(b) VL_{CD3} and VH_{CD19};

B. a Domain IB, comprising a charged Heterodimer-Promoting Domain comprising the amino acid sequence of **SEQ ID NO:12**, wherein the Domain IB is separated from the Domain 1A by a polypeptide linker;

C. a Domain IC, comprising a CH2-CH3 Domain of an antibody; and

II. the second polypeptide chain comprises, in the N-terminal to C-terminal direction:

A. a Domain IIA, comprising

(1) a sub-Domain (IIA1), which comprises a VL Domain capable of binding to either CD19 (VL_{CD19}) or CD3 (VL_{CD3}); and

(2) a sub-Domain (IIA2), which comprises a VH Domain capable of binding to either CD19 (VH_{CD19}) or CD3 (VH_{CD3});

wherein the sub-Domains IIA1 and IIA2 are separated from one another by a polypeptide linker, and are:

(a) VL_{CD19} and VH_{CD3}, if the sub-Domains IA1 and IA2 are VL_{CD3} and VH_{CD19}; or

(b) VL_{CD3} and VH_{CD19}, if the sub-Domains IA1 and IA2 are VL_{CD19} and VH_{CD3};

B. a Domain IIB, comprising a charged Heterodimer-Promoting Domain comprising the amino acid sequence of **SEQ ID NO:13**, wherein the Domain IIB is separated from the Domain IIA by a polypeptide linker, and wherein the charged Heterodimer-Promoting Domain of the Domain IB and the charged Heterodimer-Promoting Domain of the Domain IIB have opposite charges; and

III. the third polypeptide chain comprises, in the N-terminal to C-terminal direction a Domain IIIC that comprises a CH2-CH3 Domain of an antibody;

wherein the VL_{CD19} and the VH_{CD19} domains form a CD19 binding domain, and the VL_{CD3} and VH_{CD3} domains form a CD3 binding domain; and the CH2-CH3 Domains of the first and third polypeptide chains form an Fc domain capable of binding to an Fc receptor, thereby forming the CD19 x CD3 bi-specific monovalent Fc diabody.

[0025] The disclosure additionally provides the embodiment of the above-indicated CD19 x CD3 bi-specific monovalent Fc diabody, wherein:

(A) the first polypeptide chain has the amino acid sequence of **SEQ ID NO:35**;

(B) the second polypeptide chain has the amino acid sequence of **SEQ ID NO:37**; and

(C) the third polypeptide chain has the amino acid sequence of **SEQ ID NO:39**.

[0031] The disclosure additionally provides the embodiment of any of the above-indicated CD19 x CD3 bi-specific monovalent Fc diabodies, which is capable of cross-reacting with both human and primate CD19 and CD3.

[0032] In another aspect, there is provided any of the above-described CD19 x CD3 bi-specific monovalent Fc diabodies for use as a pharmaceutical.

[0033] In yet another aspect, there is provided any of the above-described CD19 x CD3 bi-specific monovalent Fc diabodies for use in the treatment of a disease or condition associated with or characterized by the expression of CD19. Also disclosed is a method of treating a disease or condition characterized by the expression of CD19, particularly wherein the disease or condition associated with or characterized by the expression of CD19 is cancer, and more particularly, wherein the cancer is selected from the group consisting of: acute myeloid leukemia (AML), chronic myelogenous leukemia (CML), including blastic crisis of CML and Abelson oncogene associated with CML (Bcr-ABL translocation), myelodysplastic syndrome (MDS), acute B lymphoblastic leukemia (B-ALL), diffuse large B cell lymphoma (DLBCL), follicular lymphoma, chronic lymphocytic leukemia (CLL), including Richter's syndrome or Richter's transformation of CLL, hairy cell leukemia (HCL), blastic plasmacytoid dendritic cell neoplasm (BPDCN), non-Hodgkin lymphomas (NHL), including mantel cell leukemia (MCL), and small lymphocytic lymphoma (SLL), Hodgkin's lymphoma, systemic mastocytosis, and Burkitt's lymphoma.

[0034] In one aspect, there is provided a covalently associated polypeptide complex, wherein the polypeptide complex comprises a first polypeptide chain and a second polypeptide chain, wherein:

(A) the first polypeptide chain comprises a polypeptide comprising the amino acid sequence of **SEQ ID NO:2** linked to a Heterodimer-Promoting Domain comprising the amino acid sequence of **SEQ ID NO:12**; and

(B) the second polypeptide chain comprises a polypeptide comprisingthe amino acid sequence of **SEQ ID NO:2** linked to a Heterodimer-Promoting Domain comprisingthe amino acid sequence of **SEQ ID NO:13**;

wherein the Heterodimer-Promoting Domains of the first polypeptide chain and the Heterodimer-Promoting Domains of the second polypeptide chain are covalently bonded to one another via a disulfide bond.

[0034a] In another aspect, there is provided a covalently associated polypeptide complex, wherein said polypeptide complex comprises a first polypeptide chain and a second polypeptide chain, wherein:

(A) said first polypeptide chain comprises a polypeptide comprising the amino acid sequence of **SEQ ID NO:3** linked to a Heterodimer-Promoting Domain comprising the amino acid sequence of **SEQ ID NO:12**; and

(B) said second polypeptide chain comprises a polypeptide comprising the amino acid sequence of **SEQ ID NO:3** linked to a Heterodimer-Promoting Domain comprising the amino acid sequence of **SEQ ID NO:13**;

wherein said Heterodimer-Promoting Domains of said first polypeptide chain and said Heterodimer-Promoting Domains of said second polypeptide chain are covalently bonded to one another via a disulfide bond.

[0035] In another aspect, there is provided a pharmaceutical composition comprising any of the above-described CD19 x CD3 bi-specific monovalent Fc diabodies and a physiologically acceptable carrier. In another aspect, there is provided a pharmaceutical composition comprising any one of the above-described covalently associated polypeptide complex and a physiologically acceptable carrier. In another aspect, there is provided use of any of the above-described CD19 x CD3 bi-specific Fc diabody, or the pharmaceutical composition above-described in the manufacture of a medicament for the treatment of a disease or condition associated with or characterized by the expression of CD19, wherein said disease or condition is cancer. The disclosure additionally concerns the use of such a pharmaceutical composition in the treatment of a disease or condition associated with or characterized by the expression of CD19, particularly wherein the disease or condition associated with or characterized by the expression of CD19 is cancer, and more particularly, wherein the cancer is selected from the group consisting of: acute myeloid leukemia (AML), chronic myelogenous leukemia (CML), including blastic crisis of CML and Abelson oncogene associated with CML (Bcr-ABL translocation), myelodysplastic syndrome (MDS), acute B lymphoblastic leukemia (B-ALL), diffuse large B cell lymphoma (DLBCL), follicular lymphoma, chronic lymphocytic leukemia (CLL), including Richter's syndrome or Richter's transformation of CLL, hairy cell leukemia (HCL), blastic plasmacytoid dendritic cell neoplasm (BPDCN), non-Hodgkin lymphomas (NHL), including mantel cell leukemia (MCL), and small lymphocytic lymphoma (SLL), Hodgkin's lymphoma, systemic mastocytosis, and Burkitt's lymphoma.

[0036] The CD19 x CD3 bi-specific monovalent diabodies and CD19 x CD3 bi-specific monovalent Fc diabodies of the present disclosure are preferably capable of exhibiting similar binding affinity to soluble human and cynomolgus monkey CD3 and a 10-fold difference in binding to CD19, as analyzed by surface plasmon resonance (SPR) technology (BIAcore), or as analyzed by flow cytometry using a CD4+ and CD8+ gated T cell population and a CD20+ gated B cell population.

[0037] The CD19 x CD3 bi-specific monovalent diabodies and CD19 x CD3 bi-specific monovalent Fc diabodies of the present disclosure are preferably capable of

administration of diabody on Day 17, so as to cause a decrease in tumor volume of about 10%, about 20%, about 40%, about 60%, about 80%, about 90% or more than 90%.

[0042] The CD19 x CD3 bi-specific monovalent diabodies and CD19 x CD3 bi-specific monovalent Fc diabodies of the present disclosure are preferably capable of exhibiting prolonged half-lives upon introduction into a recipient human or non-human animal. Such half-lives can be measured by introducing the diabody into a human FcRn transgenic mouse (United States Patents No. 6,992,234 and 7,358,416; Haraya, K. (2014) "*Application Of Human FcRn Transgenic Mice As A Pharmacokinetic Screening Tool Of Monoclonal Antibody*," Xenobiotica 2014 Jul 17:1-8; Proetzel, G. *et al.* (2014) "*Humanized FcRn mouse models for evaluating pharmacokinetics of human IgG antibodies*," Methods 65(1):148-153; Stein, C. *et al.* (2012) "*Clinical Chemistry Of Human FcRn Transgenic Mice*," Mamm. Genome 23(3-4):259-269; Roopenian, D.C. *et al.* (2010) "*Human FcRn Transgenic Mice For Pharmacokinetic Evaluation Of Therapeutic Antibodies*," Methods Molec. Biol. 602:93-104). The measurement is conducted using a B6.Cg-*Fcgrt*^{tm1Dcr} (CAG-FCGRT)276Dcr/DcrJ mouse (Stock Number 004919), available from the Jackson Laboratories, Bar Harbor, Maine, US.

[0043] For the avoidance of any doubt, the diabodies of the disclosure may exhibit one, two, three, more than three or all of the functional attributes described herein. Thus the diabodies of the disclosure may exhibit any combination of the functional attributes described herein.

[0043a] In another aspect, there is provided a polynucleotide encoding a polypeptide comprising the amino acid sequence of SEQ ID NO: 35, SEQ ID NO: 37, and/or SEQ ID NO: 39. In another aspect, there is provided an expression vector comprising the above-described polynucleotide.

[0044] The diabodies of the present disclosure may be for use as a pharmaceutical. Preferably, the diabodies are for use in the treatment of a disease or condition associated with or characterized by the expression of CD19. The disclosure also relates to the use of diabodies of the disclosure in the manufacture of a pharmaceutical composition, preferably for the treatment of a disease or condition associated with or characterized by the expression of CD19 as further defined herein.

[0045] The disease or condition associated with or characterized by the expression of CD19 may be a B cell malignancy (Campo, E. *et al.* (2011) "*The 2008 WHO*

What Is Claimed Is:

Claim 1. A CD19 x CD3 bi-specific monovalent Fc diabody capable of specific binding to CD19 and to CD3, wherein the diabody comprises a first, a second and a third polypeptide chain, wherein said polypeptide chains form a covalently bonded complex, and wherein:

I. said first polypeptide chain comprises, in the N-terminal to C-terminal direction:

A. a Domain IA, comprising

(1) a sub-Domain (IA1), which comprises a VL Domain capable of binding to either CD19 (VL_{CD19}) or CD3 (VL_{CD3}); and

(2) a sub-Domain (IA2), which comprises a VH Domain capable of binding to either CD19 (VH_{CD19}) or CD3 (VH_{CD3});

wherein said sub-Domains IA1 and IA2 are separated from one another by a polypeptide linker, and are either

(a) VL_{CD19} and VH_{CD3}; or

(b) VL_{CD3} and VH_{CD19};

B. a Domain IB, comprising a charged Heterodimer-Promoting Domain comprising the amino acid sequence of **SEQ ID NO:12**, wherein said Domain IB is separated from said Domain 1A by a polypeptide linker;

C. a Domain IC, comprising a CH2-CH3 Domain of an antibody; and

II. said second polypeptide chain comprises, in the N-terminal to C-terminal direction:

A. a Domain IIA, comprising

(1) a sub-Domain (IIA1), which comprises a VL Domain capable of binding to either CD19 (VL_{CD19}) or CD3 (VL_{CD3}); and

(2) a sub-Domain (IIA2), which comprises a VH Domain capable of binding to either CD19 (VH_{CD19}) or CD3 (VH_{CD3});

wherein said sub-Domains IIA1 and IIA2 are separated from one another by a polypeptide linker, and are:

(a) VL_{CD19} and VH_{CD3}, if said sub-Domains IA1 and IA2 are VL_{CD3} and VH_{CD19}; or

(b) VL_{CD3} and VH_{CD19}, if said sub-Domains IA1 and IA2 are VL_{CD19} and VH_{CD3};

B. a Domain IIB, comprising a charged Heterodimer-Promoting Domain comprising the amino acid sequence of **SEQ ID NO:13**, wherein said Domain IIB is separated from said Domain IIA by a polypeptide linker, and wherein said charged Heterodimer-Promoting Domain of said Domain IB and said charged Heterodimer-Promoting Domain of said Domain IIB have opposite charges; and

III. said third polypeptide chain comprises, in the N-terminal to C-terminal direction a Domain IIIC that comprises a CH2-CH3 Domain of an antibody;

wherein said VL_{CD19} and said VH_{CD19} domains form a CD19 binding domain, and said VL_{CD3} and VH_{CD3} domains form a CD3 binding domain; and said CH2-CH3 Domains of said first and third polypeptide chains form an Fc domain capable of binding to an Fc receptor, thereby forming said CD19 x CD3 bi-specific monovalent Fc diabody.

Claim 2. The CD19 x CD3 bi-specific monovalent Fc diabody of claim 1, wherein:

(A) said Domains IB and IIB each comprise a cysteine residue that covalently bonds said first polypeptide chain to said second polypeptide chain via a disulfide bond; and

(B) said Domains IC and IIIC each comprise a cysteine residue that covalently bonds said first polypeptide chain to said third polypeptide chain via a disulfide bond.

Claim 3. The CD19 x CD3 bi-specific monovalent Fc diabody of any one of claims 1-2, wherein said VL_{CD19} comprises the amino acid sequence of **SEQ ID NO:17** and said VH_{CD19} comprises the amino acid sequence of **SEQ ID NO:21**.

Claim 4. The CD19 x CD3 bi-specific monovalent Fc diabody of any one of claims 1-3, wherein said VL_{CD3} comprises the amino acid sequence of **SEQ ID NO:25** and said VH_{CD3} comprises the amino acid sequence of **SEQ ID NO:29**.

Claim 5. The CD19 x CD3 bi-specific monovalent Fc diabody of any one of claims 1-4, wherein said CH2-CH3 Domain of said Domain IC comprises the amino acid sequence of **SEQ ID NO:15** and said CH2-CH3 Domain of said Domain IIIC comprises the amino acid sequence of **SEQ ID NO:16**.

Claim 6. The CD19 x CD3 bi-specific monovalent Fc diabody of any one of claims 1-5, wherein said polypeptide linker that separates said Domain IB from said Domain 1A comprises the amino acid sequence of **SEQ ID NO: 2**, and said polypeptide linker that separates said Domain IIB from said Domain IIA comprises the amino acid sequence of **SEQ ID NO: 2**.

Claim 7. The CD19 x CD3 bi-specific monovalent Fc diabody of any one of claims 1-5, wherein said polypeptide linker that separates said Domain IB from said Domain 1A comprises the amino acid sequence of **SEQ ID NO: 3**, and said polypeptide linker that separates said Domain IIB from said Domain IIA comprises the amino acid sequence of **SEQ ID NO: 3**.

Claim 8. The CD19 x CD3 bi-specific monovalent Fc diabody of any one of claims 1-6, wherein:

(A) said first polypeptide chain comprises the amino acid sequence of **SEQ ID NO:35**;

(B) said second polypeptide chain comprises the amino acid sequence of **SEQ ID NO:37**; and

(C) said third polypeptide chain comprises the amino acid sequence of **SEQ ID NO:39**.

Claim 9. The CD19 x CD3 bi-specific monovalent Fc diabody of any one of claims 1-8, which is capable of cross-reacting with both human and primate CD19 and CD3.

Claim 10. A covalently associated polypeptide complex, wherein said polypeptide complex comprises a first polypeptide chain and a second polypeptide chain, wherein:

(A) said first polypeptide chain comprises a polypeptide comprising the amino acid sequence of **SEQ ID NO:2** linked to a Heterodimer-Promoting Domain comprising the amino acid sequence of **SEQ ID NO:12**; and

(B) said second polypeptide chain comprises a polypeptide comprising the amino acid sequence of **SEQ ID NO:2** linked to a Heterodimer-Promoting Domain comprising the amino acid sequence of **SEQ ID NO:13**;

wherein said Heterodimer-Promoting Domains of said first polypeptide chain and said Heterodimer-Promoting Domains of said second polypeptide chain are covalently bonded to one another via a disulfide bond.

Claim 11. A covalently associated polypeptide complex, wherein said polypeptide complex comprises a first polypeptide chain and a second polypeptide chain, wherein:

(A) said first polypeptide chain comprises a polypeptide comprising the amino acid sequence of **SEQ ID NO:3** linked to a Heterodimer-Promoting Domain comprising the amino acid sequence of **SEQ ID NO:12**; and

(B) said second polypeptide chain comprises a polypeptide comprising the amino acid sequence of **SEQ ID NO:3** linked to a Heterodimer-Promoting Domain comprising the amino acid sequence of **SEQ ID NO:13**;

wherein said Heterodimer-Promoting Domains of said first polypeptide chain and said Heterodimer-Promoting Domains of said second polypeptide chain are covalently bonded to one another via a disulfide bond.

Claim 12. A pharmaceutical composition comprising the CD19 x CD3 bi-specific monovalent Fc diabody of any one of claims 1-9 and a physiologically acceptable carrier.

Claim 13. A pharmaceutical composition comprising the covalently associated polypeptide complex of any one of claims 10-11 and a physiologically acceptable carrier.

Claim 14. Use of the CD19 x CD3 bi-specific Fc diabody of any one of claims 1-9, or the pharmaceutical composition of claim 12, in the manufacture of a medicament for the treatment of a disease or condition associated with or characterized by the expression of CD19, wherein said disease or condition is cancer.

Claim 15. The use of claim 14, wherein said cancer 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), diffuse large B cell lymphoma (DLBCL), follicular lymphoma, chronic lymphocytic leukemia (CLL), Richter's syndrome, Richter's transformation of CLL,

hairy cell leukemia (HCL), blastic plasmacytoid dendritic cell neoplasm (BPDCN), non-Hodgkin lymphomas (NHL), mantel cell leukemia (MCL), small lymphocytic lymphoma (SLL), Hodgkin's lymphoma, systemic mastocytosis, and Burkitt's lymphoma.

Claim 16. A polynucleotide encoding a polypeptide comprising the amino acid sequence of **SEQ ID NO:35**, **SEQ ID NO: 37**, and/or **SEQ ID NO:39**.

Claim 17. An expression vector comprising the polynucleotide of claim 16.

Claim 18. The polynucleotide of claim 16, which comprises the sequence of **SEQ ID NO:36**, **SEQ ID NO:38**, and/or **SEQ ID NO:40**.