the tumor cell, but leads to effective tumor killing (see *e.g.*, Cao *et al.* (2003) *"Bispecific Antibody Conjugates In Therapeutics,"* Adv. Drug. Deliv. Rev. 55:171-197).

[0015] Several bispecific molecules targeting CD123 and CD3 capable of mediating T cell redirected cell killing of CD123-expressing malignant cells are in development (see, *e.g.*, Vey, N., *et al.* (2017) "*Interim Results From A Phase 1 First-In-Human Study Of Flotetuzumab, a CD123 x CD3 Bispecific DART Molecule In AML/MDS*," Annals of Oncology, 28(S5)5, mdx373.001; Godwin, C.D., *et al.* (2017) "*Bispecific Anti-CD123 x Anti-CD3 Adaptir™ Molecules APVO436 and APVO437 Have Broad Activity Against Primary Human AML Cells In Vitro*" Blood. 130(S1): 2639; Forslund, A., *et al.* (2016) "*Ex Vivo Activity Profile of the CD123xCD3 Duobody® Antibody JNJ-63709178 Against Primary Acute Myeloid Leukemia Bone Marrow Samples*" Blood 128(22):2875.). However, efforts to employ bispecific binding molecules that are capable of targeting a T cell to the location of a hematologic malignancy have not been fully successful. Hence, an unmet need remains to develop new strategies for the treatment of hematologic malignancies with **CD123 x CD3** bispecific binding molecules. The present invention directly addresses this need and others, as described below.

SUMMARY ~~OF THE INVENTION~~:

[0016] The present ~~invention~~ disclosure is directed to a method of treating a hematologic malignancy such as acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS), including hematologic malignancies that are refractive to chemotherapeutic and/or hypomethylating agents. The method concerns administering a **CD123 x CD3** bispecific binding molecule to a patient in an amount effective to stimulate the killing of cells of the hematologic malignancy in the patient. The present disclosure~~invention~~ is particularly directed to the ~~embodiment~~ example of such method in which a cellular sample from the patient prior to such administration evidences an expression of one or more target genes that is increased relative to a baseline level of expression of such genes, for example, a baseline level of expression of such genes in a reference population of individuals who are suffering from the hematologic malignancy, or with respect to the level of expression of a reference gene.

[0017] In detail, the disclosure~~invention~~ provides 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 the method comprises:

(a) evaluating the expression of one or more target genes in a cellular sample from the patient prior to the administration of the **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 the one or more target genes is found to be increased relative to the expression of the 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.

[0018] The ~~invention~~disclosure further provides the example~~embodiment~~ of such methods wherein the method evaluates: (i) the expression of one or more target gene; and (ii) one or more reference gene whose expression is not characteristically associated with the hematologic malignancy.

[0019] The ~~invention~~disclosure further provides the example~~embodiment~~ of such methods that comprises evaluating the expression of the one or more target genes relative to the baseline expression of the one or more reference genes of the patient.

[0020] The ~~invention~~disclosure further provides the example~~embodiment~~ of such methods that comprises evaluating the expression of the one or more target genes of a patient relative to the expression of the one or more target genes of an individual who is suffering from the hematologic malignancy or of a population of such individuals. The ~~invention~~disclosure further provides the example~~embodiment~~ of such methods wherein the expression of the one or more target genes of such patient is greater than the first quartile (*i.e.*, greater than the bottom 25%), greater than the second quartile (*i.e.*, greater than the bottom 50%), or greater than the third quartile (*i.e.*, greater than the bottom 75%) of the expression levels of such target gene(s) of such individual or of such population of individuals who are suffering from the hematologic malignancy.

[0021] The ~~invention~~disclosure further provides the example~~embodiment~~ of such methods that comprises evaluating the expression of the one or more target genes of a patient relative to the expression of the one or more target genes of an individual who had previously been unsuccessfully treated for a hematologic malignancy using the methods and compositions of the present ~~invention~~disclosure (*e.g.*, an individual who did not successfully respond to a treatment for a hematologic malignancy using a **CD123 x CD3** bispecific molecule), or a population of such individuals. The ~~invention~~disclosure further provides the example~~embodiment~~ of such methods wherein the expression of the one or more target genes of such patient is greater than the first quartile (*i.e.*, greater than the bottom 25%), greater than the second quartile (*i.e.*, greater than the bottom 50%), or greater than the third quartile (*i.e.*, greater than the bottom 75%) of the expression levels of such target gene(s) of such individual or of such population of unsuccessfully treated individuals.

[0022] The ~~invention~~disclosure further provides the example~~embodiment~~ of such methods that comprises evaluating the expression of the one or more target genes of a patient relative to the expression of the one or more target genes of an individual who had previously been successfully treated for a hematologic malignancy using the methods and compositions of the present ~~invention~~disclosure (*e.g.*, an individual who successfully responded to a treatment for a hematologic malignancy using a **CD123 x CD3** bispecific molecule) or a population of such individuals. The ~~invention~~disclosure further provides the example~~embodiment~~ of such methods wherein the expression of the one or more target genes of such patient is within the first quartile (*i.e.*, within the bottom 25%) of the expression levels of such target gene(s), within the second quartile (*i.e.*, between the bottom 25% and 50%), or within the third quartile (*i.e.*, between the bottom 50% and 75%) of the expression levels of such target gene(s) of such individual or such population of successfully treated individuals.

[0023] The ~~invention~~disclosure further provides the example~~embodiment~~ of such methods wherein the relative expression level of the one or more target genes in the population is established by averaging the gene expression level in cellular samples obtained from the population of individuals.

[0024] The ~~invention~~disclosure further provides the example~~embodiment~~ of such methods wherein such patient exhibits an expression level of at least one of such target genes:

(a) that is greater than the first quartile of the expression levels of such target gene in a population of individuals who are suffering from the hematologic malignancy; or

(b) that is greater than the first quartile of the expression levels of such target gene in a population of individuals who did not successfully respond to a treatment for the 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 such target gene in a population of individuals who successfully responded to a treatment for a hematologic malignancy that used a **CD123 x CD3** bispecific molecule.

[0025] The ~~invention~~disclosure further provides the example~~embodiment~~ of such methods wherein such patient exhibits an expression level of at least one of such target genes:

(a) that is greater than the second quartile of the expression levels of such target gene in a population of individuals who are suffering from the hematologic malignancy; or

(b) that is greater than the second quartile of the expression levels of such target gene in a population of individuals who did not successfully respond to a treatment for the hematologic malignancy that used a **CD123 x CD3** bispecific molecule; or

(c) that is within at least the second quartile of the expression levels of such target gene in a population of individuals who successfully responded to a treatment for the hematologic malignancy that used a **CD123 x CD3** bispecific molecule.

[0026] The ~~invention~~disclosure further provides the example~~embodiment~~ of such methods wherein such patient exhibits an expression level of at least one of such target genes:

(a) that is greater than the third quartile of the expression levels of such target gene in a population of individuals who are suffering from said hematologic malignancy; or

(b) that is greater than the third quartile of the expression levels of such 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; The ~~invention~~disclosure further provides the example~~embodiment~~ of such methods wherein such method further comprises administering a treatment dosage of the **CD123 x CD3** bispecific molecule to the patient if the patient is determined to be a suitable responder to such treatment, and to such methods wherein the administration of the **CD123 x CD3** bispecific molecule stimulates the killing of cells of the hematologic malignancy in the patient.

[0027] The ~~invention~~disclosure further provides a method of treating a hematologic malignancy, wherein the method comprises:

(a) employing the method of any one of the above example~~embodiment~~s to determine whether a patient would be a suitable responder to the use of a **CD123 x CD3** bispecific molecule to treat the hematologic malignancy;

(b) administering a treatment dosage of the **CD123 x CD3** bispecific molecule to the patient if the patient is determined to be a suitable responder to such treatment;

wherein the administration of the **CD123 x CD3** bispecific molecule stimulates the killing of cells of the hematologic malignancy in the patient.

[0027a] In one aspect, the present disclosure refers to use of a **CD123 x CD3** bispecific molecule in the manufacture of a medicament for treating a hematologic malignancy, wherein a treatment dosage of said **CD123 x CD3** bispecific molecule is to be administered to a patient who has been determined to be a suitable responder to such treatment, wherein said determination of suitability 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;

wherein said administration of said **CD123 x CD3** bispecific molecule stimulates the killing of cells of said hematologic malignancy in said patient.

[0028] The ~~invention~~disclosure further provides the example~~embodiment~~ of such methods that additionally comprises evaluating the expression of such one or more target genes in a cellular sample obtained from the patient one or more times after the initiation of the treatment.

[0029] The ~~invention~~disclosure further provides the example~~embodiment~~ of such methods wherein the cellular sample is a bone marrow or a blood sample. Particularly, the example~~embodiment~~ of such methods wherein the cellular sample is a bone marrow sample.

[0030] The ~~invention~~disclosure further provides the example~~embodiment~~ of such methods that further comprises detecting the expression level of one or more target genes in a sample of the patient's bone marrow. The ~~invention~~disclosure further provides the example~~embodiment~~ of such methods that further comprises detecting the expression level of one or more reference genes.

[0031] The ~~invention~~disclosure further provides the example~~embodiment~~ of such methods that comprise detecting the expression level of such one or more target genes and/or such one or more reference genes in a sample of the patient's bone marrow, particularly prior to administration of a **CD123 x CD3** bispecific molecule.

[0032] The ~~invention~~disclosure further provides the example~~embodiment~~ of such methods wherein the evaluation of expression or the determination of whether the 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 the target gene expression levels to the expression levels of one or more reference genes.

[0033] The ~~invention~~disclosure further provides the example~~embodiment~~ of such methods wherein the evaluation of expression or the determination of whether the 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 for each target gene in one or more cellular sample(s) in 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.

[0034] The ~~invention~~disclosure further provides the example~~embodiment~~ of such methods wherein the one or more reference genes comprise one or more of: ABCF1, G6PD, NRDE2, OAZ1, POLR2A, SDHA, STK11IP, TBC1D10B, TBP, and UBB.

[0035] The ~~invention~~disclosure further provides the example~~embodiment~~ of such methods wherein a gene signature score is determined for the one or more target genes. In specific example~~embodiment~~s of the ~~invention~~disclosure such gene signature score is determined from the raw RNA levels of each target gene 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 such 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.

[0036] The ~~invention~~disclosure further provides the example~~embodiment~~ of such methods wherein a patient gene signature score that:

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

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

(c) is within at least the first quartile of the scores for the gene signature calculated from the expression levels of one or more of the target genes in a population of individuals who successfully responded to a treatment for the hematologic malignancy that used a **CD123 x CD3** bispecific molecule,

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

[0037] The ~~invention~~disclosure further provides the example~~embodiment~~ of such methods wherein a patient gene signature score that:

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

(b) is greater than the second quartile for the gene signature calculated from the expression levels of one or more of the target genes in a population of individuals who did not successfully respond to a treatment for the hematologic malignancy that used a **CD123 x CD3** bispecific molecule; or

(c) is within at least the second quartile of the scores for the gene signature calculated from the expression levels of one or more of the target genes in a population of individuals who successfully responded to a treatment for the hematologic malignancy that used a **CD123 x CD3** bispecific molecule,

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

[0038] The ~~invention~~disclosure further provides the example~~embodiment~~ of such methods wherein a patient gene signature score that:

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

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

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

[0039] The ~~invention~~disclosure further provides the example~~embodiment~~ of such methods wherein the **CD123 x CD3** bispecific molecule is a bispecific antibody or a bispecific molecule comprising an scFv.

[0040] The ~~invention~~disclosure further provides the example~~embodiment~~ of such methods wherein the **CD123 x CD3** bispecific molecule is JNJ-63709178, XmAb14045 or APVO436.

[0041] The ~~invention~~disclosure further provides the example~~embodiment~~ of such methods wherein the **CD123 x CD3** bispecific molecule is a covalently bonded bispecific diabody having two, three, or four polypeptide chains.

[0042] The ~~invention~~disclosure further provides the example~~embodiment~~ of such methods wherein the **CD123 x CD3** bispecific molecule comprises:

(a) a VH_{CD123} Domain comprising the CDRs of **SEQ ID NO:6**; and

(b) a VL_{CD123} Domain comprising the CDRs of **SEQ ID NO:10**.

[0043] The ~~invention~~disclosure further provides the example~~embodiment~~ of such methods wherein the **CD123 x CD3** bispecific molecule comprises:

(a) a VH_{CD123} Domain comprising **SEQ ID NO:6**; and

(b) a VL_{CD123} Domain comprising **SEQ ID NO:10**.

[0044] The ~~invention~~disclosure further provides the example~~embodiment~~ of such methods wherein the **CD123 x CD3** bispecific molecule comprises:

(a) a VH_{CD3} Domain comprising the CDRs of **SEQ ID NO:14**; and

(b) a VL_{C23} Domain comprising the CDRs of **SEQ ID NO:1**.

[0045] The ~~invention~~disclosure further provides the example~~embodiment~~ of such methods wherein the **CD123 x CD3** bispecific molecule comprises:

(a) a VH_{CD3} Domain comprising **SEQ ID NO:14**; and

(b) a VL_{CD3} Domain comprising **SEQ ID NO:1**.

[0046] The ~~invention~~disclosure further provides the example~~embodiment~~ of such methods wherein the **CD123 x CD3** bispecific molecule is a diabody that comprises:

(a) a first polypeptide chain comprising the amino acid sequence of **SEQ ID NO:21**; and

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

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

[0047] The ~~invention~~disclosure further provides the example~~embodiment~~ of such methods wherein the hematologic malignancy of such 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.

[0048] The ~~invention~~disclosure further provides the example~~embodiment~~s of such methods wherein the hematologic malignancy of such patient is AML, MDS, BPDCN, or T-ALL.

[0049] The ~~invention~~disclosure further provides the example~~embodiment~~ of such methods wherein the hematologic malignancy of such patient is refractory to chemotherapy (**CTX**), such as being refractory to cytarabine/anthracycline-based cytotoxic chemotherapy or refractory to hypomethylating agents (**HMA**) chemotherapy.

[0050] The ~~invention~~disclosure further provides the example~~embodiment~~ of such methods that further comprises determining the level expression of CD123 of blast cells (cancer cells) as compared to a corresponding baseline level CD123 expressed by normal peripheral blood mononuclear cells (PBMCs).

[0051] The ~~invention~~disclosure further provides the example~~embodiment~~ of such methods wherein the level of expression is determined by measuring the cell surface expression of CD123. The ~~invention~~disclosure further provides the example~~embodiment~~ of such methods wherein the cell surface expression of CD123 is increased by at least about 20% relative to a baseline level of expression. The ~~invention~~disclosure further provides the example~~embodiment~~ of such methods wherein the increase in CD123 expression renders the patient more responsive to treatment with the **CD123 x CD3** bispecific molecule.

[0052] The ~~invention~~disclosure further provides the example~~embodiment~~ of such methods wherein the effective dosage of the **CD123 x CD3** bispecific molecule is selected from the group consisting of about 30, about 60, about 100, about 200, about 300, about 400, and about 500 ng/kg patient weight/day.

[0053] The ~~invention~~disclosure further provides the example~~embodiment~~ of all of the above-described methods wherein the treatment dosage is administered as a continuous infusion. The ~~invention~~disclosure further provides the example~~embodiment~~ of such methods wherein the treatment

dosage is about 30 ng/kg/day administered by continuous infusion for 1 day, followed by a treatment dosage of about 60 ng/kg patient weight/day administered by continuous infusion for 1 day, followed by a treatment dosage of about 100 ng/kg/day administered by continuous infusion for 1 day, followed by a treatment dosage of about 200 ng/kg/day administered by continuous infusion for 1 day, followed by a treatment dosage of about 300 ng/kg/day administered by continuous infusion for 1 day, followed by a treatment dosage of about 400 ng/kg/day administered by continuous infusion for 1 day, followed by a treatment dosage of about 500 ng/kg/day administered by continuous infusion for 1 day. The ~~invention~~disclosure further provides the example~~embodiment~~ of such methods wherein the treatment dosage further comprises administration of about 500 ng/kg/day administered by continuous infusion for up to an additional 21 days.

[0054] The ~~invention~~disclosure further provides the example~~embodiment~~ of all of the above-described methods wherein the patient is a human patient.

BRIEF DESCRIPTION OF THE DRAWINGS:

[0055] **Figures 1A-1C** illustrate the overall structure of exemplary diabody molecules. **Figure 1A** provides the structure of the first and second polypeptide chains of a two chain **CD123 x CD3** bispecific diabody ("**DART-A**" also known as flotetuzumab) having two epitope-binding domains, Heterodimer-Promoting Domains and a cysteine containing linker. **Figures 1B-1C** provide the overall structure of a **CD123 x CD3** bispecific diabody having two epitope-binding domains composed of three polypeptide chains. Two of the polypeptide chains possess a CH2 and CH3 Domain, such that the associated chains form all or part of an Fc Domain. The polypeptide chains comprising the VL and VH Domain further comprise a Heterodimer-Promoting Domain and a linker. A cysteine residue may be present in a linker (**Figures 1A** and **1B**) and/or in the Heterodimer-Promoting Domain (**Figure 1C**). VL and VH Domains that recognize the same epitope are shown using the same shading or fill pattern.

[0056] **Figure 2** illustrates the expression of the top 10 genes associated with complete response to flotetuzumab (complete remission (CR), complete remission with partial hematopoietic recovery (CRh), complete remission with incomplete

WHAT IS CLAIMED IS:

Claim 1. ~~A method of determining whether a patient would be a suitable responder to the use~~Use of a **CD123 x CD3** bispecific molecule in the manufacture of a medicament for treating ~~to treat~~ a hematologic malignancy, wherein ~~said method comprises:~~ a treatment dosage of said **CD123 x CD3** bispecific molecule is to be administered to a patient who has been determined to be a suitable responder to such treatment, wherein said determination of suitability 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~~.~~;

wherein said administration of said **CD123 x CD3** bispecific molecule stimulates the killing of cells of said hematologic malignancy in said patient.

Claim 2. The use of claim 1, 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 3. The use of claim 2, wherein said hematologic malignancy of said patient is AML.

Claim 4. The use of any one of claims 1-3, wherein said hematologic malignancy of said patient is refractory to chemotherapy.

Claim ~~2~~5. The ~~method~~ use of any one of claims 1-4~~claim 1~~, wherein said determination of suitability~~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~~6. The ~~method~~ use of any one of claims ~~1 2~~1-5, wherein said determination of suitability~~method~~ comprises determining whether said patient would be a suitable responder to such treatment by 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~~7. The ~~method~~ use of any one of claims ~~1 3~~1-6, wherein said determination of suitability~~method~~ comprises determining whether said patient would be a suitable responder to such treatment by 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~~8. The ~~method~~ use of any one of claims ~~1-4~~1-7, 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~~9. The ~~method~~ use of any one of claims ~~1-5~~7-8, 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~~10. The ~~method~~ use of any one of claims ~~1-8~~1-9, wherein said cellular sample is a bone marrow sample.

Claim ~~10~~11. The ~~method~~ use of any one of claims ~~1-9~~1-10, wherein ~~said evaluation of expression or~~ said determination of whether ~~said~~ a 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~~12. The ~~method~~ use of any one of claims ~~1-10~~1-11, wherein ~~said evaluation of expression or~~ said determination of whether ~~said~~ a 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~~13. The ~~method~~ use of any one of claims ~~1-11~~1-12, 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~~ use of any one of claims 1-13~~claim 13~~, wherein ~~said~~ a gene signature score is determined for said one or more target genes 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 ~~transfromed~~ transformed RNA values by the number of target genes in the signature, to generate a gene signature score.

Claim 15. The ~~method~~ use of ~~any one of claims 13-14~~claim 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~~ use 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~~ use of claim 16, wherein said **CD123 x CD3** bispecific molecule is JNJ-63709178, XmAb14045 or APVO436.

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

Claim 19. The ~~method~~ use of claim 18, wherein said covalently bonded bispecific diabody comprises~~:~~

~~(a)~~ a first polypeptide chain that comprises ~~having~~ the amino acid sequence of **SEQ ID NO:21**~~; and~~

~~(b)~~ covalently bonded via a disulfide bond to a second polypeptide chain ~~having~~ that comprises 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~~20. The ~~method~~ use of any one of claims 1-~~21~~19, wherein said hematologic malignancy of said patient is refractory to chemotherapy.

Claim ~~23~~21. The ~~method~~ use of any one of claims 1-~~22~~20, 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~~22. The ~~method~~ use of any one of claims 1-2~~3~~1, wherein said treatment dosage is to be administered by continuous infusion.

~~Claim 25. The method of any one of claims 1-24, wherein said patient is a human patient.~~