Summary:

[0024] The present disclosure is directed to multivalent DR5-Binding Molecules that comprise Binding Domain(s) of anti-DR5 antibodies, and particularly Binding Domain(s) of anti-human DR5 antibodies. The DR5-Binding Molecules of the present disclosure include bivalent and tetravalent molecules having two, three or four DR5-Binding Domains each capable of binding human DR5. In particular, the present disclosure is directed to multivalent DR5-Binding Molecules that comprise diabodies, and more particularly, diabodies that comprise a covalently bonded complex of two or more polypeptide chains. The disclosure particularly pertains to such multivalent DR5-Binding Molecules that comprise fragments of the anti-DR5 antibodies DR5 mAb 1 and/or DR5 mAb 2, and/or humanized and chimeric versions of such antibodies.

[0025] In detail, in one aspect, there is provided a multivalent DR5-Binding Molecule that is a bispecific binding molecule, capable of simultaneously binding to two different epitopes of human Death Receptor 5 (DR5), wherein the multivalent DR5-Binding Molecule comprises four antigen-binding domains each capable of binding human DR5. In another aspect, there is provided a multivalent DR5-Binding Molecule that is a monospecific binding molecule, capable of binding to an epitope of human DR5, wherein the multivalent DR5-Binding Molecule comprises four antigen-binding domains each capable of binding human DR5. The disclosure particularly concerns the embodiment of all such multivalent DR5-Binding Molecules capable of simultaneously binding to two, three, or four human DR5 polypeptides.

[0026] The disclosure further concerns the embodiments of such multivalent DR5-Binding Molecules, wherein the multivalent DR5-Binding Molecule is an Fc Region-containing diabody, the diabody being a covalently bonded complex that comprises two pairs of polypeptides, wherein each pair comprises a first polypeptide chain and a second polypeptide chain.

[0027] The disclosure further concerns the embodiments of such multivalent DR5-Binding Molecules, wherein:

(A) the first polypeptide chain comprises, in the N-terminal to C-terminal direction:

(i) a variable light chain (VL) Domain of a monoclonal antibody capable of binding to a first DR5 epitope (VL1);

(ii) a first peptide linker (Linker 1);

(iii) a variable heavy chain (VH) Domain of a monoclonal antibody capable of binding to a second DR5 epitope (VH2);

(iv) a second peptide linker (Linker 2);

(v) a Heterodimer-Promoting Domain comprising a E-coil Domain or a K-coil Domain;

(vi) a third peptide linker (Linker 3); and

(vii) a polypeptide portion of an IgG Fc Region having CH2 and CH3 domains of an IgG immunoglobulin Fc Region; and

(B) the second polypeptide chain comprises, in the N-terminal to C-terminal direction:

(i) a VL Domain of a monoclonal antibody capable of binding to the second DR5 epitope (VL2);

(ii) a first peptide linker (Linker 1);

(iii) a VH Domain of a monoclonal antibody capable of binding to the first DR5 epitope (VH1);

(iv) a second peptide linker (Linker 2); and

(v) a Heterodimer-Promoting Domain comprising a E-coil Domain or a K-coil Domain, wherein the Heterodimer-Promoting Domain of the first polypeptide chain and the Heterodimer-Promoting Domain of the second polypeptide chain are not both E-coil Domains or both K-coil Domains;

and wherein:

(a) the VL1 Domain of the first polypeptide chain and the VH1 Domain of the second polypeptide chain form an Antigen-Binding Domain capable of specific binding to a first epitope of DR5;

(b) the VH2 Domain of the first polypeptide chain and the VL1 Domain of the second polypeptide chain form an Antigen-Binding Domain capable of specific binding to a second epitope of DR5; and

(c) the CH2-CH3 portions of the pair of first polypeptide chains form an IgG Fc Region.

[0028] The disclosure further concerns the embodiments of such multivalent DR5-Binding Molecules, wherein:

(i) the Linker 1 has the amino acid sequence of **SEQ ID NO:33**,

(ii) the Linker 1 has the amino acid sequence of **SEQ ID NO:47**,

(iii) the E-coil Domain has the amino acid sequence of SEQ ID NO: **SEQ ID NO:41**,

(iv) the K-coil Domain has the amino acid sequence of **SEQ ID NO:42**,

(v) the Linker 3 has the amino acid sequence of **SEQ ID NO:51**, and

(vi) the CH2-CH3 domain has the amino acid sequence of **SEQ ID NO:1 or SEQ ID NO:102**, wherein the C-terminal residue is optionally included.

[0029] The disclosure further concerns the embodiments of all such multivalent DR5-Binding Molecules, wherein the Fc Region comprises one or more amino acid modifications that reduce the affinity of the variant Fc Region for an FcγR or stabilizes the Fc Region. The disclosure further concerns the embodiments of all such DR5-Binding Molecule, wherein the modificiations comprise the substitution of L234A; L235A; or L234A and L235A.

[0030] The disclosure particularly concerns the embodiments of such multivalent DR5-Binding Molecules, wherein the VL1 comprises a CDR_L1 Domain, a CDR_L2 Domain, and a CDR_L3 Domain, and the VH1 comprises a CDR_H1 Domain, a CDR_H2 Domain and a CDR_H3 Domain, wherein:

(i) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of DR5 mAb 1, and respectively have the amino acid sequences: **SEQ ID NO:4**, **SEQ ID NO:5**, and **SEQ ID NO:6**, and the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy

Chain CDRs of DR5 mAb 1, and respectively have the amino acid sequences: **SEQ ID NO:9**, **SEQ ID NO:10**, and **SEQ ID NO:11**; or

(ii) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of DR5 mAb 2, and, respectively have the amino acid sequences: **SEQ ID NO:14**, **SEQ ID NO:15**, and **SEQ ID NO:16**, and the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of DR5 mAb 2, and respectively have the amino acid sequences: **SEQ ID NO:19**, **SEQ ID NO:20**, and **SEQ ID NO:21**; or

(iii) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of hDR5 mAb 2 VL-3, and, respectively have the amino acid sequences: **SEQ ID NO:165**, **SEQ ID NO:15**, and **SEQ ID NO:16**, and the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of hDR5 mAb 2 VH-3, and respectively have the amino acid sequences: **SEQ ID NO:19**, **SEQ ID NO:20**, and **SEQ ID NO:21**; or

(iv) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of DR5 mAb 3, and, respectively have the amino acid sequences: **SEQ ID NO:55**, **SEQ ID NO:56**, and **SEQ ID NO:57**, and the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of DR5 mAb 3, and respectively have the amino acid sequences: **SEQ ID NO:59**, **SEQ ID NO:60**, and **SEQ ID NO:61**; or

(v) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of DR5 mAb 4, and, respectively have the amino acid sequences: **SEQ ID NO:63**, **SEQ ID NO:64**, and **SEQ ID NO:65**, and the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of DR5 mAb 4, and respectively have the amino acid sequences: **SEQ ID NO:67**, **SEQ ID NO:68**, and **SEQ ID NO:69**; or

(vi) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of DR5 mAb 5, and, respectively have the amino acid

sequences: **SEQ ID NO:71**, **SEQ ID NO:72**, and **SEQ ID NO:73**, and the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of DR5 mAb 5, and respectively have the amino acid sequences: **SEQ ID NO:75**, **SEQ ID NO:76**, and **SEQ ID NO:77**; or

(vii) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of DR5 mAb 6, and, respectively have the amino acid sequences: **SEQ ID NO:79**, **SEQ ID NO:80**, and **SEQ ID NO:81**, and the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of DR5 mAb 6, and respectively have the amino acid sequences: **SEQ ID NO:83**, **SEQ ID NO:84**, and **SEQ ID NO:85**; or

(viii) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of DR5 mAb 7, and, respectively have the amino acid sequences: **SEQ ID NO:87**, **SEQ ID NO:88**, and **SEQ ID NO:89**, and the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of DR5 mAb 7, and respectively have the amino acid sequences: **SEQ ID NO:91**, **SEQ ID NO:92**, and **SEQ ID NO:93**; or

(ix) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of DR5 mAb 8, and, respectively have the amino acid sequences: **SEQ ID NO:95**, **SEQ ID NO:96**, and **SEQ ID NO:97**, and the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of DR5 mAb 8, and respectively have the amino acid sequences: **SEQ ID NO:99**, **SEQ ID NO:100**, and **SEQ ID NO:101.**

[0031] The disclosure particularly concerns the embodiments of such multivalent DR5-Binding Molecules, wherein the VL2 comprises a CDR_L1 Domain, a CDR_L2 Domain, and a CDR_L3 Domain, and the VH2 comprises a CDR_H1 Domain, a CDR_H2 Domain and a CDR_H3 Domain, wherein:

(i) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of DR5 mAb 1, and respectively have the amino acid

sequences: **SEQ ID NO:4**, **SEQ ID NO:5**, and **SEQ ID NO:6**, and the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of DR5 mAb 1, and respectively have the amino acid sequences: **SEQ ID NO:9**, **SEQ ID NO:10**, and **SEQ ID NO:11**; or

(ii) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of DR5 mAb 2, and, respectively have the amino acid sequences: **SEQ ID NO:14**, **SEQ ID NO:15**, and **SEQ ID NO:16**, and the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of DR5 mAb 2, and respectively have the amino acid sequences: **SEQ ID NO:19**, **SEQ ID NO:20**, and **SEQ ID NO:21**; or

(iii) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of DR5 mAb 2, and, respectively have the amino acid sequences: **SEQ ID NO:165**, **SEQ ID NO:15**, and **SEQ ID NO:16**, and the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of DR5 mAb 2, and respectively have the amino acid sequences: **SEQ ID NO:19**, **SEQ ID NO:20**, and **SEQ ID NO:21**; or

(iv) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of DR5 mAb 3, and, respectively have the amino acid sequences: **SEQ ID NO:55**, **SEQ ID NO:56**, and **SEQ ID NO:57**, and the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of DR5 mAb 3, and respectively have the amino acid sequences: **SEQ ID NO:59**, **SEQ ID NO:60**, and **SEQ ID NO:61**; or

(v) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of DR5 mAb 4, and, respectively have the amino acid sequences: **SEQ ID NO:63**, **SEQ ID NO:64**, and **SEQ ID NO:65**, and the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of DR5 mAb 4, and respectively have the amino acid sequences: **SEQ ID NO:67**, **SEQ ID NO:68**, and **SEQ ID NO:69**; or

(vi) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of DR5 mAb 5, and, respectively have the amino acid sequences: **SEQ ID NO:71**, **SEQ ID NO:72**, and **SEQ ID NO:73**, and the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of DR5 mAb 5, and respectively have the amino acid sequences: **SEQ ID NO:75**, **SEQ ID NO:76**, and **SEQ ID NO:77**; or

(vii) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of DR5 mAb 6, and, respectively have the amino acid sequences: **SEQ ID NO:79**, **SEQ ID NO:80**, and **SEQ ID NO:81**, and the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of DR5 mAb 6, and respectively have the amino acid sequences: **SEQ ID NO:83**, **SEQ ID NO:84**, and **SEQ ID NO:85**; or

(viii) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of DR5 mAb 7, and, respectively have the amino acid sequences: **SEQ ID NO:87**, **SEQ ID NO:88**, and **SEQ ID NO:89**, and the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of DR5 mAb 7, and respectively have the amino acid sequences: **SEQ ID NO:91**, **SEQ ID NO:92**, and **SEQ ID NO:93**; or

(ix) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of DR5 mAb 8, and, respectively have the amino acid sequences: **SEQ ID NO:95**, **SEQ ID NO:96**, and **SEQ ID NO:97**, and the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of DR5 mAb 8, and respectively have the amino acid sequences: **SEQ ID NO:99**, **SEQ ID NO:100**, and **SEQ ID NO:101.**

[0032] The disclosure further concerns the embodiments of such multivalent DR5-Binding Molecules, wherein the VL1 and the VL2 comprise the same CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain, and wherein the VH1 and the VH2 comprise the

same CDR_H1 Domain, CDR_H2 Domain and CDR_H3 Domain, and particularly concerns the embodiment of such multivalent DR5-Binding Molecules, wherein:

(i) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of DR5 mAb 1, and respectively have the amino acid sequences: **SEQ ID NO:4**, **SEQ ID NO:5**, and **SEQ ID NO:6**, and the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of DR5 mAb 1, and respectively have the amino acid sequences: **SEQ ID NO:9**, **SEQ ID NO:10**, and **SEQ ID NO:11**; or

(ii) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of DR5 mAb 2, and, respectively have the amino acid sequences: **SEQ ID NO:14**, **SEQ ID NO:15**, and **SEQ ID NO:16**, and the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of DR5 mAb 2, and respectively have the amino acid sequences: **SEQ ID NO:19**, **SEQ ID NO:20**, and **SEQ ID NO:21**; or

(iii) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of hDR5 mAb 2, and, respectively have the amino acid sequences: **SEQ ID NO:165**, **SEQ ID NO:15**, and **SEQ ID NO:16**, and the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of DR5 mAb 2, and respectively have the amino acid sequences: **SEQ ID NO:19**, **SEQ ID NO:20**, and **SEQ ID NO:21**.

[0033] The disclosure further concerns the embodiments of such multivalent DR5-Binding Molecules, wherein the VL1 and the VL2 do not comprise the same CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain, and wherein the VH1 and the VH2 do not comprise the same CDR_H1 Domain, CDR_H2 Domain and CDR_H3 Domain, and particularly concerns the embodiment of such multivalent DR5-Binding Molecules, wherein:

(i) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain of VL1 are the Light Chain CDRs of DR5 mAb 1, and respectively have the amino

acid sequences: **SEQ ID NO:4**, **SEQ ID NO:5**, and **SEQ ID NO:6**, and the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain of VH1 are the Heavy Chain CDRs of DR5 mAb 1, and respectively have the amino acid sequences: **SEQ ID NO:9**, **SEQ ID NO:10**, and **SEQ ID NO:11**; and the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain of VL2 are the Light Chain CDRs of DR5 mAb 2 or hDR5 mAb2, and, respectively have the amino acid sequences: **SEQ ID NO:14 or 165**, **SEQ ID NO:15**, and **SEQ ID NO:16**, and the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain of VH2 are the Heavy Chain CDRs of DR5 mAb 2, and respectively have the amino acid sequences: **SEQ ID NO:19**, **SEQ ID NO:20**, and **SEQ ID NO:21**; or

(ii) the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain of VL1 are the Light Chain CDRs of DR5 mAb 2 or hDR5 mAb2, and, respectively have the amino acid sequences: **SEQ ID NO:14 or 165**, **SEQ ID NO:15**, and **SEQ ID NO:16**, and the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain of VH1 are the Heavy Chain CDRs of DR5 mAb 2, and respectively have the amino acid sequences: **SEQ ID NO:19**, **SEQ ID NO:20**, and **SEQ ID NO:21**; and the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain of VL2 are the Light Chain CDRs of DR5 mAb 1, and respectively have the amino acid sequences: **SEQ ID NO:4**, **SEQ ID NO:5**, and **SEQ ID NO:6**, and the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain of VH2 are the Heavy Chain CDRs of DR5 mAb 1, and respectively have the amino acid sequences: **SEQ ID NO:9**, **SEQ ID NO:10**, and **SEQ ID NO:11**.

[0034] The disclosure further concerns the embodiments of such multivalent DR5-Binding Molecules, wherein:

(A) (i) the VL1 has the amino acid sequence of **SEQ ID NO:3**, and the VH1 has the amino acid sequence of **SEQ ID NO:8**; or

(ii) the VL1 has the amino acid sequence of **SEQ ID NO:13**, and the VH1 has the amino acid sequence of **SEQ ID NO:18**; or

(iii) the VL1 has the amino acid sequence of **SEQ ID NO:23**, and the VH1 has the amino acid sequence of **SEQ ID NO:31**; or

(viii) the VL2 has the amino acid sequence of **SEQ ID NO:54**, and the VH2 has the amino acid sequence of **SEQ ID NO:58**; or

(ix) the VL2 has the amino acid sequence of **SEQ ID NO:62**, and the VH2 has the amino acid sequence of **SEQ ID NO:66**; or

(x) the VL2 has the amino acid sequence of **SEQ ID NO:70**, and the VH1 has the amino acid sequence of **SEQ ID NO:74**; or

(xi) the VL2 has the amino acid sequence of **SEQ ID NO:78**, and the VH1 has the amino acid sequence of **SEQ ID NO:82**; or

(xii) the VL2 has the amino acid sequence of **SEQ ID NO:86**, and the VH1 has the amino acid sequence of **SEQ ID NO:90**; or

(xiii) the VL2 has the amino acid sequence of **SEQ ID NO:94**, and the VH2 has the amino acid sequence of **SEQ ID NO:98**.

[0035] The disclosure further concerns the embodiments of such multivalent DR5-Binding Molecules, wherein the VL1 and the VL2 have the same amino acid sequence, and wherein the VH1 and the VH2 have the same amino acid sequence.

[0036] The disclosure further concerns the embodiments of such multivalent DR5-Binding Molecules, wherein the VL1 and the VL2 do not have the same amino acid sequence, and wherein the VH1 and the VH2 do not have the same amino acid sequence.

[0037] The disclosure further concerns the embodiments of such multivalent DR5-Binding Molecules, wherein the multivalent DR5-Binding Molecule is an Fc Region-containing diabody, the diabody being a covalently bonded complex that comprises two pairs of polypeptides wherein:

(i) the first polypeptide chain has the amino acid sequence of **SEQ ID NO:116** or **SEQ ID NO:120**, and the second polypeptide chain has the amino acid sequence of **SEQ ID NO:118**; or

(ii) the first polypeptide chain has the amino acid sequence of **SEQ ID NO:122** or **SEQ ID NO:126**, and the second polypeptide chain has the amino acid sequence of **SEQ ID NO:124**; or

(iii) the first polypeptide chain has the amino acid sequence of **SEQ ID NO:128** or **SEQ ID NO:132**, and the second polypeptide chain has the amino acid sequence of **SEQ ID NO:130**; or

(iv) the first polypeptide chain has the amino acid sequence of **SEQ ID NO:134** or **SEQ ID NO:138**, and the second polypeptide chain has the amino acid sequence of **SEQ ID NO:136**; or

(v) the first polypeptide chain has the amino acid sequence of **SEQ ID NO:140** or **SEQ ID NO:144**, and the second polypeptide chain has the amino acid sequence of **SEQ ID NO:142**; or

(vi) the first polypeptide chain has the amino acid sequence of **SEQ ID NO:146** or **SEQ ID NO:150**, and the second polypeptide chain has the amino acid sequence of **SEQ ID NO:148**; or

(vii) the first polypeptide chain has the amino acid sequence of **SEQ ID NO:152** or **SEQ ID NO:156**, and the second polypeptide chain has the amino acid sequence of **SEQ ID NO:154**; or

(vi) the first polypeptide chain has the amino acid sequence of **SEQ ID NO:158** or **SEQ ID NO:162**, and the second polypeptide chain has the amino acid sequence of **SEQ ID NO:160**.

[0037a] In one aspect, there is provided a DR5-binding molecule having a VL Domain comprising a CDR_L1 Domain, a CDR_L2 Domain, and a CDR_L3 Domain, and a VH1 Domain comprising a CDR_H1 Domain, a CDR_H2 Domain and a CDR_H3 Domain, wherein:

(i) said CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of DR5 mAb 1, and respectively have the amino acid sequences: **SEQ ID NO:4**, **SEQ ID NO:5**, and **SEQ ID NO:6**, and said CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of DR5 mAb 1, and respectively have the amino acid sequences: **SEQ ID NO:9**, **SEQ ID NO:10**, and **SEQ ID NO:11**; or

(ii) said CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of DR5 mAb 2, and, respectively have the amino acid sequences: **SEQ ID NO:14**, **SEQ ID NO:15**, and **SEQ ID NO:16**, and said CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of DR5 mAb 2, and respectively have the amino acid sequences: **SEQ ID NO:19**, **SEQ ID NO:20**, and **SEQ ID NO:21**; or

(iii) said CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of hDR5 mAb 2 VL-3, and, respectively have the amino acid sequences: **SEQ ID NO: 165, SEQ ID NO:15**, and **SEQ ID NO:16**, and said CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of hDR5 mAb 2 VH-3, and respectively have the amino acid sequences: **SEQ ID NO:19**, **SEQ ID NO:20**, and **SEQ ID NO:21**.

[0038] In another aspect, there is provided a composition comprising any of the above described multivalent DR5-Binding Molecules and an excipient. The disclosure further concerns such compositions further comprising a histone deacetylase inhibitor.

[0039] In one aspect, there is provided use of any of the above described multivalent DR5-Binding Molecules, or any of the above described compositions, in the manufacture of a medicament for promoting cell death by exposing said cell to said molecule. The disclosure further concerns methods of promoting cell death comprising exposing a cell to any of the above described multivalent DR5-Binding Molecules. In particular, where the cell is a tumor cell. The disclosure further concerns such uses and methods of promoting cell death further comprising exposing the cell to a histone deacetylase inhibitor.

[0040] The disclosure further concerns the embodiments in which any of the above-described multivalent DR5-Binding Molecules is used in the treatment of cancer. In one aspect, there is provided use of any of the above described multivalent DR5-Binding Molecules, or any of the above described compositions, in the manufacture of a medicament for the treatment of cancer. The disclosure further concerns the embodiments in which any of the above-described

multivalent DR5-binding molecules is used in combination with a histone deacetylase inhibitor in the treatment of cancer.

[0041] The disclosure further concerns the embodiments in which any of the above-described multivalent DR5-Binding Molecules is detectably labled and is used in the diagnosis or prognosis of cancer. In one aspect, there is provided use of any of the above described multivalent DR5-Binding Molecules, or any of the above described compositions, in the manufacture of a medicament for the diagnosis or prognosis of cancer, wherein said molecule is detectably labeled.

[0042] The disclosure particularly concerns such use of any of the above described multivalent DR5-Binding Molecules in the treatment or diagnosis or prognosis of cancer, wherein the cancer is characterized by the presence of a cancer cell selected from the group consisting of a cell of: an adrenal gland tumor, an AIDS-associated cancer, an alveolar soft part sarcoma, an astrocytic tumor, bladder cancer, bone cancer, a brain and spinal cord cancer, a metastatic brain tumor, a breast cancer, a carotid body tumors, a cervical cancer, a chondrosarcoma, a chordoma, a chromophobe renal cell carcinoma, a clear cell carcinoma, a colon cancer, a colorectal cancer, a cutaneous benign fibrous histiocytoma, a desmoplastic small round cell tumor, an ependymoma, a Ewing's tumor, an extraskeletal myxoid chondrosarcoma, a fibrogenesis imperfecta ossium, a fibrous dysplasia of the bone, a gallbladder or bile duct cancer, gastric cancer, a gestational trophoblastic disease, a germ cell tumor, a head and neck cancer, hepatocellular carcinoma, an islet cell tumor, a Kaposi's Sarcoma, a kidney cancer, a leukemia, a lipoma/benign lipomatous tumor, a liposarcoma/malignant lipomatous tumor, a liver cancer, a lymphoma, a lung cancer, a medulloblastoma, a melanoma, a meningioma, a multiple endocrine neoplasia, a multiple myeloma, a myelodysplastic syndrome, a neuroblastoma, a neuroendocrine tumors, an ovarian cancer, a pancreatic cancer, a papillary thyroid carcinoma, a parathyroid tumor, a pediatric cancer, a peripheral nerve sheath tumor, a phaeochromocytoma, a pituitary tumor, a prostate cancer, a posterious uveal melanoma, a rare hematologic disorder, a renal metastatic cancer, a rhabdoid tumor, a rhabdomysarcoma, a sarcoma, a skin cancer, a soft-tissue sarcoma, a squamous cell cancer, a stomach cancer, a synovial sarcoma, a testicular cancer, a thymic carcinoma, a thymoma, a thyroid metastatic cancer, and a uterine cancer.

[0043] The disclosure particularly concerns such use of any of the above described multivalent DR5-Binding Molecules in the treatment or diagnosis or prognosis of cancer, wherein the cancer is acolorectal cancer, hepatocellular carcinoma, glioma, kidney cancer, breast cancer, multiple myeloma, bladder cancer, neuroblastoma; sarcoma, non-Hodgkin's lymphoma, non-small cell lung cancer, ovarian cancer, pancreatic cancer or a rectal cancer.

[0044] The disclosure particularly concerns such use of any of the above described multivalent DR5-Binding Molecules in the treatment or diagnosis or prognosis of cancer, wherein the cancer is acute myeloid leukemia (AML), chronic myelogenous leukemia (CML), acute B lymphoblastic leukemia (B-ALL), chronic lymphocytic leukemia (CLL), hairy cell leukemia (HCL), blastic plasmacytoid dendritic cell neoplasm (BPDCN), non-Hodgkin's lymphomas (NHL), including mantel cell leukemia (MCL), and small lymphocytic lymphoma (SLL), Hodgkin's lymphoma, systemic mastocytosis, or Burkitt's lymphoma.

Brief Description of the Drawings:

[0045] **Figure 1** provides a schematic of a representative covalently bonded diabody molecule having two epitope binding sites composed of two polypeptide chains, each having an E-coil or K-coil Heterodimer-Promoting Domain. VL and VH Domains that recognize the same epitope are shown using the same shading. In certain embodiments, the epitopes are different epitopes of the same antigen resulting in a bispecific molecule that is monovalent for each epitope, but is bivalent with respect to the antigen (*e.g.*, DR5). In certain embodiments the epitopes are the same epitope (*e.g.*, the same VL Domain CDRs and VH Domain CDRs are used on each chain) resulting in a monospecific molecule that is bivalent.

[0046] **Figure 2** provides a schematic of a representative covalently bonded diabody molecule having two epitope binding sites composed of two polypeptide chains, each having a CH2 and CH3 Domain, such that the associated chains form an Fc Region that comprises all or part of a naturally occurring Fc Region. VL and VH Domains that recognize the same epitope are shown using the same shading. In certain embodiments, the epitopes are different epitopes of the same antigen resulting in a

What Is Claimed Is:

Claim 1. A multivalent DR5-Binding Molecule that is a bispecific binding molecule, capable of simultaneously binding to two different epitopes of human Death Receptor 5 (DR5), wherein said multivalent DR5-Binding Molecule comprises four antigen-binding domains each capable of binding human DR5.

Claim 2. A multivalent DR5-Binding Molecule that is a monospecific binding molecule, capable of binding to an epitope of human DR5, wherein said multivalent DR5-Binding Molecule comprises four antigen-binding domains each capable of binding human DR5.

Claim 3. The multivalent DR5-Binding Molecule of claim 1 or 2, wherein said multivalent DR5-Binding Molecule is capable of simultaneously binding to two, three, or four human DR5 polypeptides.

Claim 4. The multivalent DR5-Binding Molecule of any one of claims 1-3, wherein said multivalent DR5-Binding Molecule is an Fc Region-containing diabody, said diabody being a covalently bonded complex that comprises two pairs of polypeptides, wherein each pair comprises a first polypeptide chain and a second polypeptide chain.

Claim 5. The multivalent DR5-Binding Molecule of claim 4, wherein:

(A) the first polypeptide chain comprises, in the N-terminal to C-terminal direction:

(i) a variable light chain (VL) Domain of a monoclonal antibody capable of binding to a first DR5 epitope (VL1);

(ii) a first peptide linker (Linker 1);

(iii) a variable heavy chain (VH) Domain of a monoclonal antibody capable of binding to a second DR5 epitope (VH2);

(iv) a second peptide linker (Linker 2);

(v) a Heterodimer-Promoting Domain comprising a E-coil Domain or a K-coil Domain;

(vi) a third peptide linker (Linker 3); and

(vii) a polypeptide portion of an IgG Fc Region having CH2 and CH3 domains of an IgG immunoglobulin Fc Region; and

(B) the second polypeptide chain comprises, in the N-terminal to C-terminal direction:

(i) a VL Domain of a monoclonal antibody capable of binding to said second DR5 epitope (VL2);

(ii) a first peptide linker (Linker 1);

(iii) a VH Domain of a monoclonal antibody capable of binding to said first DR5 epitope (VH1);

(iv) a second peptide linker (Linker 2); and

(v) a Heterodimer-Promoting Domain comprising a E-coil Domain or a K-coil Domain, wherein said Heterodimer-Promoting Domain of said first polypeptide chain and said Heterodimer-Promoting Domain of said second polypeptide chain are not both E-coil Domains or both K-coil Domains;

and wherein:

(a) the VL1 Domain of said first polypeptide chain and the VH1 Domain of said second polypeptide chain form an Antigen-Binding Domain capable of specific binding to a first epitope of DR5;

(b) said VH2 Domain of said first polypeptide chain and said VL1 Domain of said second polypeptide chain form an Antigen-Binding Domain capable of specific binding to a second epitope of DR5; and

(c) the CH2-CH3 portions of the pair of first polypeptide chains form an IgG Fc Region.

Claim 6. The multivalent DR5-Binding Molecule of claim 5, wherein said VL1 comprises a CDR_L1 Domain, a CDR_L2 Domain, and a CDR_L3 Domain, and said VH1 comprises a CDR_H1 Domain, a CDR_H2 Domain and a CDR_H3 Domain, wherein:

(i) said CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of DR5 mAb 1, and respectively have the amino acid sequences: **SEQ ID NO:4**, **SEQ ID NO:5**, and **SEQ ID NO:6**, and said CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of DR5 mAb 1, and respectively have the amino acid sequences: **SEQ ID NO:9**, **SEQ ID NO:10**, and **SEQ ID NO:11**; or

(ii) said CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of DR5 mAb 2, and, respectively have the amino acid sequences: **SEQ ID NO:14**, **SEQ ID NO:15**, and **SEQ ID NO:16**, and said CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of DR5 mAb 2, and respectively have the amino acid sequences: **SEQ ID NO:19**, **SEQ ID NO:20**, and **SEQ ID NO:21**; or

(iii) said CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of hDR5 mAb 2 VL-3, and, respectively have the amino acid sequences: **SEQ ID NO:165**, **SEQ ID NO:15**, and **SEQ ID NO:16**, and said CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of hDR5 mAb 2 VH-3, and respectively have the amino acid sequences: **SEQ ID NO:19**, **SEQ ID NO:20**, and **SEQ ID NO:21**; or

(iv) said CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of DR5 mAb 3, and, respectively have the amino acid sequences: **SEQ ID NO:55**, **SEQ ID NO:56**, and **SEQ ID NO:57**, and said CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of DR5 mAb 3, and

respectively have the amino acid sequences: **SEQ ID NO:59**, **SEQ ID NO:60**, and **SEQ ID NO:61**; or

(v) said CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of DR5 mAb 4, and, respectively have the amino acid sequences: **SEQ ID NO:63**, **SEQ ID NO:64**, and **SEQ ID NO:65**, and said CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of DR5 mAb 4, and respectively have the amino acid sequences: **SEQ ID NO:67**, **SEQ ID NO:68**, and **SEQ ID NO:69**; or

(vi) said CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of DR5 mAb 5, and, respectively have the amino acid sequences: **SEQ ID NO:71**, **SEQ ID NO:72**, and **SEQ ID NO:73**, and said CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of DR5 mAb 5, and respectively have the amino acid sequences: **SEQ ID NO:75**, **SEQ ID NO:76**, and **SEQ ID NO:77**; or

(vii) said CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of DR5 mAb 6, and, respectively have the amino acid sequences: **SEQ ID NO:79**, **SEQ ID NO:80**, and **SEQ ID NO:81**, and said CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of DR5 mAb 6, and respectively have the amino acid sequences: **SEQ ID NO:83**, **SEQ ID NO:84**, and **SEQ ID NO:85**; or

(viii) said CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of DR5 mAb 7, and, respectively have the amino acid sequences: **SEQ ID NO:87**, **SEQ ID NO:88**, and **SEQ ID NO:89**, and said CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of DR5 mAb 7, and respectively have the amino acid sequences: **SEQ ID NO:91**, **SEQ ID NO:92**, and **SEQ ID NO:93**; or

(ix) said CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of DR5 mAb 8, and, respectively have the

amino acid sequences: **SEQ ID NO:95**, **SEQ ID NO:96**, and **SEQ ID NO:97**, and said CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of DR5 mAb 8, and respectively have the amino acid sequences: **SEQ ID NO:99**, **SEQ ID NO:100**, and **SEQ ID NO:101.**

Claim 7. The multivalent DR5-Binding Molecule of claim 5 or 6, wherein said VL2 comprises a CDR_L1 Domain, a CDR_L2 Domain, and a CDR_L3 Domain, and said VH2 comprises a CDR_H1 Domain, a CDR_H2 Domain and a CDR_H3 Domain, wherein:

(i) said CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of DR5 mAb 1, and respectively have the amino acid sequences: **SEQ ID NO:4**, **SEQ ID NO:5**, and **SEQ ID NO:6**, and said CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of DR5 mAb 1, and respectively have the amino acid sequences: **SEQ ID NO:9**, **SEQ ID NO:10**, and **SEQ ID NO:11**; or

(ii) said CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of DR5 mAb 2, and, respectively have the amino acid sequences: **SEQ ID NO:14**, **SEQ ID NO:15**, and **SEQ ID NO:16**, and said CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of DR5 mAb 2, and respectively have the amino acid sequences: **SEQ ID NO:19**, **SEQ ID NO:20**, and **SEQ ID NO:21**; or

(iii) said CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of DR5 mAb 2, and, respectively have the amino acid sequences: **SEQ ID NO:165**, **SEQ ID NO:15**, and **SEQ ID NO:16**, and said CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of DR5 mAb 2, and respectively have the amino acid sequences: **SEQ ID NO:19**, **SEQ ID NO:20**, and **SEQ ID NO:21**; or

(iv) said CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of DR5 mAb 3, and, respectively have the

amino acid sequences: **SEQ ID NO:55**, **SEQ ID NO:56**, and **SEQ ID NO:57**, and said CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of DR5 mAb 3, and respectively have the amino acid sequences: **SEQ ID NO:59**, **SEQ ID NO:60**, and **SEQ ID NO:61**; or

(v) said CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of DR5 mAb 4, and, respectively have the amino acid sequences: **SEQ ID NO:63**, **SEQ ID NO:64**, and **SEQ ID NO:65**, and said CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of DR5 mAb 4, and respectively have the amino acid sequences: **SEQ ID NO:67**, **SEQ ID NO:68**, and **SEQ ID NO:69**; or

(vi) said CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of DR5 mAb 5, and, respectively have the amino acid sequences: **SEQ ID NO:71**, **SEQ ID NO:72**, and **SEQ ID NO:73**, and said CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of DR5 mAb 5, and respectively have the amino acid sequences: **SEQ ID NO:75**, **SEQ ID NO:76**, and **SEQ ID NO:77**; or

(vii) said CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of DR5 mAb 6, and, respectively have the amino acid sequences: **SEQ ID NO:79**, **SEQ ID NO:80**, and **SEQ ID NO:81**, and said CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of DR5 mAb 6, and respectively have the amino acid sequences: **SEQ ID NO:83**, **SEQ ID NO:84**, and **SEQ ID NO:85**; or

(viii) said CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of DR5 mAb 7, and, respectively have the amino acid sequences: **SEQ ID NO:87**, **SEQ ID NO:88**, and **SEQ ID NO:89**, and said CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of DR5 mAb 7, and

respectively have the amino acid sequences: **SEQ ID NO:91**, **SEQ ID NO:92**, and **SEQ ID NO:93**; or

(ix) said CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of DR5 mAb 8, and, respectively have the amino acid sequences: **SEQ ID NO:95**, **SEQ ID NO:96**, and **SEQ ID NO:97**, and said CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of DR5 mAb 8, and respectively have the amino acid sequences: **SEQ ID NO:99**, **SEQ ID NO:100**, and **SEQ ID NO:101.**

Claim 8. The multivalent DR5-Binding Molecule of claim 7, wherein said VL1 and said VL2 comprise the same CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain, and wherein said VH1 and said VH2 comprise the same CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain.

Claim 9. The multivalent DR5-Binding Molecule of claim 8, wherein said CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of DR5 mAb 1, and respectively have the amino acid sequences: **SEQ ID NO:4**, **SEQ ID NO:5**, and **SEQ ID NO:6**, and said CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of DR5 mAb 1, and respectively have the amino acid sequences: **SEQ ID NO:9**, **SEQ ID NO:10**, and **SEQ ID NO:11**.

Claim 10. The multivalent DR5-Binding Molecule of claim 8, wherein said CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of DR5 mAb 2, and, respectively have the amino acid sequences: **SEQ ID NO:14**, **SEQ ID NO:15**, and **SEQ ID NO:16**, and said CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of DR5 mAb 2, and respectively have the amino acid sequences: **SEQ ID NO:19**, **SEQ ID NO:20**, and **SEQ ID NO:21**.

Claim 11. The multivalent DR5-Binding Molecule of claim 8, wherein said CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of hDR5 mAb 2, and, respectively have the amino acid

sequences: **SEQ ID NO:165**, **SEQ ID NO:15**, and **SEQ ID NO:16**, and said CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of DR5 mAb 2, and respectively have the amino acid sequences: **SEQ ID NO:19**, **SEQ ID NO:20**, and **SEQ ID NO:21**.

Claim 12. The multivalent DR5-Binding Molecule of claim 7, wherein said VL1 and said VL2 do not comprise the same CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain, and wherein said VH1 and said VH2 do not comprise the same CDR_H1 Domain, CDR_H2 Domain, CDR_H3 Domain.

Claim 13. The multivalent DR5-Binding Molecule of claim 12, wherein:

(i) said CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain of VL1 are the Light Chain CDRs of DR5 mAb 1, and respectively have the amino acid sequences: **SEQ ID NO:4**, **SEQ ID NO:5**, and **SEQ ID NO:6**, and said CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain of VH1 are the Heavy Chain CDRs of DR5 mAb 1, and respectively have the amino acid sequences: **SEQ ID NO:9**, **SEQ ID NO:10**, and **SEQ ID NO:11**; and

(ii) said CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain of VL2 are the Light Chain CDRs of DR5 mAb 2 or hDR5 mAb2, and, respectively have the amino acid sequences: **SEQ ID NO:14 or 165**, **SEQ ID NO:15**, and **SEQ ID NO:16**, and said CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain of VH2 are the Heavy Chain CDRs of DR5 mAb 2, and respectively have the amino acid sequences: **SEQ ID NO:19**, **SEQ ID NO:20**, and **SEQ ID NO:21**.

Claim 14. The multivalent DR5-Binding Molecule of claim 12, wherein:

(i) said CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain of VL1 are the Light Chain CDRs of DR5 mAb 2 or hDR5 mAb2, and, respectively have the amino acid sequences: **SEQ ID NO:14 or 165**, **SEQ ID NO:15**, and **SEQ ID NO:16**, and said CDR_H1 Domain, CDR_H2

Claim 17. The multivalent DR5-Binding Molecule of claim 16, wherein said VL1 and said VL2 have the same amino acid sequence, and wherein said VH1 and said VH2 have the same amino acid sequence.

Claim 18. The multivalent DR5-Binding Molecule of claim 16, wherein said VL1 and said VL2 do not have the same amino acid sequence, and wherein said VH1 and said VH2 do not have the same amino acid sequence.

Claim 19. The multivalent DR5-Binding Molecule of any one of claims 5-18, wherein:

(i) said Linker 1 has the amino acid sequence of **SEQ ID NO:33**,

(ii) said Linker 1 has the amino acid sequence of **SEQ ID NO:47**,

(iii) said E-coil Domain has the amino acid sequence of SEQ ID NO: **SEQ ID NO:41**,

(iv) said K-coil Domain has the amino acid sequence of **SEQ ID NO:42**,

(v) said Linker 3 has the amino acid sequence of **SEQ ID NO:51**, and

(vi) said CH2-CH3 domain has the amino acid sequence of **SEQ ID NO:1 or SEQ ID NO:102**, wherein the C-terminal residue is optionally included.

Claim 20. The multivalent DR5-Binding Molecule of any one of claims 4-19, wherein said Fc Region comprises one or more amino acid modifications that reduce the affinity of the variant Fc Region for an FcγR or stabilizes said Fc Region.

Claim 21. The multivalent DR5-Binding Molecule of claim 20, wherein said modifications comprise the substitution of L234A; L235A; or L234A and L235A.

Claim 22. The multivalent DR5-Binding Molecule of claim 5, wherein:

(i) said first polypeptide chain has the amino acid sequence of **SEQ ID NO:116** or **SEQ ID NO:120**, and said second polypeptide chain has the amino acid sequence of **SEQ ID NO:118**; or

(ii) said first polypeptide chain has the amino acid sequence of **SEQ ID NO:122** or **SEQ ID NO:126**, and said second polypeptide chain has the amino acid sequence of **SEQ ID NO:124**; or

(iii) said first polypeptide chain has the amino acid sequence of **SEQ ID NO:128** or **SEQ ID NO:132**, and said second polypeptide chain has the amino acid sequence of **SEQ ID NO:130**; or

(iv) said first polypeptide chain has the amino acid sequence of **SEQ ID NO:134** or **SEQ ID NO:138**, and said second polypeptide chain has the amino acid sequence of **SEQ ID NO:136**; or

(v) said first polypeptide chain has the amino acid sequence of **SEQ ID NO:140** or **SEQ ID NO:144**, and said second polypeptide chain has the amino acid sequence of **SEQ ID NO:142**; or

(vi) said first polypeptide chain has the amino acid sequence of **SEQ ID NO:146** or **SEQ ID NO:150**, and said second polypeptide chain has the amino acid sequence of **SEQ ID NO:148**; or

(vii) said first polypeptide chain has the amino acid sequence of **SEQ ID NO:152** or **SEQ ID NO:156**, and said second polypeptide chain has the amino acid sequence of **SEQ ID NO:154**; or

(vi) said first polypeptide chain has the amino acid sequence of **SEQ ID NO:158** or **SEQ ID NO:162**, and said second polypeptide chain has the amino acid sequence of **SEQ ID NO:160**.

Claim 23. A composition comprising the multivalent DR5-Binding Molecule of any one of claims 1-22 and an excipient.

Claim 24. The composition of claim 23, further comprising a histone deacetylase inhibitor.

Claim 25. Use of the multivalent DR5-Binding Molecule of any one of claims 1-22, or the composition of any one of claims 23-24, in the manufacture of a medicament for promoting cell death by exposing said cell to said molecule.

Claim 26. The use of claim 25, wherein said cell is a tumor cell.

Claim 27. The use of claim 25, wherein said tumor cell is a cancer stem cell-like cell.

Claim 28. The use of claim 25, 26, or 27, wherein said cell is additionally exposed to a histone deacetylase inhibitor.

Claim 29. Use of the multivalent DR5-Binding Molecule of any one of claims 1-22, or the composition of any one of claims 23-24, in the manufacture of a medicament for the treatment of cancer.

Claim 30. The use of claim 29, wherein said medicament is used in combination with a histone deacetylase inhibitor.

Claim 31. Use of the multivalent DR5-Binding Molecule of any one of claims 1-22, or the composition of any one of claims 23-24, in the manufacture of a medicament for the diagnosis or prognosis of cancer, wherein said molecule is detectably labeled.

Claim 32. The use of any of claims 29-31, wherein said cancer is characterized by the presence of a cancer cell selected from the group consisting of a cell of: an adrenal gland tumor, an AIDS-associated cancer, an alveolar soft part sarcoma, an astrocytic tumor, bladder cancer, bone cancer, a brain and spinal cord cancer, a metastatic brain tumor, a breast cancer, a carotid body tumors, a cervical cancer, a chondrosarcoma, a chordoma, a chromophobe renal cell carcinoma, a clear cell carcinoma, a colon cancer, a colorectal cancer, a cutaneous benign fibrous histiocytoma, a desmoplastic small round cell tumor, an ependymoma, a Ewing's tumor, an extraskeletal myxoid chondrosarcoma, a fibrogenesis imperfecta ossium, a fibrous dysplasia of the bone, a gallbladder or bile duct cancer, gastric cancer, a gestational trophoblastic disease, a germ cell tumor, a head and neck cancer, hepatocellular carcinoma, an islet cell tumor, a Kaposi's Sarcoma, a kidney cancer, a leukemia, a lipoma/benign lipomatous tumor, a liposarcoma/malignant lipomatous tumor, a liver cancer, a lymphoma, a lung cancer, a medulloblastoma, a melanoma, a meningioma, a multiple endocrine neoplasia, a multiple myeloma, a myelodysplastic syndrome, a neuroblastoma, a neuroendocrine tumors, an ovarian cancer, a pancreatic cancer, a papillary thyroid carcinoma, a parathyroid tumor, a pediatric cancer, a peripheral nerve sheath tumor,

a phaeochromocytoma, a pituitary tumor, a prostate cancer, a posterious uveal melanoma, a rare hematologic disorder, a renal metastatic cancer, a rhabdoid tumor, a rhabdomysarcoma, a sarcoma, a skin cancer, a soft-tissue sarcoma, a squamous cell cancer, a stomach cancer, a synovial sarcoma, a testicular cancer, a thymic carcinoma, a thymoma, a thyroid metastatic cancer, and a uterine cancer.

Claim 33. The use of any of claims 29-31, wherein said cancer is colorectal cancer, hepatocellular carcinoma, glioma, kidney cancer, breast cancer, multiple myeloma, bladder cancer, neuroblastoma; sarcoma, non-Hodgkin's lymphoma, non-small cell lung cancer, ovarian cancer, pancreatic cancer or a rectal cancer.

Claim 34. The use of any of claims 29-31, wherein said cancer is acute myeloid leukemia (AML), chronic myelogenous leukemia (CML), acute B lymphoblastic leukemia (B-ALL), chronic lymphocytic leukemia (CLL), hairy cell leukemia (HCL), blastic plasmacytoid dendritic cell neoplasm (BPDCN), non-Hodgkin's lymphomas (NHL), including mantel cell leukemia (MCL), and small lymphocytic lymphoma (SLL), Hodgkin's lymphoma, systemic mastocytosis, or Burkitt's lymphoma.

Claim 35. A DR5-binding molecule having a VL Domain comprising a CDR_L1 Domain, a CDR_L2 Domain, and a CDR_L3 Domain, and a VH1 Domain comprising a CDR_H1 Domain, a CDR_H2 Domain and a CDR_H3 Domain, wherein:

(i) said CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of DR5 mAb 1, and respectively have the amino acid sequences: **SEQ ID NO:4**, **SEQ ID NO:5**, and **SEQ ID NO:6**, and said CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of DR5 mAb 1, and respectively have the amino acid sequences: **SEQ ID NO:9**, **SEQ ID NO:10**, and **SEQ ID NO:11**; or

(ii) said CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of DR5 mAb 2, and, respectively have the amino acid sequences: **SEQ ID NO:14**, **SEQ ID NO:15**, and **SEQ ID NO:16**, and said CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of DR5 mAb 2, and respectively have the amino acid sequences: **SEQ ID NO:19**, **SEQ ID NO:20**, and **SEQ ID NO:21**; or

(iii) said CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of hDR5 mAb 2 VL-3, and, respectively have the amino acid sequences: **SEQ ID NO: 165**, **SEQ ID NO:15**, and **SEQ ID NO:16**, and said CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain are the Heavy Chain CDRs of hDR5 mAb 2 VH-3, and respectively have the amino acid sequences: **SEQ ID NO:19**, **SEQ ID NO:20**, and **SEQ ID NO:21**.

Claim 36. A composition comprising the DR5-Binding Molecule of claim 35 and an excipient.