

is capable of immunospecifically binding to an Epitope II present on a second antigen, wherein the Antigen-Binding Domain I and the Antigen-Binding Domain II are both Diabody-Type Binding Domains;

- (II) an Antigen-Binding Domain III that is capable of immunospecifically binding to an Epitope III present on a third antigen; and
- (III) an Fc Domain that is formed by the complexing of two CH2-CH3 Domains to one another;

wherein one of Epitope I, Epitope II or Epitope III is an epitope of an Effector Cell Antigen, a second of Epitope I, Epitope II or Epitope III is an epitope of a first Cancer Antigen, and the third of Epitope I, Epitope II or Epitope III is an epitope of a second Cancer Antigen, and wherein the Antigen-Binding Domains I, II and III of the Binding Molecules mediate coordinated binding of an immune system effector cell expressing the Effector Cell Antigen and a cancer cell expressing the first and second Cancer Antigens.

[0041a] In one aspect, there is provided a Tri-Specific Binding Molecule capable of immunospecifically binding to three different epitopes, comprising:

- (I) four different polypeptide chains covalently complexed together;
- (II) an Antigen-Binding Domain I that is capable of immunospecifically binding to an Epitope I present on a first antigen, and an Antigen-Binding Domain II that is capable of immunospecifically binding to an Epitope II present on a second antigen;
- (III) an Antigen-Binding Domain III that is capable of immunospecifically binding to an Epitope III present on a third antigen; and
- (IV) a Fc Domain, wherein:
 - (A) one of Epitope I, Epitope II or Epitope III is an epitope of an Effector Cell Antigen, a second of Epitope I, Epitope II or Epitope III is an epitope of a first Cancer Antigen, and a third of Epitope I, Epitope II or Epitope III is an epitope of a second Cancer Antigen;

(B) a first polypeptide chain comprises, in the N-terminus to C-terminus direction:

(VL_I Domain)—(Linker 1)—(VH_{II} Domain)—(Linker 2)—(Heterodimer-Promoting Domain)—(Linker 3)—(CH2-CH3 Domain); or

(CH2-CH3 Domain)—(Linker 4)—(VL_I Domain)—(Linker 1)—(VH_{II} Domain)—(Linker 2)—(Heterodimer-Promoting Domain); or

(Cysteine-Containing Domain)—(CH2-CH3 Domain)—(Linker 4)—(VL_I Domain)—(Linker 1)—(VH_{II} Domain)—(Linker 2)—(Heterodimer-Promoting Domain);

(C) a second polypeptide chain comprises, in the N-terminus to C-terminus direction:

(VL_{II} Domain)—(Linker 1)—(VH_I Domain)—(Linker 2)—(Heterodimer-Promoting Domain);

(D) a third polypeptide chain comprises, in the N-terminus to C-terminus direction:

(VH_{III} Domain)—(Cysteine-Containing Domain)—(CH2-CH3 Domain);

(E) a fourth polypeptide chain comprises, in the N-terminus to C-terminus direction:

(VL_{III} Domain)—(Cysteine-Containing Domain);

(F) the VL_I Domain is a Light Chain Variable Domain of an immunoglobulin capable of binding to Epitope I, the VH_I Domain is a Heavy Chain Variable Domain of an immunoglobulin capable of binding to Epitope I, the VL_{II} Domain is a Light Chain Variable Domain of an immunoglobulin capable of binding to Epitope II, the VH_{II} Domain is a Heavy Chain Variable Domain of an immunoglobulin capable of binding to Epitope II, the VL_{III}

Domain is a Light Chain Variable Domain of an immunoglobulin capable of binding to Epitope III, and the VH_{III} Domain is a Heavy Chain Variable Domain of an immunoglobulin capable of binding to Epitope III: and

(G) the VL_I Domain and the VH_I Domain associate to form the Antigen-Binding Domain I, the VL_{II} Domain and the VH_{II} Domain associate to form the Antigen-Binding Domain II, the VL_{III} Domain and the VH_{III} Domain associate to form the Antigen-Binding Domain III, and the CH2-CH3 Domain of the first polypeptide chain and the CH2-CH3 Domain of the third polypeptide chain associate to form the Fc Domain.

[0041b] In another aspect, there is provided a Tri-Specific Binding Molecule capable of immunospecifically binding to three different epitopes, comprising:

(I) three different polypeptide chains covalently complexed together;

(II) an Antigen-Binding Domain I that is capable of immunospecifically binding to an Epitope I present on a first antigen, and an Antigen-Binding Domain II that is capable of immunospecifically binding to an Epitope II present on a second antigen;

(III) an Antigen-Binding Domain III that is capable of immunospecifically binding to an Epitope III present on a third antigen; and

(IV) a Fc Domain; wherein:

(A) one of Epitope I, Epitope II or Epitope III is an epitope of an Effector Cell Antigen, a second of Epitope I, Epitope II or Epitope III is an epitope of a first Cancer Antigen, and a third of Epitope I, Epitope II or Epitope III is an epitope of a second Cancer Antigen;

(B) a first polypeptide chain comprises, in the N-terminus to C-terminus direction:

(VL_I Domain)—(Linker 1)—(VH_{II} Domain)—(Linker 2)—(Heterodimer-Promoting Domain)—(Linker 3)—(CH2-CH3 Domain); or

(CH2-CH3 Domain)—(Linker 4)—(VL_I Domain)—(Linker 1)—(VH_{II} Domain)—(Linker 2)—(Heterodimer-Promoting Domain); or

(Cysteine-Containing Domain)—(CH2-CH3 Domain)—(Linker 4)—(VL_I Domain)—(Linker 1)—(VH_{II} Domain)—(Linker 2)—(Heterodimer-Promoting Domain);

(C) a second polypeptide chain comprises, in the N-terminus to C-terminus direction:

(VL_{II} Domain)—(Linker 1)—(VH_I Domain)—(Linker 2)—(Heterodimer-Promoting Domain);

(D) a third polypeptide chain comprises, in the N-terminus to C-terminus direction:

(VL_{III} Domain)—(Flexible Linker)—(VH_{III} Domain)—(Cysteine-Containing Domain)—(CH2-CH3 Domain); or

(Cysteine-Containing Domain 1)—(VL_{III} Domain)—(Flexible Linker)—(VH_{III} Domain)—(Cysteine-Containing Domain 2)—(Cysteine-Containing Domain)—(CH2-CH3 Domain);

(E) the VL_I Domain is a Light Chain Variable Domain of an immunoglobulin capable of binding to Epitope I, the VH_I Domain is a Heavy Chain Variable Domain of an immunoglobulin capable of binding to Epitope I, the VL_{II} Domain is a Light Chain Variable Domain of an immunoglobulin capable of binding to Epitope II, the VH_{II} Domain is a Heavy Chain Variable Domain of an immunoglobulin capable of binding to Epitope II, the VL_{III} Domain is a Light Chain Variable Domain of an immunoglobulin capable of binding to Epitope III, and the VH_{III} Domain is a Heavy Chain Variable Domain of an immunoglobulin capable of binding to Epitope III; and

(F) the VL_I Domain and the VH_I Domain associate to form the Antigen-Binding Domain I, the VL_{II} Domain and the VH_{II} Domain associate to form the Antigen-Binding Domain II, the VL_{III} Domain and the VH_{III}

Domain associate to form the Antigen-Binding Domain III, and the CH2-CH3 Domain of the first polypeptide chain and the CH2-CH3 Domain of the third polypeptide chain associate to form the Fc Domain.

[0042] The disclosure particularly concerns the embodiment of such Tri-Specific Binding Molecules wherein the Fc Domain is capable of binding to an Fc Receptor arrayed on the surface of a cell.

[0043] The disclosure additionally concerns the embodiment of such Tri-Specific Binding Molecules wherein the Effector Cell Antigen is arrayed on the surface of an effector cell and wherein the Cancer Antigens are arrayed on the surface of a cancer cell, and wherein the immunospecific binding is sufficient to co-localize the Effector Cell Antigen, and the Cancer Antigens, thereby facilitating the activation of the effector cell against the cancer cell.

[0044] The disclosure additionally concerns the embodiment of such Tri-Specific Binding Molecules wherein the Effector Cell Antigen is selected from the group consisting of: CD2, CD3, CD16, CD19, CD20, CD22, CD32B, CD64, the B cell Receptor (BCR), the T cell Receptor (TCR), and the NKG2D Receptor.

[0045] The disclosure additionally concerns the embodiment of such Tri-Specific Binding Molecules wherein the first and second Cancer Antigens are independently selected from the group consisting of: colon cancer antigen 19.9; a gastric cancer

[00118] **hDR5 mAb 2 VL-5** is preferably encoded by a polynucleotide (SEQ ID NO:30) having the sequence shown below:

```
gatattcaga tgacccagag tccctcattt ctgtccgcct ccgtcgggtga
ccgcgtgact attacttgtc gggcttctca ggatgtcaac accgcctggg
cttggtacca gcagaagccc ggtaaagcac ctaagctgct gatctattgg
gccagcactc ggcacaccgg agtcccagat aggttctctg gcagtggatc
agggacagac tttaccctga caattagctc cctgcagccc gaggatatcg
ctacttacta ttgtcagcag cactacatca ctccttggac cttcggcgagg
ggcacaaaac tggaaatcaa a
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[00119] The amino acid sequence of the VH Domain of **hDR5 mAb 2 VH-2** (SEQ ID NO:31) is shown below (CDR residues are shown underlined):

```
QVQLVQSGAE VKKPGASVKV SCKASGYTFT EYILHWVRQA PGQGLEWMGW
FYPGNNNIKY NEKFKDRVTI TADKSTSTVY MELSSLRSED TAVYYCARHE
QPGGYFDYWG QGTLVTVSS
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[00120] **hDR5 mAb 2 VH-2** is preferably encoded by a polynucleotide (SEQ ID NO:32) having the sequence shown below:

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caggtccagc tgggtgcagag tgggggcagag gtgaaaaagc caggggcatc
agtgaaagtg tcttgtaaag catcagggtta tacatttact gagtacatcc
tgactgggtg ggcacaggca ccaggacagg gactggaatg gatgggggtgg
ttctaccctg gcaacaacaa cattaagtac aacgagaagt ttaaagaccg
ggtgaccatc acagcggata agtctaccag tacagtctat atggagctga
gctccctgag aagcgaagac accgccgtct actattgcgc tcgccacgaa
caggggtccag gttactttga ttattggggg caggggaactc tggtcacagt
cagctcc
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[00121] The CDR1 of the VL Domain of **hDR5 mAb 2 VL-3**, **hDR5 mAb 2 VL-4** and **hDR5 mAb VL-5** has the amino acid sequence: **RASQDVNTAVA** (SEQ ID NO:320).

c. **Drozitumab ("DR5 mAb 3")**

[00122] The amino acid sequence of the VL Domain of **drozitumab ("DR5 mAb 3")** (SEQ ID NO:54) is shown below (CDR residues are shown underlined):

```
SELTQDPAVS VALGQTVRIT CSGDSLRSYY ASWYQQKPG QAPVLVIYGA
NNRPSGIPDR FSGSSSGNTA SLTITGAQAE DEADYYCNSA DSSGNHVVFG
GGTKLTVLG
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CDR_L1 of DR5 mAb 3 (SEQ ID NO:55): **SGDSLRSYYAS**

CDR_L2 of DR5 mAb 3 (SEQ ID NO:56): **GANNRPS**

CDR_L3 of DR5 mAb 3 (SEQ ID NO:57): **NSADSSGNHVV**

18;8(10):e77769; Barderas, R. *et al.* (2012) “High Expression Of IL-13 Receptor A2 In Colorectal Cancer Is Associated With Invasion, Liver Metastasis, And Poor Prognosis,” *Cancer Res.* 72(11):2780-2790; Kasaian, M.T. *et al.* (2011) “IL-13 Antibodies Influence IL-13 Clearance In Humans By Modulating Scavenger Activity Of IL-13R α 2,” *J. Immunol.* 187(1):561-569; Bozinov, O. *et al.* (2010) “Decreasing Expression Of The Interleukin-13 Receptor IL-13R α 2 In Treated Recurrent Malignant Gliomas,” *Neurol. Med. Chir. (Tokyo)* 50(8):617-621; Fujisawa, T. *et al.* (2009) “A novel role of interleukin-13 receptor alpha2 in pancreatic cancer invasion and metastasis,” *Cancer Res.* 69(22):8678-8685). Antibodies that immunospecifically bind to IL13R α 2 are commercially available (Abnova Corporation, Biorbyt, LifeSpan BioSciences, United States Biologicals; see also PCT Publication No. WO 2008/146911). The amino acid sequence of the Light Chain Variable Domain of an exemplary anti-IL13R α 2 antibody (“**hu08**,” PCT Publication No. WO 2014/072888) is shown below (CDR residues are shown underlined): (SEQ ID NO:321):

DIQMTQSPSS LSASVGDRVT ITCKASQDVG TAVAWYQQKP GKAPKLLIYS
ASYRSTGVPS RFGSGSGTD FTLTISSLQP EDFATYYCQH HYSAPWTFGG
 GTKVEIK

[00178] The amino acid sequence of the Heavy Chain Variable Domain of such exemplary anti-IL13R α 2 antibody (“**hu08**,” PCT Publication No. WO 2014/072888) is shown below (CDR residues are shown underlined): (SEQ ID NO:322):

EVQLVESGGG LVQPGGSLRL SCAASGFTFS RNGMSWVRQA PGKGLEWVAT
VSSGGSYIYY ADSVKGRFTI SRDNAKNSLY LQMNSLRAED TAVYYCARQG
TTALATRFFD VWGQGTLLTV SS

13. Integrin Beta6-Binding Domains

[00179] Integrin β 6 (**ITGB6**) is a subtype of integrin that is expressed exclusively on the surfaces of epithelial cells and is a receptor for extracellular matrix (ECM) proteins. ITGB6 expression is specifically expressed in tumor tissues (such as those of colon, prostate, kidney cancer), but is generally undetectable in healthy epithelial tissue (Liang, B. *et al.* (2014) “*Integrin β 6-targeted Immunoliposomes Mediate Tumor Specific Drug Delivery and Enhance Therapeutic Efficacy in Colon Carcinoma*,” *Clin. Cancer Res.* Dec 30. pii: clincanres.1194.2014). Monoclonal antibodies that immunospecifically bind to ITGB6 are available commercially (e.g., MAB2075Z clone R6G9, EMD Millipore; see also, Weinacker, A. *et al.* (1994) “*Role Of The*

What Is Claimed Is:

Claim 1. A Tri-Specific Binding Molecule capable of immunospecifically binding to three different epitopes, comprising:

(I) four different polypeptide chains covalently complexed together;

(II) an Antigen-Binding Domain I that is capable of immunospecifically binding to an Epitope I present on a first antigen, and an Antigen-Binding Domain II that is capable of immunospecifically binding to an Epitope II present on a second antigen;

(III) an Antigen-Binding Domain III that is capable of immunospecifically binding to an Epitope III present on a third antigen; and

(IV) a Fc Domain, wherein:

(A) one of Epitope I, Epitope II or Epitope III is an epitope of an Effector Cell Antigen, a second of Epitope I, Epitope II or Epitope III is an epitope of a first Cancer Antigen, and a third of Epitope I, Epitope II or Epitope III is an epitope of a second Cancer Antigen;

(B) a first polypeptide chain comprises, in the N-terminus to C-terminus direction:

(VL_I Domain)—(Linker 1)—(VH_{II} Domain)—(Linker 2)—
(Heterodimer-Promoting Domain)—(Linker 3)—(CH2-CH3 Domain);
or

(CH2-CH3 Domain)—(Linker 4)—(VL_I Domain)—(Linker 1)—(VH_{II} Domain)—(Linker 2)—(Heterodimer-Promoting Domain); or

(Cysteine-Containing Domain)—(CH2-CH3 Domain)—(Linker 4)—
(VL_I Domain)—(Linker 1)—(VH_{II} Domain)—(Linker 2)—
(Heterodimer-Promoting Domain);

(C) a second polypeptide chain comprises, in the N-terminus to C-terminus direction:

(VL_{II} Domain)—(Linker 1)—(VH_I Domain)—(Linker 2)—
(Heterodimer-Promoting Domain);

(D) a third polypeptide chain comprises, in the N-terminus to C-terminus direction:

(VH_{III} Domain)—(Cysteine-Containing Domain)—(CH2-CH3
Domain);

(E) a fourth polypeptide chain comprises, in the N-terminus to C-terminus direction:

(VL_{III} Domain)—(Cysteine-Containing Domain);

(F) the VL_I Domain is a Light Chain Variable Domain of an immunoglobulin capable of binding to Epitope I, the VH_I Domain is a Heavy Chain Variable Domain of an immunoglobulin capable of binding to Epitope I, the VL_{II} Domain is a Light Chain Variable Domain of an immunoglobulin capable of binding to Epitope II, the VH_{II} Domain is a Heavy Chain Variable Domain of an immunoglobulin capable of binding to Epitope II, the VL_{III} Domain is a Light Chain Variable Domain of an immunoglobulin capable of binding to Epitope III, and the VH_{III} Domain is a Heavy Chain Variable Domain of an immunoglobulin capable of binding to Epitope III: and

(G) the VL_I Domain and the VH_I Domain associate to form the Antigen-Binding Domain I, the VL_{II} Domain and the VH_{II} Domain associate to form the Antigen-Binding Domain II, the VL_{III} Domain and the VH_{III} Domain associate to form the Antigen-Binding Domain III, and the CH2-CH3 Domain of the first polypeptide chain and the CH2-CH3 Domain of the third polypeptide chain associate to form the Fc Domain.

Claim 2. The Tri-Specific Binding Molecule of claim 1, wherein the Cysteine-Containing Domain of the third polypeptide chain is chosen from a CH1 Domain and/or a Hinge Domain and the Cysteine-Containing Domain of the fourth polypeptide chain is a CL Domain.

Claim 3. The Tri-Specific Binding Molecule of claim 1 or claim 2, wherein (i) the first polypeptide chain and the second polypeptide chain are covalently bonded to one another; (ii) the first polypeptide chain and the third polypeptide chain are covalently bonded to one another; and (iii) the third polypeptide chain and the fourth polypeptide chain are covalently bonded to one another.

Claim 4. A Tri-Specific Binding Molecule capable of immunospecifically binding to three different epitopes, comprising:

(I) three different polypeptide chains covalently complexed together;

(II) an Antigen-Binding Domain I that is capable of immunospecifically binding to an Epitope I present on a first antigen, and an Antigen-Binding Domain II that is capable of immunospecifically binding to an Epitope II present on a second antigen;

(III) an Antigen-Binding Domain III that is capable of immunospecifically binding to an Epitope III present on a third antigen; and

(IV) a Fc Domain; wherein:

(A) one of Epitope I, Epitope II or Epitope III is an epitope of an Effector Cell Antigen, a second of Epitope I, Epitope II or Epitope III is an epitope of a first Cancer Antigen, and a third of Epitope I, Epitope II or Epitope III is an epitope of a second Cancer Antigen;

(B) a first polypeptide chain comprises, in the N-terminus to C-terminus direction:

(VL_I Domain)—(Linker 1)—(VH_{II} Domain)—(Linker 2)—
(Heterodimer-Promoting Domain)—(Linker 3)—(CH2-CH3 Domain);
or

(CH2-CH3 Domain)—(Linker 4)—(VL_I Domain)—(Linker 1)—(VH_{II} Domain)—(Linker 2)—(Heterodimer-Promoting Domain); or

(Cysteine-Containing Domain)—(CH2-CH3 Domain)—(Linker 4)—
(VL_I Domain)—(Linker 1)—(VH_{II} Domain)—(Linker 2)—
(Heterodimer-Promoting Domain);

(C) a second polypeptide chain comprises, in the N-terminus to C-terminus direction:

(VL_{II} Domain)—(Linker 1)—(VH_I Domain)—(Linker 2)—
(Heterodimer-Promoting Domain);

(D) a third polypeptide chain comprises, in the N-terminus to C-terminus direction:

(VL_{III} Domain)—(Flexible Linker)—(VH_{III} Domain)—(Cysteine-Containing Domain)—(CH2-CH3 Domain); or

(Cysteine-Containing Domain 1)—(VL_{III} Domain)—(Flexible Linker)—(VH_{III} Domain)—(Cysteine-Containing Domain 2)—
(Cysteine-Containing Domain)—(CH2-CH3 Domain);

(E) the VL_I Domain is a Light Chain Variable Domain of an immunoglobulin capable of binding to Epitope I, the VH_I Domain is a Heavy Chain Variable Domain of an immunoglobulin capable of binding to Epitope I, the VL_{II} Domain is a Light Chain Variable Domain of an immunoglobulin capable of binding to Epitope II, the VH_{II} Domain is a Heavy Chain Variable Domain of an immunoglobulin capable of binding to Epitope II, the VL_{III} Domain is a Light Chain Variable Domain of an immunoglobulin capable of binding to Epitope III, and the VH_{III} Domain is a Heavy Chain Variable Domain of an immunoglobulin capable of binding to Epitope III; and

(F) the VL_I Domain and the VH_I Domain associate to form the Antigen-Binding Domain I, the VL_{II} Domain and the VH_{II} Domain associate to form the Antigen-Binding Domain II, the VL_{III} Domain and the VH_{III} Domain associate to form the Antigen-Binding Domain III, and the CH2-CH3 Domain of the first polypeptide chain and the CH2-CH3 Domain of the third polypeptide chain associate to form the Fc Domain.

Claim 5. The Tri-Specific Binding Molecule of claim 4, wherein the Cysteine-Containing Domain 1 of the third polypeptide chain is a CL Domain and the Cysteine-Containing Domain 2 of the third polypeptide chain is chosen from a CH1 Domain and/or a Hinge Domain.

Claim 6. The Tri-Specific Binding Molecule of any one of claims 1-5, wherein:
the Linker 2 comprises a cysteine residue, or
the Heterodimer-Promoting Domain comprises a cysteine residue, or
the Linker 2 comprises a cysteine residue and the Heterodimer-Promoting Domain comprises a cysteine residue.

Claim 7. The Tri-Specific Binding Molecule of any one of claims 1-6, wherein:
the CH2-CH3 Domain of the first polypeptide chain is a knob-bearing CH2-CH3 Domain and the CH2-CH3 Domain of the third polypeptide chain is a hole-bearing CH2-CH3 Domain; or
the CH2-CH3 Domain of the third polypeptide chain is a knob-bearing CH2-CH3 Domain and the CH2-CH3 Domain of the first polypeptide chain is a hole-bearing CH2-CH3 Domain.

Claim 8. The Tri-Specific Binding Molecule of any one of claims 1-7, wherein the CH2-CH3 Domain of the first polypeptide chain and the third polypeptide chain independently comprises:

(A) one substitution selected from the group consisting of:

F243L, R292P, Y300L, V305I, and P396L;

(B) two substitutions selected from the group consisting of:

(1) F243L and P396L;

(2) F243L and R292P; and

(3) R292P and V305I;

(C) three substitutions selected from the group consisting of:

- (1) F243L, R292P and Y300L;
- (2) F243L, R292P and V305I;
- (3) F243L, R292P and P396L; and
- (4) R292P, V305I and P396L;

(D) four substitutions selected from the group consisting of:

- (1) F243L, R292P, Y300L and P396L; and
- (2) F243L, R292P, V305I and P396L; or

(E) five substitutions selected from the group consisting of:

- (1) F243L, R292P, Y300L, V305I and P396L; and
- (2) L235V, F243L, R292P, Y300L and P396L

Claim 9. The Tri-Specific Binding Molecule of any one of claims 1-8, wherein:

the Heterodimer-Promoting Domain on the first polypeptide chain is an E-coil Domain and the Heterodimer-Promoting Domain on the second polypeptide chain is a K-coil Domain; or

the Heterodimer-Promoting Domain on the first polypeptide chain is an K-coil Domain and the Heterodimer-Promoting Domain on the second polypeptide chain is a E-coil Domain.

Claim 10. The Tri-Specific Binding Molecule of any one of claims 1-9, wherein:

the Linker 1 comprises the sequence of SEQ ID NO: 33;

the Linker 2 comprises the sequence of SEQ ID NO: 34 or 47;

the Heterodimer-Promoting Domain comprises the sequence of SEQ ID NO: 35, 36, 37, 38, 39, 40, 41 or 42;

the Linker 3 comprises the sequence of SEQ ID NO: 46, 47, 48, 49, 50, 51, 152, or GCG or GGG;

the Linker 4 comprises the sequence of SEQ ID NO: 50 or 152;

the CH2-CH3 Domain comprises the sequence of SEQ ID NO: 52 or 53;

the CH1-Hinge Domain comprises the sequence of SEQ ID NO: 207, 208 or 209; or

the Cysteine-Containing Domain comprises the sequence of SEQ ID NO: 34, 36, 38, 48, 210 or 211.

Claim 11. The Tri-Specific Binding Molecule of claim 10, wherein the Heterodimer-Promoting Domain of SEQ ID NO: 41 or 42 is present when Linker 2 comprises the sequence of SEQ ID NO: 47, or the Heterodimer-Promoting Domain of SEQ ID NO: 39, 40, 41 or 42 is present when Linker 2 comprises the sequence of SEQ ID NO: 34.

Claim 12. The Tri-Specific Binding Molecule of any one of claims 1-11, wherein:

- (A) the Epitope I, Epitope II and Epitope III are, respectively, an epitope of the first Cancer Antigen, an epitope of the second Cancer Antigen and an epitope of the Effector Cell Antigen;
 - (B) the Epitope I, Epitope II and Epitope III are, respectively, an epitope of the first Cancer Antigen, an epitope of the Effector Cell Antigen and an epitope of the second Cancer Antigen;
 - (C) the Epitope I, Epitope II and Epitope III are, respectively, an epitope of second Cancer Antigen, an epitope of the first Cancer Antigen, and an epitope of the Effector Cell Antigen;
 - (D) the Epitope I, Epitope II and Epitope III are, respectively, an epitope of the second Cancer Antigen, an epitope of the Effector Cell Antigen and an epitope of the first Cancer Antigen;
 - (E) the Epitope I, Epitope II and Epitope III are, respectively, an epitope of the Effector Cell Antigen, an epitope of the first Cancer Antigen, and an epitope of the second Cancer Antigen;
- or

- (F) the Epitope I, Epitope II and Epitope III are, respectively, an epitope of the Effector Cell Antigen, an epitope of second Cancer Antigen, and an epitope of the first Cancer Antigen.

Claim 13. The Tri-Specific Binding Molecule of any one of claims 1-12, wherein the Effector Cell Antigen is CD2, CD3, CD16, CD19, CD20, CD22, CD32B, CD64, B cell Receptor (BCR), T cell Receptor (TCR), or NKG2D Receptor.

Claim 14. The Tri-Specific Binding Molecule of any of claims 1-13, wherein:

- (A) the epitope of an Effector Cell Antigen is a CD2 epitope recognized by antibody Lo-CD2a;
- (B) the epitope of an Effector Cell Antigen is a CD3 epitope recognized by antibody OKT3, M291, YTH12.5 or Anti-CD3 mAb 2, which antibody Anti-CD3 mAb 2 comprises SEQ ID NO:104 and SEQ ID NO:108 or 112;
- (C) the epitope of an Effector Cell Antigen is a CD16 epitope recognized by antibody 3G8 or A9;
- (D) the epitope of an Effector Cell Antigen is a CD19 epitope recognized by antibody MD1342, MEDI-551, blinatumomab or HD37;
- (E) the epitope of an Effector Cell Antigen is a CD20 epitope recognized by antibody rituximab, ibritumomab, ofatumumab, and tositumomab;
- (F) the epitope of an Effector Cell Antigen is a CD22 epitope recognized by antibody epratuzumab;
- (G) the epitope of an Effector Cell Antigen is a CD32B epitope recognized by antibody CD32B mAb 1, which antibody CD32B mAb 1 comprises SEQ ID NO:126 and SEQ ID NO:127;
- (H) the epitope of an Effector Cell Antigen is a CD64 epitope recognized by antibody CD64 mAb 1, which CD64 mAb 1 comprises SEQ ID NO:128 and SEQ ID NO:129;

- (I) the epitope of an Effector Cell Antigen is a BCR/CD79 epitope recognized by antibody CD79 mAb 1, which antibody CD79 mAb 1 comprises SEQ ID NO:130 and SEQ ID NO:131;
- (J) the epitope of an Effector Cell Antigen is a TCR epitope recognized by antibody BMA 031;
- (K) the epitope of an Effector Cell Antigen is a NKG2D Receptor epitope recognized by antibody KYK-2.0; or
- (L) one of Epitope I, Epitope II or Epitope III is an epitope of an Effector Cell Antigen and the Antigen-Binding Domain that is capable of immunospecifically binding to the epitope comprises the six CDRs of SEQ ID NO:102 and 103; 104 and 108; 104 and 112; 114 and 115; 116 and 117; 118 and 119; 120 and 121; 122 and 123; 124 and 125; 126 and 127; 128 and 129; 130 and 131; 132 and 133; 134 and 135; or 136 and 137; or comprises one or more of SEQ ID NO: 102-104, 108, 112, 114 and 115-137.

Claim 15. The Tri-Specific Binding Molecule of any one of claims 1-14, wherein the first Cancer Antigen and the second Cancer Antigen are independently chosen from: colon cancer antigen 19.9; a gastric cancer mucin; antigen 4.2; glycoprotein A33 (gpA33); ADAM-9; gastric cancer antigen AH6; ALCAM; malignant human lymphocyte antigen APO-1; cancer antigen B1; B7-H3; beta-catenin; blood group ALeb/Ley; Burkitt's lymphoma antigen-38.13, colonic adenocarcinoma antigen C14; ovarian carcinoma antigen CA125; Carboxypeptidase M; CD5; CD19; CD20; CD22; CD23; CD25; CD27; CD28; CD30 ; CD33; CD36; CD45; CD46; CD52 ; CD79a/CD79b; CD103; CD317 ; CDK4; carcinoembryonic antigen (CEA); CEACAM5; CEACAM6; CO17-1A; CO-43 (blood group Leb); CO-514 (blood group Lea); CTA-1; CTLA4; Cytokeratin 8; antigen D1.1; antigen D156-22; DR5; E1 series (blood group B); EGFR (Epidermal Growth Factor Receptor); Ephrin receptor A2 (EphA2); ErbB1; ErbB3; ErbB4; GAGE-1; GAGE-2; GD2/GD3/GM2; lung adenocarcinoma

antigen F3; antigen FC10.2; G49, ganglioside GD2; ganglioside GD3; ganglioside GM2; ganglioside GM3; GD2; GD3; GICA 19-9; GM2; gp100; human leukemia T cell antigen Gp37; melanoma antigen gp75; gpA33; HER2 antigen (p185HER2); human milk fat globule antigen (HMFG); human papillomavirus-E6/human papillomavirus-E7; high molecular weight melanoma antigen (HMW-MAA); I antigen (differentiation antigen) I(Ma); Integrin Alpha-V-Beta-6 Integrin β 6 (ITGB6); Interleukin-13; Receptor α 2 (IL13R α 2); JAM-3; KID3; KID31; KS 1/4 pan-carcinoma antigen; human lung carcinoma antigens L6 and L20; LEA; LUCA-2; M1:22:25:8; M18; M39; MAGE-1; MAGE-3; MART; MUC-1; MUM-1; Myl; N-acetylglucosaminyltransferase; neoglycoprotein; NS-10; OFA-1; OFA-2; Oncostatin M; p15; melanoma-associated antigen p97; polymorphic epithelial mucin (PEM); polymorphic epithelial mucin antigen (PEMA); PIPA; prostate-specific antigen (PSA); prostate-specific membrane antigen (PSMA); prostatic acid phosphate; R24; ROR1; sphingolipids; SSEA-1; SSEA-3; SSEA-4; sTn; T cell receptor derived peptide; T5A7; TAG-72; TL5 (blood group A); TNF- α receptor; TNF- β receptor; TNF- γ receptor; TRA-1-85 (blood group H); Transferrin Receptor; tumor-specific transplantation antigen (TSTA), oncofetal antigen-alpha-fetoprotein (AFP); VEGF, VEGFR; VEP8; VEP9; VIM-D5; and Y hapten, Le^y; and 5T4.

- Claim 16. The Tri-Specific Binding Molecule of claim 15, wherein one of Epitope I, Epitope II or Epitope III is an epitope of a Cancer Antigen and the Antigen-Binding Domain that is capable of immunospecifically binding to the epitope comprises the six CDRs of SEQ ID NO: 3 and 8; 13 and 18; 23 and 31; 25 and 31; 27 and 31; 29 and 31; 54 and 58; 62 and 66; 70 and 74; 78 and 82; 86 and 90; 94 and 98; 153 and 158; 163 and 167; 172 and 177; 181 and 186; 191 and 192; 193 and 194; 195 and 196; 197 and 198; 199 and 200; 201 and 202; 203 and 204; 205 and 206; 302 and 303; 304 and 305; 306 and 307; 308 and 309; 310 and 311; 312 and 313; 314 and 315; or 321 and

322; or comprises one or more of SEQ ID NO: 3, 8, 13, 18, 23, 25, 27, 29, 54, 58, 62, 66, 70, 74, 78, 82, 86, 90, 94, 98, 153, 158, 163, 167, 172, 177, 181, 186, 191-206, 302-315, 321 and 322.

- Claim 17. A nucleic acid composition comprising polynucleotides that encode polypeptide chains of the Tri-Specific Binding Molecule of any one of claims 1-16.
- Claim 18. A pharmaceutical composition comprising the Tri-Specific Binding Molecule of any one of claims 1-16, and a pharmaceutically acceptable carrier, excipient or diluent.
- Claim 19. A Tri-Specific Binding Molecule of any one of claims 1-16, or a composition of claim 18, for use as a medicament.
- Claim 20. Use of a Tri-Specific Binding Molecule of any one of claims 1-16 or a composition of claim 18 in the manufacture of a medicament to treat a cancer.
- Claim 21. The use of claim 20, wherein the cancer is characterized by the presence of a cancer 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 histiocyoma, 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 posterior uveal melanoma, a hematological malignancy, a renal metastatic cancer, a rhabdoid tumor, a rhabdomyosarcoma, 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, or a uterine cancer.

Claim 22. The use of claim 20 or claim 21, wherein the cancer is a colorectal cancer, a hepatocellular carcinoma, a glioma, a kidney cancer, a breast cancer, a multiple myeloma, bladder cancer, a neuroblastoma, a sarcoma, a non-Hodgkin's lymphoma, a non-small cell lung cancer, an ovarian cancer, a pancreatic cancer, a rectal cancer, 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 lymphoma (NHL), mantle cell leukemia (MCL), small lymphocytic lymphoma (SLL), Hodgkin's lymphoma, systemic mastocytosis, or Burkitt's lymphoma.