determined to be a suitable responder to such treatment;
- wherein said administration of said **CD123 x CD3** bispecific molecule stimulates the killing of cells of said hematologic malignancy in said patient.
- Claim 9. The method of any one of claims 1-8, wherein said cellular sample is a bone marrow sample.
- Claim 10. The method of any one of claims 1-9, wherein said evaluation of expression or said determination of whether said patient would be a suitable responder to the use of a **CD123 x CD3** bispecific molecule to treat a hematologic malignancy is performed by:
- (a) determining the gene expression levels for each target gene in one or more cellular sample(s) using a gene expression platform; and
 - (b) comparing said target gene expression levels to the expression levels of one or more reference genes.
- Claim 11. The method of any one of claims 1-10, wherein said evaluation of expression or said determination of whether said patient would be a suitable responder to the use of a **CD123 x CD3** bispecific molecule to treat a hematologic malignancy is performed by:
- (a) measuring the raw RNA levels in for each target gene in one more cellular sample using a gene expression platform, wherein

the gene expression platform comprises a reference gene set of housekeeping genes, and

- (b) assigning a relative expression value, for each of the measured raw RNA levels for the target genes using the measured RNA levels of the internal reference genes.

Claim 12. The method of any one of claims 1-11, wherein said one or more reference genes comprise one or more of: ABCF1, G6PD, NRDE2, OAZ1, POLR2A, SDHA, STK11IP, TBC1D10B, TBP, and UBB.

Claim 13. The method of any one of claims 1-12, wherein a gene signature score is determined for said one or more target genes.

Claim 14. The method of claim 13, wherein said gene signature score is determined by a process comprising:

- (a) measuring the raw RNA levels for each target gene in one more cellular sample using a gene expression platform comprising a reference gene set of housekeeping genes,
- (b) normalizing each of the measured raw RNA levels to the geometric mean of said housekeeping genes, and optionally further normalizing each RNA value to a standard,
- (c) log transforming each normalized RNA value,
- (d) summing the log transformed RNA values for each target gene in the signature, and
- (e) dividing the sum of the normalized log transformed RNA values by the number of target genes in the signature, to generate a gene signature score.

Claim 15. The method of any one of claims 13-14, wherein a patient gene signature score that:

- (a) is greater than the first quartile of scores for said gene signature calculated from the expression levels of one or more of said target genes in a population of individuals who are suffering from said hematologic malignancy; or

- (b) is greater than the first quartile of scores for said gene signature calculated from the expression levels of one or more of said target genes in a population of individuals who did not successfully respond to a treatment for said hematologic malignancy that used a **CD123 x CD3** bispecific molecule; or
- (c) is within at least the first quartile of the scores for said gene signature calculated from the expression levels of one or more of said target genes in a population of individuals who successfully responded to a treatment for said hematologic malignancy that used a **CD123 x CD3** bispecific molecule,

is indicative of a more favorable patient response to treatment with said **CD123 x CD3** bispecific molecule.

Claim 16. The method of any one of claims 1-15, wherein said **CD123 x CD3** bispecific molecule is a bispecific antibody or bispecific molecule comprising an scFv.

Claim 17. The method of claim 16, wherein said **CD123 x CD3** bispecific molecule is JNJ-63709178, XmAb14045 or APVO436.

Claim 18. The method of any one of claims 1-15, wherein said **CD123 x CD3** bispecific molecule is a covalently bonded bispecific diabody having two, three, or four polypeptide chains.

Claim 19. The method of claim 18, wherein said diabody comprises:

- (a) a first polypeptide chain having the amino acid sequence of **SEQ ID NO:21**; and
- (b) a second polypeptide chain having the amino acid sequence of **SEQ ID NO:23**; and

wherein the first and said second polypeptide chains are covalently bonded to one another by a disulfide bond.

- Claim 20. The method of any one of claims 1-19, wherein said hematologic malignancy of said patient is selected from the group consisting of: acute myeloid leukemia (AML), chronic myelogenous leukemia (CML), blastic crisis of CML, Abelson oncogene-associated with CML (Bcr-ABL translocation), myelodysplastic syndrome (MDS), acute B lymphoblastic leukemia (B-ALL), acute T lymphoblastic leukemia (T-ALL), chronic lymphocytic leukemia (CLL), Richter's syndrome, Richter's transformation of CLL, hairy cell leukemia (HCL), blastic plasmacytoid dendritic cell neoplasm (BPDCN), non-Hodgkin's lymphoma (NHL), including mantle cell lymphoma (MCL) and small lymphocytic lymphoma (SLL), Hodgkin's lymphoma, systemic mastocytosis, and Burkitt's lymphoma.
- Claim 21. The method of claim 21, wherein said hematologic malignancy of said patient is AML.
- Claim 22. The method of any one of claims 1-21, wherein said hematologic malignancy of said patient is refractory to chemotherapy.
- Claim 23. The method of any one of claims 1-22, wherein said treatment dosage of said **CD123 x CD3** bispecific molecule includes at least one dose selected from the group consisting of about 30, about 60, about 100, about 200, about 300, about 400 and about 500ng/kg patient weight/day.
- Claim 24. The method of any one of claims 1-23, wherein said treatment dosage is administered by continuous infusion.
- Claim 25. The method of any one of claims 1-24, wherein said patient is a human patient.