

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, and wherein at least one of said antigen-binding domains comprises three Light Chain CDR Domains (CDR_L1, CDR_L2 and CDR_L3) and three Heavy Chain CDR Domains (CDR_H1, CDR_H2 and CDR_H3) wherein: (i) said CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of DR5 mAb 1, and respectively comprise the amino acid sequences of 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 comprise the amino acid sequences of 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 or hDR5 mAb 2 VL-3, and, respectively comprise the amino acid sequences of 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 are the Heavy Chain CDRs of DR5 mAb 2, and respectively comprise the amino acid sequences of SEQ ID NO:19, SEQ ID NO:20, and SEQ ID NO:21. 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, and wherein said antigen-binding domains comprise three Light Chain CDR Domains (CDR_L1, CDR_L2 and CDR_L3) and three Heavy Chain CDR Domains (CDR_H1, CDR_H2 and CDR_H3) wherein: (i) said CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of DR5 mAb 1, and respectively comprise the amino acid sequences of 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 comprise the amino acid sequences of 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 or hDR5 mAb 2 VL-3, and, respectively comprise the amino acid sequences of 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 are the Heavy Chain CDRs of DR5 mAb 2, and respectively comprise the amino acid sequences of SEQ ID NO:19, SEQ ID NO:20, and SEQ ID NO:21. 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:

- (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 comprise 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 comprise 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 comprise 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 comprise 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 comprise 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 comprise 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 the treatment of cancer by 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

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, and wherein at least one of said antigen-binding domains comprises three Light Chain CDR Domains (CDR_L1, CDR_L2 and CDR_L3) and three Heavy Chain CDR Domains (CDR_H1, CDR_H2 and CDR_H3) wherein:
- (i) said CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of DR5 mAb 1, and respectively comprise the amino acid sequences of 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 comprise the amino acid sequences of 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 or hDR5 mAb 2 VL-3, and, respectively comprise the amino acid sequences of 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 are the Heavy Chain CDRs of DR5 mAb 2, and respectively comprise the amino acid sequences of SEQ ID NO:19, SEQ ID NO:20, and SEQ ID NO:21.
- 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, and wherein said antigen-binding domains comprise three Light Chain CDR

Domains (CDR_L1, CDR_L2 and CDR_L3) and three Heavy Chain CDR Domains (CDR_H1, CDR_H2 and CDR_H3) wherein:

- (i) said CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain are the Light Chain CDRs of DR5 mAb 1, and respectively comprise the amino acid sequences of 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 comprise the amino acid sequences of 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 or hDR5 mAb 2 VL-3, and, respectively comprise the amino acid sequences of 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 are the Heavy Chain CDRs of DR5 mAb 2, and respectively comprise the amino acid sequences of SEQ ID NO:19, SEQ ID NO:20, and SEQ ID NO:21.

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 VL2 comprises the CDR_{L1} Domain, CDR_{L2} Domain, and CDR_{L3} Domain of DR5 mAb 1, respectively comprising the amino acid sequences of SEQ ID NO:4, SEQ ID NO:5, and SEQ ID NO:6, and said VH2 comprises the CDR_{H1} Domain, CDR_{H2} Domain, and CDR_{H3} Domain of DR5 mAb 1, respectively comprising the amino acid sequences of SEQ ID NO:9, SEQ ID NO:10, and SEQ ID NO:11, and 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 of said VL1 are the Light Chain CDRs of DR5 mAb 1, and respectively comprise 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 said VH1 are the Heavy Chain CDRs of DR5 mAb 1, and respectively comprise 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 of said VL1 are the Light Chain CDRs of DR5 mAb 2, and, respectively comprise 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 of said VH1 are the Heavy Chain CDRs of DR5 mAb 2, and respectively comprise 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 of said VL1 are the Light Chain CDRs of hDR5 mAb 2 VL-3, and, respectively comprise 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 of said VH1 are the Heavy Chain CDRs of hDR5 mAb 2 VH-3, and respectively comprise 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 of said VL1 are the Light Chain CDRs of DR5 mAb 3, and, respectively comprise 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 of said VH1 are the Heavy Chain CDRs of DR5 mAb 3, and respectively comprise 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 of said VL1 are the Light Chain CDRs of DR5 mAb 4, and, respectively comprise 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 of said VH1 are the Heavy Chain CDRs of DR5 mAb 4, and respectively comprise 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 of said VL1 are the Light Chain CDRs of DR5 mAb 5, and, respectively comprise 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 of said VH1 are the Heavy Chain CDRs of DR5 mAb 5, and respectively comprise 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 of said VL1 are the Light Chain CDRs of DR5 mAb 6, and, respectively comprise 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 of said VH1 are the Heavy Chain CDRs of DR5 mAb 6, and respectively comprise 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 of said VL1 are the Light Chain CDRs of DR5 mAb 7, and, respectively comprise 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 of said VH1 are the Heavy Chain CDRs of DR5 mAb 7, and respectively comprise 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 of said VL1 are the Light Chain CDRs of DR5 mAb 8, and, respectively comprise 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 of said VH1 are the Heavy Chain CDRs of DR5 mAb 8, and respectively comprise 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, wherein said VL2 comprises the CDR_{L1} Domain, CDR_{L2} Domain, and CDR_{L3} Domain of DR5 mAb 2 or hDR5 mAb 2 VL-3, respectively comprising the

amino acid sequences: **SEQ ID NO:14** or **165**, **SEQ ID NO:15**, and **SEQ ID NO:16**, and said VH2 comprises the CDR_{H1} Domain, CDR_{H2} Domain, and CDR_{H3} Domain of DR5 mAb 2, respectively comprising the amino acid sequences: **SEQ ID NO:19**, **SEQ ID NO:20**, and **SEQ ID NO:21**, and 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 of **said VL1** are the Light Chain CDRs of DR5 mAb 1, and respectively comprise 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 **said VH1** are the Heavy Chain CDRs of DR5 mAb 1, and respectively comprise 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 of **said VL1** are the Light Chain CDRs of DR5 mAb 2, and, respectively comprise 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 of **said VH1** are the Heavy Chain CDRs of DR5 mAb 2, and respectively comprise 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 of **said VL1** are the Light Chain CDRs of hDR5 mAb 2 VL-3, and, respectively comprise 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 of **said VH1** are the Heavy Chain CDRs of hDR5 mAb 2 VH-3, and respectively comprise 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 of **said VL1** are the Light Chain CDRs of DR5 mAb **3**, and, respectively comprise 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 of **said VH1** are the Heavy Chain CDRs of DR5 mAb **3**, and respectively comprise 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 of **said VL1** are the Light Chain CDRs of DR5 mAb **4**, and, respectively comprise 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 of **said VH1** are the Heavy Chain CDRs of DR5 mAb **4**, and respectively comprise 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 of **said VL1** are the Light Chain CDRs of DR5 mAb **5**, and, respectively comprise 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 of **said VH1** are the Heavy Chain CDRs of DR5 mAb **5**, and respectively comprise 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 of **said VL1** are the Light Chain CDRs of DR5 mAb **6**, and, respectively comprise 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 of **said VH1** are the Heavy Chain CDRs of DR5 mAb **6**, and respectively comprise 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 of **said VL1** are the Light Chain CDRs of DR5 mAb 7, and, respectively comprise 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 of **said VH1** are the Heavy Chain CDRs of DR5 mAb 7, and respectively comprise 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 of **said VL1** are the Light Chain CDRs of DR5 mAb 8, and, respectively comprise 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 of **said VH1** are the Heavy Chain CDRs of DR5 mAb 8, and respectively comprise 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 5, wherein said VL1 comprises the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain of DR5 mAb 1, respectively comprising the amino acid sequences: SEQ ID NO:4, SEQ ID NO:5, and SEQ ID NO:6, and said VH1 comprises the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain of DR5 mAb 1, respectively comprising the amino acid sequences: SEQ ID NO:9, SEQ ID NO:10, and SEQ ID NO:11, and 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 of said VL2 are the Light Chain CDRs of DR5 mAb 1, and respectively comprise 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 said VH2 are the Heavy Chain CDRs of DR5 mAb 1, and respectively

comprise 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 of said VL2 are the Light Chain CDRs of DR5 mAb 2, and, respectively comprise 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 of said VH2 are the Heavy Chain CDRs of DR5 mAb 2, and respectively comprise 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 of said VL2 are the Light Chain CDRs of DR5 mAb 2, and, respectively comprise 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 of said VH2 are the Heavy Chain CDRs of DR5 mAb 2, and respectively comprise 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 of said VL2 are the Light Chain CDRs of DR5 mAb 3, and, respectively comprise 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 of said VH2 are the Heavy Chain CDRs of DR5 mAb 3, and respectively comprise 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 of said VL2 are the Light Chain CDRs of DR5 mAb 4, and, respectively comprise 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 of said VH2 are the Heavy Chain CDRs of DR5 mAb 4, and respectively

comprise 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 of said VL2 are the Light Chain CDRs of DR5 mAb 5, and, respectively comprise 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 of said VH2 are the Heavy Chain CDRs of DR5 mAb 5, and respectively comprise 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 of said VL2 are the Light Chain CDRs of DR5 mAb 6, and, respectively comprise 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 of said VH2 are the Heavy Chain CDRs of DR5 mAb 6, and respectively comprise 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 of said VL2 are the Light Chain CDRs of DR5 mAb 7, and, respectively comprise 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 of said VH2 are the Heavy Chain CDRs of DR5 mAb 7, and respectively comprise 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 of said VL2 are the Light Chain CDRs of DR5 mAb 8, and, respectively comprise 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 of said VH2 are the Heavy Chain CDRs of DR5 mAb 8, and respectively

comprise the amino acid sequences: **SEQ ID NO:99**, **SEQ ID NO:100**, and **SEQ ID NO:101**.

- Claim 9. The multivalent DR5-Binding Molecule of claim 5, wherein said VL1 comprises the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain of DR5 mAb 2 or hDR5 mAb 2 VL-3, respectively comprising the amino acid sequences: **SEQ ID NO:14** or **165**, **SEQ ID NO:5**, and **SEQ ID NO:6**, and said VH1 comprises the CDR_H1 Domain, CDR_H2 Domain, and CDR_H3 Domain of DR5 mAb 2, respectively comprising the amino acid sequences: **SEQ ID NO:9**, **SEQ ID NO:10**, and **SEQ ID NO:11**, and 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 of **said VL2** are the Light Chain CDRs of DR5 mAb 1, and respectively comprise 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 **said VH2** are the Heavy Chain CDRs of DR5 mAb 1, and respectively comprise 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 of **said VL2** are the Light Chain CDRs of DR5 mAb 2, and, respectively comprise 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 of **said VH2** are the Heavy Chain CDRs of DR5 mAb 2, and respectively comprise 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 of **said VL2** are the Light Chain CDRs of hDR5 mAb 2 VL-3, and, respectively comprise 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 of **said VH2** are the Heavy Chain CDRs of hDR5 mAb 2 VH-3, and respectively comprise 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 of **said VL2** are the Light Chain CDRs of DR5 mAb **3**, and, respectively comprise 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 of **said VH2** are the Heavy Chain CDRs of DR5 mAb **3**, and respectively comprise 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 of **said VL2** are the Light Chain CDRs of DR5 mAb **4**, and, respectively comprise 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 of **said VH2** are the Heavy Chain CDRs of DR5 mAb **4**, and respectively comprise 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 of **said VL2** are the Light Chain CDRs of DR5 mAb **5**, and, respectively comprise 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 of **said VH2** are the Heavy Chain CDRs of DR5 mAb **5**, and respectively comprise 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 of **said VL2** are the Light Chain CDRs of DR5 mAb **6**, and, respectively comprise 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 of said VH2 are the Heavy Chain CDRs of DR5 mAb 6, and respectively comprise 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 of said VL2 are the Light Chain CDRs of DR5 mAb 7, and, respectively comprise 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 of said VH2 are the Heavy Chain CDRs of DR5 mAb 7, and respectively comprise 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 of said VL2 are the Light Chain CDRs of DR5 mAb 8, and, respectively comprise 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 of said VH2 are the Heavy Chain CDRs of DR5 mAb 8, and respectively comprise the amino acid sequences: SEQ ID NO:99, SEQ ID NO:100, and SEQ ID NO:101.

Claim 10. The multivalent DR5-Binding Molecule of claim 7 or 8, 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 11. The multivalent DR5-Binding Molecule of claim 8, wherein said CDR_{L1} Domain, CDR_{L2} Domain, and CDR_{L3} Domain of said VL2 are the Light Chain CDRs of DR5 mAb 1, and respectively comprise 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 said VH2 are the Heavy Chain CDRs of DR5 mAb 1, and

respectively comprise the amino acid sequences: **SEQ ID NO:9**, **SEQ ID NO:10**, and **SEQ ID NO:11**.

Claim 12. The multivalent DR5-Binding Molecule of claim 8, wherein said CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain of said VL2 are the Light Chain CDRs of DR5 mAb 2 or hDR5 mAb 2 VL-3, and, respectively comprise 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 said VH2 are the Heavy Chain CDRs of DR5 mAb 2, and respectively comprise the amino acid sequences: **SEQ ID NO:19**, **SEQ ID NO:20**, and **SEQ ID NO:21**.

Claim 13. The multivalent DR5-Binding Molecule of any one of claims 7-10, 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 14. The multivalent DR5-Binding Molecule of claim 13, 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 comprise 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 comprise 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 comprise 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

comprise the amino acid sequences: **SEQ ID NO:19**, **SEQ ID NO:20**, and **SEQ ID NO:21**.

Claim 15. The multivalent DR5-Binding Molecule of claim 13, 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 comprise 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 VH1 are the Heavy Chain CDRs of DR5 mAb 2, and respectively comprise the amino acid sequences: **SEQ ID NO:19**, **SEQ ID NO:20**, and **SEQ ID NO:21**; and
- (ii) said CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain of VL2 are the Light Chain CDRs of DR5 mAb 1, and respectively comprise 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 VH2 are the Heavy Chain CDRs of DR5 mAb 1, and respectively comprise the amino acid sequences: **SEQ ID NO:9**, **SEQ ID NO:10**, and **SEQ ID NO:11**.

Claim 16. The multivalent DR5-Binding Molecule of claim 5, wherein said VL2 comprises the amino acid sequence of **SEQ ID NO:3** and said VH2 comprises the amino acid sequence of **SEQ ID NO:8**, and wherein:

- (i) said VL1 comprises the amino acid sequence of **SEQ ID NO:3**, and said VH1 comprises the amino acid sequence of **SEQ ID NO:8**; or
- (ii) said VL1 comprises the amino acid sequence of **SEQ ID NO:13**, and said VH1 comprises the amino acid sequence of **SEQ ID NO:18**; or
- (iii) said VL1 comprises the amino acid sequence of **SEQ ID NO:23**, and said VH1 comprises the amino acid sequence of **SEQ ID NO:31**; or

- (iv) said VL1 comprises the amino acid sequence of **SEQ ID NO:25**, and said VH1 comprises the amino acid sequence of **SEQ ID NO:31**; or
- (vi) said VL1 comprises the amino acid sequence of **SEQ ID NO:27**, and said VH1 comprises the amino acid sequence of **SEQ ID NO:31**; or
- (vii) said VL1 comprises the amino acid sequence of **SEQ ID NO:29**, and said VH1 comprises the amino acid sequence of **SEQ ID NO:31**; or
- (viii) said VL1 comprises the amino acid sequence of **SEQ ID NO:54**, and said VH1 comprises the amino acid sequence of **SEQ ID NO:58**; or
- (ix) said VL1 comprises the amino acid sequence of **SEQ ID NO:62**, and said VH1 comprises the amino acid sequence of **SEQ ID NO:66**; or
- (x) said VL1 comprises the amino acid sequence of **SEQ ID NO:70**, and said VH1 comprises the amino acid sequence of **SEQ ID NO:74**; or
- (xi) said VL1 comprises the amino acid sequence of **SEQ ID NO:78**, and said VH1 comprises the amino acid sequence of **SEQ ID NO:82**; or
- (xii) said VL1 comprises the amino acid sequence of **SEQ ID NO:86**, and said VH1 comprises the amino acid sequence of **SEQ ID NO:90**; or
- (xiii) said VL1 comprises the amino acid sequence of **SEQ ID NO:94**, and said VH1 comprises the amino acid sequence of **SEQ ID NO:98**.

Claim 17. The multivalent DR5-Binding Molecule of claim 5, wherein said VL2 comprises the amino acid sequence of **SEQ ID NO:13, 23, 25, 27, or 29** and said VH2 comprises the amino acid sequence of **SEQ ID NO:18, or 31**, and wherein:

- (i) said VL1 comprises the amino acid sequence of **SEQ ID NO:3**, and said VH1 comprises the amino acid sequence of **SEQ ID NO:8**; or
- (ii) said VL1 comprises the amino acid sequence of **SEQ ID NO:13**, and said VH1 comprises the amino acid sequence of **SEQ ID NO:18**; or
- (iii) said VL1 comprises the amino acid sequence of **SEQ ID NO:23**, and said VH1 comprises the amino acid sequence of **SEQ ID NO:31**; or
- (iv) said VL1 comprises the amino acid sequence of **SEQ ID NO:25**, and said VH1 comprises the amino acid sequence of **SEQ ID NO:31**; or
- (vi) said VL1 comprises the amino acid sequence of **SEQ ID NO:27**, and said VH1 comprises the amino acid sequence of **SEQ ID NO:31**; or
- (vii) said VL1 comprises the amino acid sequence of **SEQ ID NO:29**, and said VH1 comprises the amino acid sequence of **SEQ ID NO:31**; or
- (viii) said VL1 comprises the amino acid sequence of **SEQ ID NO:54**, and said VH1 comprises the amino acid sequence of **SEQ ID NO:58**; or
- (ix) said VL1 comprises the amino acid sequence of **SEQ ID NO:62**, and said VH1 comprises the amino acid sequence of **SEQ ID NO:66**; or
- (x) said VL1 comprises the amino acid sequence of **SEQ ID NO:70**, and said VH1 comprises the amino acid sequence of **SEQ ID NO:74**; or
- (xi) said VL1 comprises the amino acid sequence of **SEQ ID NO:78**, and said VH1 comprises the amino acid sequence of **SEQ ID NO:82**; or

- (xii) said VL1 comprises the amino acid sequence of **SEQ ID NO:86**, and said VH1 comprises the amino acid sequence of **SEQ ID NO:90**; or
- (xiii) said VL1 comprises the amino acid sequence of **SEQ ID NO:94**, and said VH1 comprises the amino acid sequence of **SEQ ID NO:98**.

Claim 18. The multivalent DR5-Binding Molecule of claim 5, wherein said VL1 comprises the amino acid sequence of SEQ ID NO:3 and said VH1 comprises the amino acid sequence of SEQ ID NO:8, and wherein:

- (i) said VL2 comprises the amino acid sequence of **SEQ ID NO:3**, and said VH2 comprises the amino acid sequence of **SEQ ID NO:8**; or
- (ii) said VL2 comprises the amino acid sequence of **SEQ ID NO:13**, and said VH2 comprises the amino acid sequence of **SEQ ID NO:18**; or
- (iii) said VL2 comprises the amino acid sequence of **SEQ ID NO:23**, and said VH2 comprises the amino acid sequence of **SEQ ID NO:31**; or
- (iv) said VL2 comprises the amino acid sequence of **SEQ ID NO:25**, and said VH2 comprises the amino acid sequence of **SEQ ID NO:31**; or
- (vi) said VL2 comprises the amino acid sequence of **SEQ ID NO:27**, and said VH2 comprises the amino acid sequence of **SEQ ID NO:31**; or
- (vii) said VL2 comprises the amino acid sequence of **SEQ ID NO:29**, and said VH2 comprises the amino acid sequence of **SEQ ID NO:31**; or
- (viii) said VL2 comprises the amino acid sequence of **SEQ ID NO:54**, and said VH2 comprises the amino acid sequence of **SEQ ID NO:58**; or

- (ix) said VL2 comprises the amino acid sequence of **SEQ ID NO:62**, and said VH2 comprises the amino acid sequence of **SEQ ID NO:66**; or
- (x) said VL2 comprises the amino acid sequence of **SEQ ID NO:70**, and said VH2 comprises the amino acid sequence of **SEQ ID NO:74**; or
- (xi) said VL2 comprises the amino acid sequence of **SEQ ID NO:78**, and said VH2 comprises the amino acid sequence of **SEQ ID NO:82**; or
- (xii) said VL2 comprises the amino acid sequence of **SEQ ID NO:86**, and said VH2 comprises the amino acid sequence of **SEQ ID NO:90**; or
- (xiii) said VL2 comprises the amino acid sequence of **SEQ ID NO:94**, and said VH2 comprises the amino acid sequence of **SEQ ID NO:98**.

Claim 19. The multivalent DR5-Binding Molecule of claim 5, wherein said VL1 comprises the amino acid sequence of **SEQ ID NO:13, 23, 25, 27, or 29** and said VH1 comprises the amino acid sequence of **SEQ ID NO:18, or 31**, and wherein:

- (i) said VL2 comprises the amino acid sequence of **SEQ ID NO:3**, and said VH2 comprises the amino acid sequence of **SEQ ID NO:8**; or
- (ii) said VL2 comprises the amino acid sequence of **SEQ ID NO:13**, and said VH2 comprises the amino acid sequence of **SEQ ID NO:18**; or
- (iii) said VL2 comprises the amino acid sequence of **SEQ ID NO:23**, and said VH2 comprises the amino acid sequence of **SEQ ID NO:31**; or
- (iv) said VL2 comprises the amino acid sequence of **SEQ ID NO:25**, and said VH2 comprises the amino acid sequence of **SEQ ID NO:31**; or

- (vi) said VL2 comprises the amino acid sequence of **SEQ ID NO:27**, and said VH2 comprises the amino acid sequence of **SEQ ID NO:31**; or
- (vii) said VL2 comprises the amino acid sequence of **SEQ ID NO:29**, and said VH2 comprises the amino acid sequence of **SEQ ID NO:31**; or
- (viii) said VL2 comprises the amino acid sequence of **SEQ ID NO:54**, and said VH2 comprises the amino acid sequence of **SEQ ID NO:58**; or
- (ix) said VL2 comprises the amino acid sequence of **SEQ ID NO:62**, and said VH2 comprises the amino acid sequence of **SEQ ID NO:66**; or
- (x) said VL2 comprises the amino acid sequence of **SEQ ID NO:70**, and said VH2 comprises the amino acid sequence of **SEQ ID NO:74**; or
- (xi) said VL2 comprises the amino acid sequence of **SEQ ID NO:78**, and said VH2 comprises the amino acid sequence of **SEQ ID NO:82**; or
- (xii) said VL2 comprises the amino acid sequence of **SEQ ID NO:86**, and said VH2 comprises the amino acid sequence of **SEQ ID NO:90**; or
- (xiii) said VL2 comprises the amino acid sequence of **SEQ ID NO:94**, and said VH2 comprises the amino acid sequence of **SEQ ID NO:98**.

Claim 20. The multivalent DR5-Binding Molecule of any one of claims 16-17, wherein said VL1 and said VL2 comprise the same amino acid sequence, and wherein said VH1 and said VH2 comprise the same amino acid sequence.

Claim 21. The multivalent DR5-Binding Molecule of any one of claims 16-19, wherein said VL1 and said VL2 do not comprise the same amino acid

sequence, and wherein said VH1 and said VH2 do not comprise the same amino acid sequence.

Claim 22. The multivalent DR5-Binding Molecule of any one of claims 5-21, wherein:

- (i) said Linker 1 comprises the amino acid sequence of **SEQ ID NO:33**,
- (ii) said Linker 1 comprises the amino acid sequence of **SEQ ID NO:47**,
- (iii) said E-coil Domain comprises the amino acid sequence of **SEQ ID NO: SEQ ID NO:41**,
- (iv) said K-coil Domain comprises the amino acid sequence of **SEQ ID NO:42**,
- (v) said Linker 3 comprises the amino acid sequence of **SEQ ID NO:51**, and
- (vi) said CH2-CH3 domain comprises the amino acid sequence of **SEQ ID NO:1 or SEQ ID NO:102**, wherein the C-terminal residue is optionally included.

Claim 23. The multivalent DR5-Binding Molecule of any one of claims 4-22, 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 24. The multivalent DR5-Binding Molecule of claim 23, wherein said modifications comprise the substitution of L234A; L235A; or L234A and L235A.

Claim 25. The multivalent DR5-Binding Molecule of claim 5, wherein:

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

- (ii) said first polypeptide chain comprises the amino acid sequence of **SEQ ID NO:122** or **SEQ ID NO:126**, and said second polypeptide chain comprises the amino acid sequence of **SEQ ID NO:124**; or
- (iii) said first polypeptide chain comprises the amino acid sequence of **SEQ ID NO:128** or **SEQ ID NO:132**, and said second polypeptide chain comprises the amino acid sequence of **SEQ ID NO:130**; or
- (iv) said first polypeptide chain comprises the amino acid sequence of **SEQ ID NO:134** or **SEQ ID NO:138**, and said second polypeptide chain comprises the amino acid sequence of **SEQ ID NO:136**; or
- (v) said first polypeptide chain comprises the amino acid sequence of **SEQ ID NO:140** or **SEQ ID NO:144**, and said second polypeptide chain comprises the amino acid sequence of **SEQ ID NO:142**; or
- (vi) said first polypeptide chain comprises the amino acid sequence of **SEQ ID NO:146** or **SEQ ID NO:150**, and said second polypeptide chain comprises the amino acid sequence of **SEQ ID NO:148**; or
- (vii) said first polypeptide chain comprises the amino acid sequence of **SEQ ID NO:152** or **SEQ ID NO:156**, and said second polypeptide chain comprises the amino acid sequence of **SEQ ID NO:154**; or
- (vi) said first polypeptide chain comprises the amino acid sequence of **SEQ ID NO:158** or **SEQ ID NO:162**, and said second polypeptide chain comprises the amino acid sequence of **SEQ ID NO:160**.

Claim 26. A composition comprising the multivalent DR5-Binding Molecule of any one of claims 1-25 and an excipient.

- Claim 27. The composition of claim 26, further comprising a histone deacetylase inhibitor.
- Claim 28. Use of the multivalent DR5-Binding Molecule of any one of claims 1-25, or the composition of any one of claims 26-27, in the manufacture of a medicament for the treatment of cancer by promoting cell death by exposing said cell to said molecule.
- Claim 29. The use of claim 28, wherein said cell is a tumor cell.
- Claim 30. The use of claim 28, wherein said tumor cell is a cancer stem cell-like cell.
- Claim 31. The use of any one of claims 28-30, wherein said cell is additionally exposed to a histone deacetylase inhibitor.
- Claim 32. Use of the multivalent DR5-Binding Molecule of any one of claims 1-25, or the composition of any one of claims 26-27, in the manufacture of a medicament for the treatment of cancer.
- Claim 33. The use of claim 32, wherein said medicament is used in combination with a histone deacetylase inhibitor.
- Claim 34. Use of the multivalent DR5-Binding Molecule of any one of claims 1-25, or the composition of any one of claims 26-27, in the manufacture of a medicament for the diagnosis or prognosis of cancer, wherein said molecule is detectably labeled.
- 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 comprise 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 comprise 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 comprise 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 comprise 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 comprise 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 comprise 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.