

2009/0285840, 2009/0203051, 2004/0092466, 2003/0091568, and 2002/0068062, and PCT Publication Nos. WO 2016/077505, WO 2014/205293, WO 2014/186364, WO 2014/124326, WO 2014/108480, WO 2013/119960, WO 2013/098797, WO 2013/049704, and WO 2011/100362). Additionally, the expression of ADAM9 has also been found to be relevant to pulmonary disease and inflammation (see, *e.g.*, US Patent Publication Nos. 2016/0068909; 2012/0149595; 2009/0233300; 2006/0270618; and 2009/0142301). Antibodies that bind to ADAM9 are commercially available from Abcam, Thermofisher, Sigma-Aldrich, and other companies.

[0011] However, despite all prior advances, a need remains for high affinity ADAM9-binding molecules that exhibit minimal binding to normal tissues and are capable of binding to human and non-human ADAM9 with similar high affinity. The present invention addresses this need and the need for improved therapeutics for cancer.

SUMMARY

[0012] The present disclosure is directed to molecules, such as monospecific antibodies and bispecific, trispecific or multispecific binding molecules, including diabodies, BiTEs, and antibodies that are capable of specifically binding to “Disintegrin and Metalloproteinase Domain-containing Protein 9” (“ADAM9”). The disclosure particularly concerns such binding molecules that are capable of exhibiting high affinity binding to human and non-human ADAM9. The disclosure further particularly relates to such molecules that are thereby cross-reactive with human ADAM9 and the ADAM9 of a non-human primate (*e.g.*, a cynomolgus monkey). The disclosure additionally pertains to all such ADAM9-binding molecules that comprise a Light Chain Variable (VL) Domain and/or a Heavy Chain Variable (VH) Domain that have been humanized and/or deimmunized so as to exhibit reduced immunogenicity upon administration of such ADAM9-binding molecule to a recipient subject. The disclosure is also directed to pharmaceutical compositions that contain any of such ADAM9-binding molecules, and to methods involving the use of any of such ADAM9-binding molecules in the treatment of cancer and other diseases and conditions.

[0013] In detail, the disclosure provides an ADAM9-binding molecule that comprises an ADAM9-binding domain, wherein such ADAM9-binding domain comprises a Light Chain Variable (VL) Domain and a Heavy Chain Variable (VH) Domain, wherein such Heavy Chain Variable Domain comprises a CDR_{H1} Domain, a CDR_{H2} Domain and a

CDR_H3 Domain, and such Light Chain Variable Domain comprises a CDR_L1 Domain, a CDR_L2 Domain, and a CDR_L3 Domain, wherein:

- (A) such CDR_H1 Domain, CDR_H2 Domain and CDR_H3 Domain have the amino acid sequence of the CDR_H1 Domain, CDR_H2 Domain and CDR_H3 Domain of a Heavy Chain Variable (VH) Domain of an optimized variant of **MAB-A**; and such CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain have the amino acid sequence of the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain of the Light Chain Variable (VL) Domain of **MAB-A**; or
- (B) such CDR_H1 Domain, CDR_H2 Domain and CDR_H3 Domain have the amino acid sequence of the CDR_H1 Domain, CDR_H2 Domain and CDR_H3 Domain of the Heavy Chain Variable (VH) Domain of **MAB-A**; and such CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain have the amino acid sequence of the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain of a Light Chain Variable (VL) Domain of an optimized variant of **MAB-A**; or
- (C) such CDR_H1 Domain, CDR_H2 Domain and CDR_H3 Domain have the amino acid sequence of the CDR_H1 Domain, CDR_H2 Domain and CDR_H3 Domain of a Heavy Chain Variable (VH) Domain of an optimized variant of **MAB-A**; and such CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain have the amino acid sequence of the CDR_L1 Domain, CDR_L2 Domain, and CDR_L3 Domain of a Light Chain Variable (VL) Domain of an optimized variant of **MAB-A**.

[0014] The disclosure particularly concerns the example of such ADAM9-binding molecules, wherein such ADAM9-binding domain possesses:

- (A) (1) the CDR_H1 Domain, CDR_H2 Domain and CDR_H3 Domain of the Heavy Chain Variable (VH) Domain of **MAB-A**; and
(2) the FR1, FR2, FR3 and FR4 of a VH Domain of a humanized variant of **MAB-A**; or
- (B) (1) the CDR_L1 Domain, CDR_L2 Domain and CDR_L3 Domain of the Light Chain Variable (VL) Domain **MAB-A**; and
(2) the FR1, FR2, FR3 and FR4 of a VL Domain of a humanized variant of **MAB-A**; or

- (C) (1) the CDR_H1 Domain, CDR_H2 Domain and CDR_H3 Domain of a Heavy Chain Variable (VH) Domain of an optimized variant of **MAB-A**; and
- (2) the FR1, FR2, FR3 and FR4 of the VH Domain of a humanized variant of **MAB-A**; or
- (D) (1) the CDR_L1 Domain, CDR_L2 Domain and CDR_L3 Domain of a Light Chain Variable (VL) Domain of an optimized variant of **MAB-A**; and
- (2) the FR1, FR2, FR3 and FR4 of the VL Domain of a humanized variant of **MAB-A**; or
- (E) (1) the Heavy Chain Variable (VH) Domain of a humanized/optimized variant of **MAB-A**; and
- (2) the VL Light Chain Variable (VL) Domain of a humanized/optimized variant of **MAB-A**.

[0015] The disclosure additionally concerns the example of all such ADAM9-binding molecules, wherein such Heavy Chain Variable (VH) Domain of such optimized variant of **MAB-A** comprises the amino acid sequence of **SEQ ID NO:15**:

EVQLVESGGG	LVKPGGSLRL	SCAASGFTFS	<u>SYWX₁</u> HWVRQA
PGKGLEWVGE	<u>IIPIX₂</u> GHTNY	<u>NEX₃FX₄X₅</u> RFTI	SLDNSKNTLY
LQMGSRAED	TAVYYCARGG	<u>YYYYX₆X₇X₈X₉X₁₀X₁₁</u>	
<u>DYWGQGTTVT</u>	VSS		

wherein: **X₁, X₂, X₃, X₄, X₅**, and **X₆** are independently selected,

wherein: **X₁** is M or I; **X₂** is N or F;

X₃ is K or R; **X₄** is K or Q;

X₅ is S or G, and **X₆** is P, F, Y, W, I, L, V, T, G or D;

wherein: **X₇, X₈, X₉, X₁₀**, and **X₁₁** are selected such that:

when **X₆** is P; **X₇** is K or R; **X₈** is F or M; **X₉** is G; **X₁₀** is W or F; and **X₁₁** is M, L or K;

when **X₆** is F, Y or W; **X₇** is N or H; **X₈** is S or K; **X₉** is G or A; **X₁₀** is T or V; and **X₁₁** is M, L or K;

when **X₆** is I, L or V; **X₇** is G; **X₈** is K; **X₉** is G or A; **X₁₀** is V; and **X₁₁** is M, L or K;

when **X₆** is T; **X₇** is G; **X₈** is K, M or N; **X₉** is G; **X₁₀** is V or T; and **X₁₁** is L or M;

when X_6 is G; X_7 is G; X_8 is S; X_9 is G; X_{10} is V; and X_{11} is L;
when X_6 is D; X_7 is S; X_8 is N; X_9 is A; X_{10} is V; and X_{11} is L.

[0016] The disclosure additionally concerns the example of all such ADAM9-binding molecules, wherein such CDR_{H1} Domain, CDR_{H2} Domain and CDR_{H3} Domain of such Heavy Chain Variable (VH) Domain of such optimized variant of **MAB-A** respectively have the amino acid sequences of:

(1) **SEQ ID NO:47** (SYWX₁H)

wherein: X_1 is M or I;

(2) **SEQ ID NO:48** (EIIPIX₂GHTNYNEX₃FX₄X₅)

wherein: X_2 , X_3 , X_4 , and X_5 are independently selected, and

wherein: X_2 is N or F; X_3 is K or R; X_4 is K or Q; and X_5 is S or G;
and

(3) **SEQ ID NO:49** (GGYYYYX₆X₇X₈X₉X₁₀X₁₁DY)

wherein: X_6 , is P, F, Y, W, I, L, V, T, G or D, and X_7 , X_8 , X_9 , X_{10} , and X_{11} are selected such that:

(A) when X_6 is P:

X_7 is K or R; X_8 is F or M; X_9 is G;

X_{10} is W or F; and X_{11} is M, L or K;

(B) when X_6 is F, Y or W:

X_7 is N or H; X_8 is S or K; X_9 is G or A;

X_{10} is T or V; and X_{11} is M, L or K;

(C) when X_6 is I, L or V:

X_7 is G; X_8 is K; X_9 is G or A;

X_{10} is V; and X_{11} is M, L or K;

(D) when X_6 is T:

X_7 is G; X_8 is K, M or N; X_9 is G;

X_{10} is V or T; and X_{11} is L or M;

(E) when X_6 is G:

X_7 is G; X_8 is S; X_9 is G;

X_{10} is V; and X_{11} is L; and

(F) when X_6 is D:

X_7 is S; X_8 is N; X_9 is A;

X_{10} is V; and X_{11} is L.

[0017] The disclosure additionally concerns the example of all such ADAM9-binding molecules, wherein such Heavy Chain Variable (VH) Domain of such optimized variant of **MAB-A** is selected from the group consisting of:

- (1) **hMAB-A VH(1) (SEQ ID NO:16);**
- (2) **hMAB-A VH(2) (SEQ ID NO:17);**
- (3) **hMAB-A VH(3) (SEQ ID NO:18);**
- (4) **hMAB-A VH(4) (SEQ ID NO:19);**
- (5) **hMAB-A VH(2A) (SEQ ID NO:20);**
- (6) **hMAB-A VH(2B) (SEQ ID NO:21);**
- (7) **hMAB-A VH(2C) (SEQ ID NO:22);**
- (8) **hMAB-A VH(2D) (SEQ ID NO:23);**
- (9) **hMAB-A VH(2E) (SEQ ID NO:24);**
- (10) **hMAB-A VH(2F) (SEQ ID NO:25);**
- (11) **hMAB-A VH(2G) (SEQ ID NO:26);**
- (12) **hMAB-A VH(2H) (SEQ ID NO:27);**
- (13) **hMAB-A VH(2I) (SEQ ID NO:28); and**
- (14) **hMAB-A VH(2J) (SEQ ID NO:29).**

[0018] The disclosure additionally concerns the example of all such ADAM9-binding molecules, wherein such Light Chain Variable (VL) Domain comprises the amino acid sequence of **SEQ ID NO:53**:

DIVMTQSPDS	LAVSLGERAT	ISCX ₁₂ <u>ASQSVD</u>
<u>YX₁₃GDSYX₁₄NWY</u>	QOKPGQPPKL	LIYA <u>AASDLES</u>
GIPARFSGSG	SGTDFTLTIS	SLEPEDFATY
YC <u>QQSX₁₅X₁₆X₁₇PF</u>	<u>TFGQGTKLEI</u>	K

wherein: X₁₂, X₁₃, X₁₄, X₁₅, X₁₆, and X₁₇, are independently selected, and

wherein: X₁₂ is K or R; X₁₃ is D or S;

X₁₄ is M or L; X₁₅ is H or Y;

X₁₆ is E or S; and X₁₇ is D or T.

[0019] The disclosure additionally concerns the example of all such ADAM9-binding molecules, wherein such CDR_L1 Domain, CDR_L2 Domain and CDR_L3 Domain of such Light Chain Variable (VL) Domain of such optimized variant of **MAB-A** respectively have the amino acid sequences of:

- (1) **SEQ ID NO:66** (X₁₂ASQSV₁₃DYX₁₄N)
wherein: X₁₂, X₁₃, X₁₄, are independently selected, and
wherein: X₁₂ is K or R; X₁₃ is D or S; and X₁₄ is M or L;
- (2) **SEQ ID NO:13** (AASDLES); and
- (3) **SEQ ID NO:67** (QQSX₁₅X₁₆X₁₇PFT)
wherein: X₁₅, X₁₆, and X₁₇, are independently selected, and
wherein: X₁₅ is H or Y; X₁₆ is E or S; and X₁₇ is D or T.

[0020] The disclosure additionally concerns the example of such ADAM9-binding molecules, wherein such Light Chain Variable (VL) Domain of such optimized variant of **MAB-A** is selected from the group consisting of:

- (1) **hMAB-A VL(1) (SEQ ID NO:54);**
- (2) **hMAB-A VL(2) (SEQ ID NO:55);**
- (3) **hMAB-A VL(3) (SEQ ID NO:56);**
- (4) **hMAB-A VL(4) (SEQ ID NO:57);**
- (5) **hMAB-A VL(2A) (SEQ ID NO:20).**

[0021] The disclosure additionally concerns the example of such ADAM9-binding molecules, wherein the ADAM9-binding domain comprises:

- (A) (1) a CDR_H1 Domain that comprises the amino acid sequence SYWMH (**SEQ ID NO:8**);
- (2) a CDR_H2 Domain that comprises the amino acid sequence EIIPIFGHTNYNEKFKS (**SEQ ID NO:35**); or
- (3) a CDR_H3 Domain that comprises the amino acid sequence GGYYYYPRQGFLDY (**SEQ ID NO:45**);

or

- (B) (1) a CDR_L1 Domain that comprises the amino acid sequence KASQSV₂DYSGDSYMN (**SEQ ID NO:62**);
- (2) a CDR_L2 Domain that comprises the amino acid sequence AASDLES (**SEQ ID NO:13**); or

- (3) a CDR_L3 Domain that comprises the amino acid sequence QQSHEDPFT (**SEQ ID NO:14**);

[0022] The disclosure additionally concerns the example of such ADAM9-binding molecules, wherein the ADAM9-binding domain comprises the CDR_H1 Domain that comprises the amino acid sequence SYWMH (**SEQ ID NO:8**), the CDR_H2 Domain that comprises the amino acid sequence EIIPIFGHTNYNEKFKS (**SEQ ID NO:35**), and the CDR_H3 Domain that comprises the amino acid sequence GGYYYYPRQGFLDY (**SEQ ID NO:45**).

[0023] The disclosure additionally concerns the example of such ADAM9-binding molecules, wherein the ADAM9-binding domain comprises the CDR_L1 Domain that comprises the amino acid sequence KASQSVSYSGDSYMN (**SEQ ID NO:62**), the CDR_L2 Domain that comprises the amino acid sequence AASDLES (**SEQ ID NO:13**), and the CDR_L3 Domain that comprises the amino acid sequence QQSHEDPFT (**SEQ ID NO:14**).

[0024] The disclosure additionally concerns the example of such ADAM9-binding molecules, wherein such ADAM9-binding domain comprises:

- (A) the Heavy Chain Variable (VH) Domain of **hMAB-A (2I.2)** (**SEQ ID NO:28**); or
- (B) the Light Chain Variable (VL) Domain of **hMAB-A (2I.2)** (**SEQ ID NO:55**); or
- (C) the Heavy Chain Variable (VH) Domain of **hMAB-A (2I.2)** (**SEQ ID NO:28**) and the Light Chain Variable (VL) Domain of **hMAB-A (2I.2)** (**SEQ ID NO:55**).

[0025] The disclosure additionally concerns the example of such ADAM9-binding molecules, wherein such ADAM9-binding domain comprises a CDR_H1 domain, a CDR_H2 domain, and a CDR_H3 domain and a CDR_L1 domain, a CDR_L2 domain, and a CDR_L3 domain having the sequences selected from the group consisting of:

- (a) **SEQ ID NOs:8, 35 and 10 and SEQ ID NOs:62, 13 and 14**, respectively
- (b) **SEQ ID NOs:8, 35 and 10 and SEQ ID NOs:63, 13 and 14**, respectively;
- (c) **SEQ ID NOs:8, 36 and 10 and SEQ ID NOs:63, 13 and 14**, respectively;
- and
- (d) **SEQ ID NOs:34, 36 and 10 and SEQ ID NO:64, 13 and 65**, respectively.

[0026] The disclosure additionally concerns the example of such ADAM9-binding molecules, wherein such ADAM9-binding domain comprises a heavy chain variable domain (VH) and a light chain variable domain (VL) having sequences that are at least 90%, at least 95%, or at least 99% identical to sequences selected from the group consisting of:

- (a) **SEQ ID NO:17** and **SEQ ID NO:55**, respectively;
- (b) **SEQ ID NO:17** and **SEQ ID NO:56**, respectively;
- (c) **SEQ ID NO:18** and **SEQ ID NO:56**, respectively; and
- (d) **SEQ ID NO:19** and **SEQ ID NO:57**, respectively.

[0027] The disclosure additionally concerns the example of such ADAM9-binding molecules, wherein such ADAM9-binding domain comprises a heavy chain variable domain (VH) and a light chain variable domain (VL) having the sequences selected from the group consisting of:

- (a) **SEQ ID NO:17** and **SEQ ID NO:55**, respectively;
- (b) **SEQ ID NO:17** and **SEQ ID NO:56**, respectively;
- (c) **SEQ ID NO:18** and **SEQ ID NO:56**, respectively; and
- (d) **SEQ ID NO:19** and **SEQ ID NO:57**, respectively.

[0028] The disclosure additionally concerns the example of such ADAM9-binding molecules, wherein such ADAM9-binding domain has at least a 150-fold enhancement in binding affinity to cyno ADAM9 and retains high affinity binding to human ADAM9 as compared to **MAB-A**.

[0028a] In one aspect, there is provided an ADAM9-binding molecule comprising a humanized ADAM9-binding domain, wherein said humanized ADAM9-binding domain comprises a Light Chain Variable (VL) Domain and a Heavy Chain Variable (VH) Domain, wherein said VH Domain comprises a CDR_{H1} Domain, a CDR_{H2} Domain and a CDR_{H3} Domain, and said VL Domain comprises a CDR_{L1} Domain, a CDR_{L2} Domain, and a CDR_{L3} Domain, wherein:

- (A) said CDR_{H1} Domain comprises the amino acid sequence of **SEQ ID NO:8** or **SEQ ID NO:34**; and
- (B) said CDR_{H2} Domain comprises the amino acid sequence of **SEQ ID NO: 9**, **SEQ ID NO:35** or **SEQ ID NO:36**; and

- (C) said CDR_H3 Domain comprises the amino acid sequence of any one of **SEQ ID NO:37, SEQ ID NO:38, SEQ ID NO:39, SEQ ID NO:40, SEQ ID NO:41, SEQ ID NO:42, SEQ ID NO:43, SEQ ID NO:44, SEQ ID NO:45 or SEQ ID NO:46**; and

wherein:

- (1) said CDR_L1 Domain comprises the amino acid sequence of **SEQ ID NO:12, SEQ ID NO:62, SEQ ID NO:63, or SEQ ID NO:64**; and
- (2) said CDR_L2 Domain comprises the amino acid sequence of **SEQ ID NO:13**; and
- (3) said CDR_L3 Domain comprises the amino acid sequence of **SEQ ID NO:14 or SEQ ID NO:65**.

[0029] The disclosure additionally concerns the example of such ADAM9-binding molecules, wherein such ADAM9-binding domain comprises a CDR_H1 domain, a CDR_H2 domain, and a CDR_H3 domain and a CDR_L1 domain, a CDR_L2 domain, and a CDR_L3 domain having the sequences selected from the group consisting of:

- (a) **SEQ ID NOs:8, 35 and 37 and SEQ ID NOs:62, 13 and 14**, respectively;
- (b) **SEQ ID NOs:8, 35 and 38 and SEQ ID NOs:62, 13 and 14**, respectively;
- (c) **SEQ ID NOs:8, 35 and 39 and SEQ ID NOs:62, 13 and 14**, respectively;
- (d) **SEQ ID NOs:8, 35 and 40 and SEQ ID NOs:62, 13 and 14**, respectively;
- (e) **SEQ ID NOs:8, 35 and 41 and SEQ ID NOs:62, 13 and 14**, respectively;
- (f) **SEQ ID NOs:8, 35 and 42 and SEQ ID NOs:62, 13 and 14**, respectively;
- (g) **SEQ ID NOs:8, 35 and 43 and SEQ ID NOs:62, 13 and 14**, respectively;
- (h) **SEQ ID NOs:8, 35 and 44 and SEQ ID NOs:62, 13 and 14**, respectively;

- (i) **SEQ ID NOs:8, 35 and 45 and SEQ ID NOs:62, 13 and 14, respectively;**
and
- (j) **SEQ ID NOs:8, 35 and 46 and SEQ ID NOs:62, 13 and 14, respectively.**

[0030] The disclosure additionally concerns the example of such ADAM9-binding molecules, wherein such ADAM9-binding domain comprises a heavy chain variable domain (VH) and a light chain variable domain (VL) having sequences that are at least 90%, at least 95%, or at least 99% identical to sequences selected from the group consisting of:

- (a) **SEQ ID NO:20 and SEQ ID NO:55, respectively;**
- (b) **SEQ ID NO:21 and SEQ ID NO:55, respectively;**
- (c) **SEQ ID NO:22 and SEQ ID NO:55, respectively;**
- (d) **SEQ ID NO:23 and SEQ ID NO:55, respectively;**
- (e) **SEQ ID NO:24 and SEQ ID NO:55, respectively;**
- (f) **SEQ ID NO:25 and SEQ ID NO:55, respectively;**
- (g) **SEQ ID NO:26 and SEQ ID NO:55, respectively;**
- (h) **SEQ ID NO:27 and SEQ ID NO:55, respectively;**
- (i) **SEQ ID NO:28 and SEQ ID NO:55, respectively; and**
- (j) **SEQ ID NO:29 and SEQ ID NO:55, respectively.**

[0031] The disclosure additionally concerns the example of such ADAM9-binding molecules, wherein such ADAM9-binding domain comprises a heavy chain variable domain (VH) and a light chain variable domain (VL) having the sequences selected from the group consisting of:

- (a) **SEQ ID NO:20 and SEQ ID NO:55, respectively;**
- (b) **SEQ ID NO:21 and SEQ ID NO:55, respectively;**
- (c) **SEQ ID NO:22 and SEQ ID NO:55, respectively;**
- (d) **SEQ ID NO:23 and SEQ ID NO:55, respectively;**
- (e) **SEQ ID NO:24 and SEQ ID NO:55, respectively;**
- (f) **SEQ ID NO:25 and SEQ ID NO:55, respectively;**
- (g) **SEQ ID NO:26 and SEQ ID NO:55, respectively;**
- (h) **SEQ ID NO:27 and SEQ ID NO:55, respectively;**
- (i) **SEQ ID NO:28 and SEQ ID NO:55, respectively; and**
- (j) **SEQ ID NO:29 and SEQ ID NO:55, respectively.**

[0032] The disclosure additionally concerns the example of all such ADAM9-binding molecules, wherein such molecule is a monospecific ADAM9-binding antibody or an ADAM9-binding fragment thereof, or wherein such molecule is a bispecific antibody.

[0033] The disclosure additionally concerns the example of all such ADAM9-binding molecules, wherein such molecule is a diabody, such diabody being a covalently bonded complex that comprises two, three, four or five polypeptide chains.

[0034] The disclosure additionally concerns the example of all such ADAM9-binding molecules, wherein such molecule is a trivalent binding molecule, such trivalent binding molecule being a covalently bonded complex that comprises three, four, five, or more polypeptide chains.

[0035] The disclosure additionally concerns the example of such ADAM9-binding molecules, wherein such molecule comprises an Albumin-Binding Domain (ABD).

[0036] The disclosure additionally concerns the example of such ADAM9-binding molecules, wherein such molecule comprises an Fc Region, and particularly the example wherein such Fc Region is a variant Fc Region that comprises:

- (a) one or more amino acid modification(s) that reduce(s) the affinity of the variant Fc Region for an FcγR; and/or
- (b) one or more amino acid modification(s) that enhance(s) the serum half-life of such ADAM9-binding molecule.

[0037] The disclosure additionally concerns the example of such ADAM9-binding molecules, wherein such one or more amino acid modification(s) that reduce(s) the affinity of the variant Fc Region for an FcγR comprise:

- (A) L234A;
- (B) L235A; or
- (C) L234A and L235A;

wherein such numbering is that of the EU index as in Kabat.

[0038] The disclosure additionally concerns the example of such ADAM9-binding molecules, wherein such one or more amino acid modification(s) that enhance(s) the serum half-life of such ADAM9-binding molecule comprise:

- (A) M252Y;

- (B) M252Y and S254T;
- (C) M252Y and T256E;
- (D) M252Y, S254T and T256E; or
- (E) K288D and H435K;

wherein such numbering is that of the EU index as in Kabat.

[0039] The disclosure additionally concerns the example of such ADAM9-binding molecules, wherein such molecule is bispecific and comprises an epitope-binding site capable of immunospecific binding to an epitope of ADAM9 and an epitope-binding site capable of immunospecific binding to an epitope of a molecule present on the surface of an effector cell.

[0040] The disclosure additionally concerns the example of such ADAM9-binding molecules, wherein such molecule comprises two epitope-binding sites capable of immunospecific binding to epitope(s) of ADAM9 and two epitope-binding sites capable of immunospecific binding to epitope(s) of a molecule present on the surface of an effector cell.

[0041] The disclosure additionally concerns the example of such ADAM9-binding molecules, wherein such molecule is trispecific and comprises:

- (a) one epitope-binding site capable of immunospecific binding to an epitope of ADAM9;
- (b) one epitope-binding site capable of immunospecific binding to an epitope of a first molecule present on the surface of an effector cell; and
- (c) one epitope-binding site capable of immunospecific binding to an epitope of a second molecule present on the surface of an effector cell.

[0042] The disclosure additionally concerns the example of such ADAM9-binding molecules, wherein such molecule is capable of simultaneously binding to ADAM9 and such molecule present on the surface of an effector cell.

[0043] The disclosure additionally concerns the example of such ADAM9-binding molecules, wherein such molecule present on the surface of an effector cell is CD2, CD3, CD8, TCR, or NKG2D.

[0044] The disclosure additionally concerns the example of such ADAM9-binding molecules, wherein such effector cell is a cytotoxic T-cell or a Natural Killer (NK) cell.

[0045] The disclosure additionally concerns the example of such ADAM9-binding molecules, wherein such first molecule present on the surface of an effector cell is CD3 and such second molecule present on the surface of an effector cell is CD8

[0046] The disclosure additionally concerns the example of such ADAM9-binding molecules, wherein such ADAM9-binding molecule mediates coordinated binding of a cell expressing ADAM9 and a cytotoxic T cell.

[0047] In one aspect, there is provided a pharmaceutical composition that comprises an effective amount of any of the above-described ADAM9-binding molecules and a pharmaceutically acceptable carrier, excipient or diluent.

[0047a] In one aspect, there is provided use of any of the above-described ADAM9-binding molecules, or the use of the above-described pharmaceutical composition in the manufacture of a medicament for the treatment of a disease or condition associated with, or characterized by, the expression of ADAM9.

[0048] The disclosure additionally concerns the use of any of the above-described ADAM9-binding molecules, or the use of the above-described pharmaceutical composition in the treatment of a disease or condition associated with, or characterized by, the expression of ADAM9.

[0049] The disclosure particularly concerns such use wherein such disease or condition associated with, or characterized by, the expression of ADAM9 is cancer, and especially wherein such cancer is selected from the group consisting: bladder cancer, breast cancer, cervical cancer, colorectal cancer (especially an adenocarcinoma, gastrointestinal carcinoid tumors, gastrointestinal stromal tumors, primary colorectal lymphoma, leiomyosarcoma, melanoma, or squamous cell carcinoma), esophageal cancer, gastric cancer, head and neck cancer, liver cancer, non-small-cell lung cancer (especially a squamous cell carcinoma, adenocarcinoma, or large-cell undifferentiated carcinoma), myeloid cancer, ovarian cancer, pancreatic cancer, prostate cancer, renal cell carcinoma, thyroid cancer, testicular cancer, and uterine cancer.

[0050] The disclosure additionally concerns a method for treating a disease or condition associated with, or characterized by, the expression of ADAM9 in a subject comprising administering to such subject an effective amount of any of the above-described ADAM9-binding molecules, or any of the above-described pharmaceutical compositions.

[0051] The disclosure particularly concerns such method wherein such disease or condition associated with, or characterized by, the expression of ADAM9 is cancer, and especially wherein such cancer is selected from the group consisting: bladder cancer, breast cancer, cervical cancer, colorectal cancer (especially an adenocarcinoma, gastrointestinal carcinoid tumors, gastrointestinal stromal tumors, primary colorectal lymphoma, leiomyosarcoma, melanoma, or squamous cell carcinoma), esophageal cancer, gastric cancer, head and neck cancer, liver cancer, non-small-cell lung cancer (especially a squamous cell carcinoma, adenocarcinoma, or large-cell undifferentiated carcinoma), myeloid cancer, ovarian cancer, pancreatic cancer, prostate cancer, renal cell carcinoma, thyroid cancer, testicular cancer, and uterine cancer.

BRIEF DESCRIPTION OF THE DRAWINGS

[0052] **Figure 1** provides a schematic of a representative covalently bonded diabody having two epitope-binding sites composed of two polypeptide chains, each having an E-coil or K-coil Heterodimer-Promoting Domain (alternative Heterodimer-Promoting Domains are provided below). A cysteine residue may be present in a linker and/or in the Heterodimer-Promoting Domain as shown in **Figure 3B**. VL and VH Domains that recognize the same epitope are shown using the same shading or fill pattern.

[0053] **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 all or part of an Fc Region. VL and VH Domains that recognize the same epitope are shown using the same shading or fill pattern.

[0054] **Figures 3A-3C** provide schematics showing representative covalently bonded tetravalent diabodies having four epitope-binding sites composed of two pairs of polypeptide chains (*i.e.*, four polypeptide chains in all). One polypeptide of each pair possesses a CH2 and CH3 Domain, such that the associated chains form all or part of an Fc Region. VL and VH Domains that recognize the same epitope are shown using the same shading or fill pattern. The two pairs of polypeptide chains may be same. In such embodiments wherein the two pairs of polypeptide chains are the same and the VL and VH Domains recognize different epitopes (as shown in **Figures 3A-3B**), the resulting molecule possesses four epitope-binding sites and is bispecific and bivalent with respect to each bound epitope. In such embodiments wherein the VL and VH Domains recognize the same

WHAT IS CLAIMED IS:

Claim 1. An ADAM9-binding molecule comprising a humanized ADAM9-binding domain, wherein said humanized ADAM9-binding domain comprises a Light Chain Variable (VL) Domain and a Heavy Chain Variable (VH) Domain, wherein said VH Domain comprises a CDR_{H1} Domain, a CDR_{H2} Domain and a CDR_{H3} Domain, and said VL Domain comprises a CDR_{L1} Domain, a CDR_{L2} Domain, and a CDR_{L3} Domain, wherein:

- (A) said CDR_{H1} Domain comprises the amino acid sequence of **SEQ ID NO:8** or **SEQ ID NO:34**; and
- (B) said CDR_{H2} Domain comprises the amino acid sequence of **SEQ ID NO: 9**, **SEQ ID NO:35** or **SEQ ID NO:36**; and
- (C) said CDR_{H3} Domain comprises the amino acid sequence of any one of **SEQ ID NO:37**, **SEQ ID NO:38**, **SEQ ID NO:39**, **SEQ ID NO:40**, **SEQ ID NO:41**, **SEQ ID NO:42**, **SEQ ID NO:43**, **SEQ ID NO:44**, **SEQ ID NO:45** or **SEQ ID NO:46**; and

wherein:

- (1) said CDR_{L1} Domain comprises the amino acid sequence of **SEQ ID NO:12**, **SEQ ID NO:62**, **SEQ ID NO:63**, or **SEQ ID NO:64**; and
- (2) said CDR_{L2} Domain comprises the amino acid sequence of **SEQ ID NO:13**; and
- (3) said CDR_{L3} Domain comprises the amino acid sequence of **SEQ ID NO:14** or **SEQ ID NO:65**.

Claim 2. The ADAM9-binding molecule of claim 1, wherein said humanized ADAM9-binding domain comprises a CDR_{H1} domain, a CDR_{H2} domain, and a CDR_{H3} domain and a CDR_{L1} domain, a CDR_{L2} domain, and a CDR_{L3} domain comprising the sequences selected from the group consisting of:

- (a) **SEQ ID NOs:8, 35 and 37** and **SEQ ID NOs:62, 13 and 14**, respectively;
- (b) **SEQ ID NOs:8, 35 and 38** and **SEQ ID NOs:62, 13 and 14**, respectively;
- (c) **SEQ ID NOs:8, 35 and 39** and **SEQ ID NOs:62, 13 and 14**, respectively;

- (d) **SEQ ID NOs:8, 35 and 40 and SEQ ID NOs:62, 13 and 14,**
respectively;
- (e) **SEQ ID NOs:8, 35 and 41 and SEQ ID NOs:62, 13 and 14,**
respectively;
- (f) **SEQ ID NOs:8, 35 and 42 and SEQ ID NOs:62, 13 and 14,**
respectively;
- (g) **SEQ ID NOs:8, 35 and 43 and SEQ ID NOs:62, 13 and 14,**
respectively;
- (h) **SEQ ID NOs:8, 35 and 44 and SEQ ID NOs:62, 13 and 14,**
respectively;
- (i) **SEQ ID NOs:8, 35 and 45 and SEQ ID NOs:62, 13 and 14,**
respectively; and
- (j) **SEQ ID NOs:8, 35 and 46 and SEQ ID NOs:62, 13 and 14,**
respectively.

Claim 3. The ADAM9-binding molecule of claim 2, wherein said humanized ADAM9-binding domain comprises:

- (A) (1) a CDR_H1 Domain that comprises the amino acid sequence SYWMH (**SEQ ID NO:8**);
 - (2) a CDR_H2 Domain that comprises the amino acid sequence EIIPIFGHTNYNEKFKS (**SEQ ID NO:35**); and
 - (3) a CDR_H3 Domain that comprises the amino acid sequence GGYYYYPRQGFLDY (**SEQ ID NO:45**);
- and
- (B) (1) a CDR_L1 Domain that comprises the amino acid sequence KASQSVDYSGDSYMN (**SEQ ID NO:62**);
 - (2) a CDR_L2 Domain that comprises the amino acid sequence AASDLES (**SEQ ID NO:13**); and
 - (3) a CDR_L3 Domain that comprises the amino acid sequence QQSHEDPFT (**SEQ ID NO:14**).

Claim 4. The ADAM9-binding molecule of any one of claims 1-3, wherein said humanized ADAM9-binding domain comprises:

- (A) the VH Domain of **SEQ ID NO:20, SEQ ID NO: 21, SEQ ID NO:22, SEQ ID NO:23, SEQ ID NO:24, SEQ ID NO:25, SEQ ID NO:26, SEQ ID NO:27, SEQ ID NO:28 or SEQ ID NO:29;**
and
- (B) the VL Domain of **SEQ ID NO:53, SEQ ID NO:54, SEQ ID NO:55, SEQ ID NO:56 or SEQ ID NO:57.**

Claim 5. The ADAM9-binding molecule of claim 4, wherein said humanized ADAM9-binding domain comprises the VH Domain of **SEQ ID NO:28** and the VL Domain of **SEQ ID NO:55**.

Claim 6. The ADAM9-binding molecule of any one of claims 1-5, wherein said molecule is a monospecific ADAM9-binding antibody or an ADAM9-binding fragment thereof.

Claim 7. The ADAM9-binding molecule of any one of claims 1-5, wherein said molecule is a bispecific antibody.

Claim 8. The ADAM9-binding molecule of any one of claims 1-5, wherein said molecule is a diabody, said diabody being a covalently bonded complex that comprises two, three, four or five polypeptide chains.

Claim 9. The ADAM9-binding molecule of any one of claims 1-5, wherein said molecule is a trivalent binding molecule, said trivalent binding molecule being a covalently bonded complex that comprises three, four, five, or more polypeptide chains.

Claim 10. The ADAM9-binding molecule of any one of claims 6-9, wherein said ADAM9-binding molecule comprises an Fc Region selected from the group consisting of: IgG1, IgG2, IgG3 and IgG4.

Claim 11. The ADAM9-binding molecule of claim 10, wherein said Fc Region is a variant Fc Region that comprises:

- (a) one or more amino acid modification(s) that reduce(s) the affinity of the variant Fc Region for an FcγR; and/or
- (b) one or more amino acid modification(s) that enhance(s) the serum half-life of said ADAM9-binding molecule.

- Claim 12. The ADAM9-binding molecule of claim 11, wherein said one or more amino acid modification(s) that reduce(s) the affinity of the variant Fc Region for an FcγR comprise:
- (A) L234A;
 - (B) L235A; or
 - (C) L234A and L235A;
- wherein said numbering is that of the EU index as in Kabat.
- Claim 13. The ADAM9-binding molecule of any one of claims 11-12, wherein said one or more amino acid modification(s) that enhance(s) the serum half-life of said ADAM9-binding molecule comprise:
- (A) M252Y;
 - (B) M252Y and S254T;
 - (C) M252Y and T256E;
 - (D) M252Y, S254T and T256E; or
 - (E) K288D and H435K;
- wherein said numbering is that of the EU index as in Kabat.
- Claim 14. The ADAM9-binding molecule of any one of claims 1-8 or 10-13, wherein said molecule is bispecific and comprises an epitope-binding site capable of immunospecific binding to an epitope of ADAM9 and an epitope-binding site capable of immunospecific binding to an epitope of a molecule present on the surface of an effector cell.
- Claim 15. The ADAM9-binding molecule of claim 14, wherein said molecule comprises two epitope-binding sites capable of immunospecific binding to epitope(s) of ADAM9 and two epitope-binding sites capable of immunospecific binding to epitope(s) of a molecule present on the surface of an effector cell.
- Claim 16. The ADAM9-binding molecule of any one of claims 1-5 or 9-13, wherein said molecule is trispecific and comprises:
- (a) one epitope-binding site capable of immunospecific binding to an epitope of ADAM9;

- (b) one epitope-binding site capable of immunospecific binding to an epitope of a first molecule present on the surface of an effector cell; and
- (c) one epitope-binding site capable of immunospecific binding to an epitope of a second molecule present on the surface of an effector cell.

Claim 17. The ADAM9-binding molecule of any one of claims 14-16, wherein said molecule present on the surface of an effector cell is CD2, CD3, CD8, TCR, or NKG2D.

Claim 18. A pharmaceutical composition that comprises an effective amount of the ADAM9-binding molecule of any of claims 1-17 and a pharmaceutically acceptable carrier, excipient or diluent.

Claim 19. Use of the ADAM9-binding molecule of any one of claims 1-17, or the pharmaceutical composition of claim 18, in the manufacture of a medicament for the treatment of a disease or condition associated with, or characterized by, the expression of ADAM9.

Claim 20. The use of claim 19, wherein said disease or condition associated with, or characterized by, the expression of ADAM9 is a cancer selected from the group consisting of: bladder cancer, breast cancer, cervical cancer, colorectal cancer, esophageal cancer, gastric cancer, head and neck cancer, liver cancer, non-small-cell lung cancer, myeloid cancer, ovarian cancer, pancreatic cancer, prostate cancer, renal cell carcinoma, thyroid cancer, testicular cancer, and uterine cancer.