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~~New~~eClaims

1. A ~~multitargeting bispecific~~ antigen-binding molecule comprising at least one polypeptide chain, wherein the molecule comprises

- (i) a first binding domain, which specifically binds to a first target cell surface antigen ~~(e.g. TAA1)~~,
- (ii) a second binding domain, which specifically binds to an extracellular epitope of the human and/or the Macaca CD3ε chain,
- (iii) a third binding domain, which specifically binds to a second target cell surface antigen ~~(e.g. TAA2)~~; and
- (iv) a fourth binding domain which specifically binds to an extracellular epitope of the human and/or the Macaca CD3ε chain,

~~wherein the antigen-binding molecule is characterized by the first and third domain comprise two antibody-derived variable domains and the second and the fourth domain comprises two antibody-derived variable domains; and wherein the structure of the binding domains are based on the structure of an antibody, and are drawn from the variable heavy chain (VH) and/or variable light chain (VL) domains of an antibody;~~

~~wherein the first binding domain is capable of binding to the first target cell surface antigen and the third binding domain is capable of binding to the second target cell surface antigen simultaneously, wherein the first target cell surface antigen and the second target cell surface antigen are on the same target cell;~~

~~wherein the molecule is a single polypeptide chain, wherein the first target cell surface antigen and the second target cell surface antigen are not identical;~~

wherein the first binding domain and the second binding domain form a first bispecific entity and the third and the fourth binding domain form a second bispecific entity, ~~and~~ and

wherein the molecule comprises a spacer entity having a molecular weight of at least about 5 kDa and/or having a length of at more than 50 amino acids, wherein the spacer entity spaces apart the first and the second bispecific entity by at least a distance of about 50 Å, wherein the ~~spacer entity indicated distance~~ is a globular protein, and is selected from a gro

~~up consisting of ubiquitin, beta 2 microglobulin, VHH antibody lama domain, PD-1 binding domain from human Programmed cell death 1 ligand 1 (PDL1), a programmed cell death protein 1 (PD1) domain, human serum albumin (HSA), and a Fc domain or dimer or trimer thereof, each Fc domain comprising two polypeptide monomers comprising each a hinge, a CH2 and a CH3 domain a hinge and a further CH2 and a CH3 domain, wherein said two polypeptide monomers are fused to each other via a peptide linker, understood as the distance between centers of mass of the first and the second bispecific entity and~~ which spacer entity is positioned between the first and the second bispecific entity, wherein the first binding domain is capable of binding to the first target cell surface antigen and the third binding domain is capable of binding to the second target cell surface antigen simultaneously, wherein the first target cell surface antigen and the second target cell surface antigen are on the same target cell.

~~2. The antigen-binding molecule according to claim 1 which is a multitargeting bispecific antigen-binding molecule.~~

~~32.-~~ The antigen-binding molecule of claim ~~21~~, wherein the arrangement of domains in an amino to carboxyl order is selected from the group consisting of

- (i.) first and second domain, spacer, third and fourth domain
- (ii.) first and second domain, spacer, fourth and third domain
- (iii.) second and the first domain, spacer, third and fourth domain, and
- (iv.) second and first domain, spacer, fourth and third domain.

~~43.~~ The antigen-binding molecule according to any of the preceding claims, wherein said spacer entity has a molecular weight of at least 10 kDa, ~~or~~ more preferably at least 15 kDa, 20 kDa or even 50 kDa, and/or wherein said spacer entity comprises an amino acid sequence which comprises more than 50 amino acids, ~~or~~ preferably at least 100 amino acids, ~~or~~ more preferably at least 250 amino acids, ~~or and even more preferably~~ at least 500 amino acids.

~~54.~~ The antigen-binding molecule according to any of the preceding claims, wherein said spacer entity is a rigid molecule which preferably folds into a secondary structure, preferably a helical structure and ~~and~~ or a ternary structure, preferably a protein domain structure, most preferably a globular protein and/or parts thereof and/or combinations of globular proteins and/or parts thereof.

65. The antigen-binding molecule according to any of the preceding claims, wherein the spacer entity is a globular protein, wherein the distance between the C alpha atoms of the first amino acid located at the N-terminus and the last amino acid at the C-terminus are spaced apart by at least 20 Å, preferably at least 30 Å, more preferably at least 50 Å, in order to effectively space apart the first and the second bispecific entity by preferably at least 50 Å.

6. The antigen-binding molecule according to any of the preceding claims, wherein said spacer entity which sufficiently spaces apart the first and the second bispecific entity is selected from a group consisting of ubiquitin, beta 2 microglobulin, SAND domain, Green fluorescent protein (GFP), VHH antibody lama domain, PSI domain from Met-receptor, Fibronectin type III domain from tenascin, Granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-4, CD137L Ectodomain, Interleukin-2, PD-1 binding domain from human Programmed cell death 1 ligand 1 (PDL1), Tim-3 (AS 24-130), MiniSOG, a programmed cell death protein 1 (PD1) domain, human serum albumin (HSA) or a derivate of any of the foregoing spacer entities, a multimer of a rigid linker and a Fc domain or dimer or trimer thereof, each Fc domain comprising two polypeptide monomers comprising each a hinge, a CH2 and a CH3 domain a hinge and a further CH2 and a CH3 domain, wherein said two polypeptide monomers are fused to each other via a peptide linker or wherein the two polypeptide monomers are linked together by non-covalent CH3-CH3 interactions and/or covalent disulfide bonds to form a heterodimer.

7. The antigen-binding molecule according to any of the preceding claims, wherein said spacer entity is at least one Fc domain, preferably one domain or two or three covalently linked domains, which or each of which comprises in an amino to carboxyl order:

hinge-CH2-CH3-linker-hinge-CH2-CH3-

~~8. The antigen-binding molecule according to any of the preceding claims~~, wherein each of said polypeptide monomers in the spacer entity has preferably an amino acid sequence that is at least 90% identical to a sequence selected from the group consisting of: SEQ ID NO: 17-24-, wherein preferably each of said polypeptide monomers has an amino acid sequence selected from SEQ ID NO: 17-24 and, wherein the CH2 domains in the spacer preferably comprises an intra domain cysteine disulfide bridge.

98. The antigen-binding molecule according to any of the preceding claims, wherein the ~~CH2 domains in the spacer comprises an intra domain cysteine disulfide bridge~~ molecule is a single polypeptide chain.

109. The antigen-binding molecule according to any of the preceding claims, wherein the spacer entity comprises an amino acid sequence selected the group consisting of SEQ ID NO: 13 and 15 to 16 and 25 to 34, ubiquitin (SEQ ID NO: 1081), beta 2 microglobulin (SEQ ID NO: 1083), SAND domain (SEQ ID NO: 1084), VHH antibody lama domain (SEQ ID NO: 1086), PD-1 binding domain from human Programmed cell death 1 ligand 1 (PDL1) (SEQ ID NO: 1093), ~~a~~ a programmed cell death protein 1 (PD1) domain (SEQ ID NO: 16), human serum albumin (has, SEQ ID NO: 15) or an amino acid with at least 90%, ~~or~~ preferably 95% or even 98% sequence identity thereof, preferably scFc (SEQ ID NO: 25).

10. The antigen-binding molecule according to any of the preceding claims 1 to 6, wherein the molecule comprises two polypeptide chains.

11. An antigen-binding molecule comprising two polypeptide chains, wherein

(i.) the first polypeptide chain comprises a first binding domain which specifically binds to a first target cell surface antigen (e.g. TAA1), a second binding domain which specifically binds to an extracellular epitope of the human and/or the Macaca CD3ε chain, and ~~the~~ first polypeptide monomer preferably comprising hinge, a CH2 and a CH3 domain, and

(ii.) wherein the second polypeptide chain comprises a third binding domain which specifically binds to a second target cell surface antigen (e.g. TAA2), a fourth binding domain which specifically binds to an extracellular epitope of the human and/or the Macaca CD3ε chain, and ~~the~~ second polypeptide monomer preferably comprising hinge, a CH2 and a CH3 domain,

wherein the two polypeptide monomers form a heterodimer pairing the CH2 and the CH3 domains of the two peptide monomers, respectively, wherein the CH2 domain of the first ~~poly~~peptide monomer is linked to the first or second domain of the first bispecific entity in C-terminal position of said entity, ~~and and~~ wherein the CH3 domain of the second ~~poly~~peptide monomer is linked to the third or fourth

domain of the second bispecific entity in N-terminal position of said entity, i.e. the N-terminus of the second polypeptide chain is at the CH2 domain of the second polypeptide monomer and the C-terminus is at the third or fourth domain,

wherein preferably the first and second polypeptide monomer form a heterodimer, thereby connecting the first and the second polypeptide chain, wherein the first ~~target-cell-surface-antigen-peptide monomer of the first peptide chain is preferably SEQ ID NO 35~~ and the second ~~target-cell-surface antigen are not identical peptide monomer of the second peptide chain is preferably SEQ ID NO 36,~~ wherein the ~~paired-CH2-and-CH3-domains-of-the~~ two peptide monomers preferably form a ~~spacer heterodimer, and and~~ wherein the first binding domains is capable of binding to the first target cell surface antigen and the third binding domain is capable of binding to the second target cell surface antigen simultaneously, wherein the first target cell surface antigen and the second target cell surface antigen are on the same target cell.

12. The antigen-binding molecule according to any of the preceding claims, wherein the antigen-binding molecule is characterized by

(i) -the first and third domain comprise two antibody-derived variable domains and the second and the fourth domain comprises two antibody-derived variable domains; and wherein the structure of the binding domains are based on the structure of an antibody, and are drawn from the variable heavy chain (VH) and/or variable light chain (VL) domains of an antibody.

(ii) the first and third domain comprise one antibody-derived variable domain and the second and the fourth domain comprises two antibody-derived variable domains;

(iii) the first and third domain comprise two antibody-derived variable domains and the second and the fourth domain comprises one antibody-derived variable domain; or

(iv) the first domain comprises one antibody-derived variable domain and the third domain comprises one antibody-derived variable domain.

~~12~~13. The antigen-binding molecule according to ~~claim 11~~any of the preceding claims 1 to 6, wherein the ~~first-antigen-binding molecule comprises two~~ polypeptide ~~monomer-chains,~~ wherein

the first polypeptide chain ~~is SEQ ID NO 35 and the second polypeptide monomer comprises a VH of the first domain, a VH second domain, the first polypeptide monomer comprising preferably a hinge, a CH2 and a CH3 domain, a VH of the third domain and a VH of the fourth domain; and~~

~~of the second polypeptide chain is SEQ ID NO 36, wherein the two polypeptide monomers comprises a VL of the first domain, a VL second domain, the first polypeptide monomer comprising preferably a hinge, a CH2 and a CH3 domain, a VL of the third domain and a VL of the fourth domain,~~

~~wherein preferably the first and second polypeptide monomer form a heterodimer-, thereby connecting the first and the second polypeptide chain.~~

~~13~~14. The antigen-binding molecule according to any of the preceding claims, wherein the antigen-binding molecule, wherein the first, second, third and fourth binding domain each comprise in an amino to carboxyl order a VH domain and a VL domain, wherein the VH and VL within each domain is connected by a peptide linker, preferably a flexible linker which comprises serine, glutamine and/or glycine as amino acid building blocks, preferably only serine (Ser, S) or glutamine (Gln, Q) and glycine (Gly, G), more preferably (G4S)_n or (G4Q)_n, even more preferably SEQ ID NO: 1 or 3.

~~14~~15. The antigen-binding molecule according to any of the preceding claims, wherein the peptide linker comprises or consists of S(G4X)_n and (G4X)_n, wherein X is selected from the group consisting of Q, T, N, C, G, A, V, I, L, and M, and wherein n is an integer selected from integers 1 to 20, preferably wherein n is 1, 2, 3, 4, 5 or 6, preferably wherein X is Q, wherein preferably the peptide linker is (G4X)_n, n is 3, and X is Q.

~~15~~16. The antigen-binding molecule according to any of the preceding claims, wherein the peptide linker between the first binding domain and the second binding domain and the third binding domain and the fourth binding domain is preferably a flexible linker which comprises serine, glutamine and/or glycine or glutamic acid, alanine and lysine as amino acid building blocks, preferably selected from the group consisting of SEQ ID NO: 1 to 4, 6 to 12 and 1125.

~~16~~17. The antigen-binding molecule according to any of the preceding claims, wherein the peptide linker between the first binding domain or the second binding domain and the spacer, and/or the third binding domain and the fourth binding domain and the spacer, respectively, is preferably a short linker rich in small and/or hydrophilic amino acids, preferably glycine and preferably SEQ ID NO: 5.

~~17~~18. The antigen-binding molecule according to any of the preceding claims, wherein any of the first target cell surface antigen and the second target cell surface antigen is selected from the group consisting of CS1, BCMA, CDH3, FLT3, CD123, CD20, CD22, EpCAM, MSLN and CLL1.

19. The antigen-binding molecule according to any of the preceding claims, wherein the first target cell surface antigen and the second target cell surface antigen are not identical, or wherein the first target cell surface antigen and the second target cell surface antigen are identical.

~~18~~20. The antigen-binding molecule according to any of the preceding claims, wherein the first target cell surface antigen and the second target cell surface antigen, respectively, are selected from the group consisting of CS1 and BCMA, BCMA and CS1, FLT3 and CD123, CD123 and FLT3, CD20 and CD22, CD22 and CD20, EpCAM and MSLN, MSLN and EpCAM, MSLN and CDH3, CDH3 and MSLN, FLT3 and CLL1, and CLL1 and FLT3.

~~19~~21. The antigen-binding molecule according to any of the preceding claims, wherein the first target cell surface antigen and/or the second target cell surface antigen is human MSLN (selected from SEQ ID NOs: 1181, 1182 and 1183), and wherein the first and/or third binding domain of the antigen-binding molecule of the invention binds to human MSLN epitope cluster E1 (SEQ ID NO: 1175, aa 296-346 position according to Kabat) as determined by murine chimere sequence analysis as described herein, but preferably not to human MSLN epitope cluster E2 (SEQ ID NO: 1176, aa 247-384 position according to Kabat), E3 (SEQ ID NO: 1177, aa 385-453 position according to Kabat), E4 (SEQ ID NO: 1178, aa 454-501 position according to Kabat) and/or E5 (SEQ ID NO: 1179 aa 502-545 position according to Kabat).

~~20~~22. The antigen-binding molecule according to any of the preceding claims wherein the first target cell surface antigen and/or the second target cell surface antigen is human CDH3 (SEQ ID NOs: 1170), and wherein the first and/or third binding domain of the antigen-binding molecule of claim 1 binds to human CDH3 epitope cluster D2B (SEQ ID NO: 1171, aa 253-290 position according to Kabat), D2C (SEQ ID NO: 1172 aa 291-327 position according to Kabat), D3A (SEQ ID NO: 1173 aa 328-363 position according to Kabat) and D4B (SEQ ID NO: 1174, aa 476-511 position according to Kabat), preferably D4B (SEQ ID NO: 1174, aa 476-511 position according to Kabat), as determined by murine chimere sequence analysis as described herein.

~~21. The antigen-binding molecule according to any of the preceding claims, wherein the second and the fourth binding domain (CD3 binding domains) both have (i.) an affinity lower than characterized by a KD value of 1.2×10^{-8} M measured by surface plasmon resonance (SPR), or (ii.) an affinity characterized by a KD value of 1.2×10^{-8} M measured by SPR.~~

~~22. The antigen-binding molecule according to any of the preceding claims, wherein the second and the fourth binding domain (CD3 binding domains) have an affinity characterized by a KD value of 1.0×10^{-7} to 5.0×10^{-6} M measured by SPR.~~

23. The antigen-binding molecule according to any of the preceding claims, wherein the second and the fourth binding domain (CD3 binding domains) both have (i.) an affinity lower than characterized by a KD value of about 1.2×10^{-8} M measured by surface plasmon resonance (SPR), or (ii.) an affinity characterized by a KD value of about 1.2×10^{-8} M measured by SPR,

wherein the second and the fourth binding domain (CD3 binding domains) preferably have an affinity characterized by a KD value of about 1.0×10^{-7} to 5.0×10^{-6} M measured by SPR, preferably about 1.0 to 3.0×10^{-6} M, more preferably about 2.5×10^{-6} M measured by SPR.

24. The antigen-binding molecule according to any of the preceding claims, wherein the second and the fourth binding domain (CD3 binding domains) have an affinity characterized by a KD value of about 1.0×10^{-7} to 5.0×10^{-6} M measured by SPR, preferably about 1.0 to 3.0×10^{-6} M, more preferably about 2.5×10^{-6} M measured by SPR.

25. The antigen-binding molecule according to any of the preceding claims, wherein each of the second and the fourth binding domain (CD3 binding domains) individually has an at least about 10-fold, preferably at least about 50-fold or more preferably at least about 100-fold lower activity than one CD3 binding domain comprising a VH according to SEQ ID NO 43 and a VL according to SEQ ID NO 44 (i.e. in a mono targeting context in contrast to a dual targeting context).

~~25~~26. The antigen-binding molecule according to any of the preceding claims, wherein the second and the fourth binding domain comprise a VH region comprising CDR-H 1, CDR-H2 and CDR-H3 selected from SEQ ID NOs 37 to 39, 45 to 47, 53 to 55, 61 to 63, 69 to 71, 436 to 438, 1126 to 1128, 1136 to 1138, 1142 to 1144, ~~and and~~ 1148 to 1150, ~~and and~~ a VL region comprising CDR-L1, CDR-

L2 and CDR-L3 selected from SEQ ID NOs 40 to 42, 48 to 50, 56 to 58, 64 to 66, 72 to 74, 439 to 441, 1129 to 1131, 1139 to 1141, 1145 to 1147, ~~and~~ and 1151 to 1153, preferably 61 to 63 and 64 to 66.

~~26~~27. The antigen-binding molecule according to any of the preceding claims, wherein the second and fourth binding domain comprise a VH region selected from SEQ ID NOs 43, 51, 59, 67, 75, 442 and 1132, ~~;~~

~~27. The antigen-binding molecule according to any of the preceding claims, preferably 67 and~~ wherein the second and fourth binding domain comprise a VL region selected from SEQ ID NOs 44, 52, 60, 68, 76, 443 and 1133, preferably 68.

28. The antigen-binding molecule according to any of the preceding claims, wherein the second and fourth binding domain comprising a VH region selected from SEQ ID NOs 43, 51, 59, 67, 75, 442 and 1132, preferably 67, and a VL region selected from SEQ ID NOs 44, 52, 60, 68, and 76, 443 and 1133, ~~preferably 68~~, wherein when the VH region is 1132 and the VL region is 1133, the second and/or fourth binding domain as scFab domain additionally comprises a CH1 domain of ~~SEQ ID NO: 1134~~ and a CLK domain of SEQ ID NO: 1135, and wherein the VH and VL region are linked to each other by a linker preferably selected from SEQ ID NO 1, and 3 and 1125.

29. The antigen-binding molecule according to any of the preceding claims, wherein the first and/or the third (target) binding domain bind to CDH3 and comprise a VH region comprising SEQ ID NO: 1154 as CDR-H 1 wherein X1, ~~wherein~~ (the number behind the "X" indicates the numerical order of the "X" in respective amino acid sequence in N- to C-orientation in the sequence table), is S or N, X2 is Y or S, X3 is P or W, ~~X4~~ is I or M and X5 is Y, N or H; SEQ ID NO: 1155 as CDR-H2 wherein X1 is K, V, N or R; X2 is A, D, R, Y, S, W or H; X3 is Y, S, P, G or T; X4 is S, G or K; X5 is A, V, D, K, G, or T; X6 is A, V, D, K, S, G or H; X7 is Y, G, or E; X8 is K, I, or N; X9 is A, S, or N; X10 is S, Q or G; X11 is S or K; X12 is F or V; and X13 is K or Q; and SEQ ID NO: 1156 as CDR-H3, wherein X1 is F or Q; X2 is R, K, S or W; X3 is G or D; X4 is Y, P or R; X5 is R, S, G, N or T; X6 is Y, A or H; X7 is F, L or M; X8 is A or V; and X9 is Y or V; and wherein the first and/or the third (target) binding domain bind to CDH3 and comprise a VL region comprising SEQ ID NO: 1158 as CDR-L 1 wherein X1 is ~~K~~ or R, X2 is A or S; X3 is Q, D, S, G or E; ~~X4~~ is S, D or N;

X5 is V, L or I; X6 is ~~Y~~K, Y, S, or H; X7 is S or N; ~~X~~8 is F, L or M; and ~~X~~9 is A, ~~N~~ or H; SEQ ID NO: 1159 as CDR-L 2 wherein X1 is Y, G, W, or N; X2 is T or A; X3 is S or K; X4 is T, N or R; X5 is L or R; X6 is E, A, V or H; and ~~X~~7 is S or E; and SEQ ID NO: 1160 as CDR-L3 wherein X1 is ~~Q~~Q or V; X2 is Q, N or H; X3 is F, L, Y, W, N, or H; X4 is A, D, Y, S or N; X5 is Q, R, S, G, W or M; X6 is T, Y or F; and X7 is F, Y or L.

30. The antigen-binding molecule according to any of the preceding claims, wherein the first and/or the third [\(target\)](#) binding domain bind to MSLN and comprise a VH region comprising SEQ ID NO: 1162 as CDR-H 1 wherein X1, ~~wherein~~ (the number behind the “X” indicates the numerical order of the “X” in respective amino acid sequence in N- to C-orientation in the sequence table), is S, G or D; X2 is Y, A, G or F; X3 is I, W, or M; and X4 is V, S, G, T, or H; SEQ ID NO: 1163 as CDR-H 2 wherein X1 is A, S, N, W, Y, or V; X2 is Y, S or N; X3 is Y, G, P, or S; X4 is D, H, S, or N; X5 is G or S; X6 is E, G or S; X7 is G, S, N, F, T or Q; X8 is S, W, K, D, I or T; X9 is Y or N; X10 is A or N; X11 is A, P, N, D, E, I or Q; X12 is D, A, S or K; X13 is V, L, or F; X14 is K or Q; and X15 is G or S; and SEQ ID NO: 1164 as CDR-H 3 wherein X1 is D, E or V; X2 is R, G, or E; X3 is Y, A, or N; X4 is S, Y, V, or H; X5 is A, P, F, Y, or H; X6 is R or S; X7 is E or G; X8 is Y or L; X9 is R, Y or L; X10 is Y or G; X11 is D or Y; X12 is R, Y, or F; X13 is M, S, F, D or Y; X14 is A, G, S, or T; X15 is L, M, or F; and X16 is ~~Y~~Y, I or V; and wherein the first and/or the third [\(target\)](#) binding domain bind to MSLN and comprise a VL region comprising SEQ ID NO: 1166 as CDR-L 1 wherein X1 is A or S; X2 is G or S; X3 is E or Q; X4 is G, S or K; X5 ~~is~~ is I, L, V or F; X6 is R, G or S; X7 ~~is~~ is D, S, N or T; X8 ~~is~~ is A, S, K or T; X9 is Y or W; X10 is ~~V~~V or L; and X11 is Y or A; SEQ ID NO 1167 as CDR-L2 wherein X1 ~~is~~ is A, G or Q; X2 is ~~A~~A or S; X3 ~~is~~ is S or T; ~~X~~4 ~~is~~ is G, S, K, I or T; X5 is R or L; ~~X~~6 is ~~A~~A, P or Q; and X7 is ~~S~~S or T; and SEQ ID NO 1168 as CDR-L 3 wherein X1 ~~is~~ is A or Q; X2 is Y, S, A, or T; X3 is G, E, Y, H or Q; X4 is A or S; X5 is S, T or F; X6 is P or T; X7 is R, A, L or F; and X8 is V or T.

31. The antigen-binding molecule according to any of the preceding claims, wherein the first and/or the third [\(target\)](#) binding domain bind to CDH3 and comprise a VH region of SEQ ID NO: 1157 wherein (the number behind the “X” indicates the numerical order of the “X” in respective amino acid sequence in N- to C-orientation in the sequence table, ~~wherein~~) X1 is Q or E; X2 is V, L; X3 is Q, E; X4 is A or G; X5 is G or E; X6 is ~~V~~V or L; X7 is ~~K~~K or V; X8 is K or Q; X9 is A or G; X10 is V or L; X11 is K or R; X12 is V or L; X13 is A or K; X14 is Y or F; X15 is T or S; X16 is T or S; X17 is S or N; X18 is Y or S; X19 is P or W; X20 is ~~I~~I or M; X21 is Y, N or H; X22 is ~~T~~T or

A, X23 is —Q or K, X24 is -V or M, X25 is -S or G, X26 is -K, V, N or R, X27 is —A, D, R, Y, S, W or H, X28 is —Y, S, P, G* or T, X29 is S, K, or G, X30 is A, V, D, K, or ,T; X31 is A, D, K, S, G, or H; X32 is —Y, G, or E, X33 is K, I, or N, X34 is A, S, or N, X35 is —S, Q, or G, X36 is -S or K, X37 is -F or V, X38 is -Q or K, X39 is -F or V, X40 is -I or M, X41 is T, or S, X42 is -V, I or R, X43 is T, K or N, X44 is —T, A, S or K, X45 is —S or N, X46 is -A, V or L, X47 is L or M, X48 is -Q or E, X49 is -L or M, X50 is -S or N, X51 is —S or R, X52 is -T or R, X53 is -A or S, X54 is -G, D or E; X55 is —T or S, X56 is —T, K, or R, X57 is S, Q, W, or R, X58 is D, or G, X59 is Y, P, or R; X60 is F, S, G, N or T, X61 is Y, A, or H, X62 is —A, -, or V, X63 is —F or M, X64 is -Y or V; X65 is —T, L or M; and a VL region of SEQ ID NO 1161 wherein X1 —is D or E; X2 Q or V; X3 is L, M; X4 is A, S or D; -X5 is F, S or T; X6 is —A or S; X7 is —A or V; X8 is —P, V or L; X9 is -D or E; X10 is -A or V; -X11 is —I or L; X12 is -T, S, or N; X13 is K or R; -X14 is A, S; or X15 is -Q, D, S, G or E; X16 is S, D or N; -X17 —is V, I or L; X18 is K, Y, S or H; X19 is S or N; X20 is —F, L or M; X21 is A, N or H; X22 is —K or Q; X23 is —A, P or V; X24 is —K or R; X25 is -I or V; X26 is -Y, G, W or N; -X27 is -T or A; -X28 is —S or K; -X29 is T, N or R; X30 is —L or R; -X31 is E, A, V or H; -X32 is S or E; X33 is —A, S, V or D; -X34 —is D or E; -X35 is T or K; -X36 is S or R; -X37 is A, S or P; X38 is F or V; -X39 is A, G; -X40 is T or V; -X41 is —Q or V; X42 is Q, N, H; X43 is F, L, Y, W, N or H; X44 is A, D, Y, S or N; X45 is Q, R, S, G, W or M; X46 is F, Y or T; X47 is F, Y or L; X48 is V or L; and X49 is D or E; (wherein all aa per position are preferably meant to be in the alternative “or” even if not explicitly stated).

32. The antigen-binding molecule according to any of the preceding claims, wherein the first and/or the third (target) binding domain bind to MSLN and comprise a VH region of SEQ ID NO: 1165 wherein, (the number behind the “X” indicates the numerical order of the “X” in respective amino acid sequence in N- to C-orientation in the sequence table, wherein) X1 is E or Q; X2 is V, L or Q; X3 is E or Q; X4 is A, G or P; X5 is E or G; X6 is V or L; X7 is V or K; -X8 is K or Q; X9 is G or S; -X10 is E, A, G or R; -X11 is S or T; -X12 is V or L; X13 is R, S or K; X14 is V or L; X15 is S or T; X16 is A, K or T; -X17 is A or V; -X18 is Y, I or F; X19 is S or T; X20 is S or F; X21 is S or T; X22 is D, G or S; X23 is Y, G, A or F; X24 is I, W or M; -X25 is G, S, V, T or H; -X26 is I or V; X27 is A or P; X28 is M, K or Q; X29 is G or -C; -X30 is I, M, V or L; X31 is A, G or S; X32 is A, S, N, W, Y or V; X33 is Y, S or N; X34 is Y, G, P or S; X35 is

D, H, S or N; ~~-~~X36 is G or S; X37 is E, G or S; X38 is G, S, N, F, T or Q; X39 is S, K, W, D, I, or T; X40 is Y or N; X41 is A or N; X42 is A, P, N, E, D, I or Q; X43 is D, A, S or K; X44 is V, L or F; ~~-~~X45 is K, Q; ~~-~~X46 is G or S; X47 is V or F; X48 is I or M; ~~-~~X49 is S or T; ~~-~~X50 is R or V; X51 is N or T; X52 is A or S; ~~-~~X53 is I or K; X54 is S or N; X55 is S, T or Q; X56 is A, L or F; ~~-~~X57 is Y, S or F; X58 is L or M; ~~-~~X59 is E, K or Q; X60 is M or L; X61 is S or N; X62 is R or S; X63 is V or L; ~~-~~X64 is R or T; ~~-~~X65 is A or S; ~~-~~X66 is D, A or E; X67 is R or ~~-~~K; ~~-~~X68 is D, E, V or L; X69 is E, R, G or P; ~~-~~X70 is R, A, N or Y; ~~-~~X71 is G, S, Y, V or H; X72 is A, P, F, D or Y; X73 is R or G; X74 is M, R, S or ~~-~~D; X75 is E or G; X76 is Y or L; X77 is Y or F; X78 is Y, S or F; X79 is A, G, S, T or H; X80 is L, M or F; X81 is Y, I or V; and X82 is L, M or T; and a VL region of SEQ ID NO 1169; (wherein the number behind the “X” indicates the numerical order of the “X” in respective amino acid sequence in N- to C-orientation in the sequence table; wherein ~~X1~~) X1 is E, S or D; X2 is Y, I or L; X3 is E, V or T; X4 is V, L or M; X5 is P or S; X6 is G or S; X7 is S or T; X8 is V or L; X9 is A, V or L; X10 is P or V; X11 is E, Q or D; X12 is R or T; X13 is A or V; X14 is S or T; X15 is I or L; X16 is S or T; X17 is A or S; X18 is G or S; X19 is E or Q; X20 is G, S or K; X21 is I, V, L or F; X22 is R, G or S; X23 is D or S; X24 is A, S, N, K or T; X25 is Y, W or M; X26 is V or L; X27 is Y or A; X28 is K or Q; X29 is A, S or V; X30 is R, V or K; X31 is V or L; X32 is A, G or Q; X33 is A or S; X34 is S or T; X35 is G, S, K, I or T; X36 is R or L; X37 is A, P or Q; X38 is S or T; X39 is I or V; X40 is E, S or D; X41 is G or N; X42 is N or T; X43 is D or T; X44 is A or F; X45 is R, G or S; X46 is L or T; X47 is E or Q; X48 is A or P; X49 is E or M; X50 is E or F; X51 is D, V or T; X52 is A or Q; X53 is Y, S, A or T; X54 is G, E, Y, H or Q; X55 is A or S; X56 is S, T or F; X57 is P or T; X58 is R, A, L or F; X59 is V or T; X60 is P or C; X61 is V or L; X62 is E or T; X63 is I or V; and ~~-~~X64 is L or K; (wherein all aa per position are preferably meant to be in the alternative “or” even if not explicitly stated).

33. The antigen-binding molecule according to any of the preceding claims, wherein the first and/or the third (target) binding domain comprise a VH region comprising CDR-H 1, CDR-H2 and CDR-H3 selected from SEQ ID NO: 77 to 79, 86 to 88, 95 to 97, 103 to 105, 111 to 113, 119 to 121, 127 to 129, 135 to 137, 143 to 145, 151 to 153, 159 to 161, 168 to 170, 177 to 179, 185 to 187, 194 to 196, 203 to 205, 212 to 214, 221 to 223, 230 to 232, 238 to 240, 334 to 336, 356 to 358, 365 to 367,

376 to 378, 385 to 387 and 194, 432 and 196, 446 to 448, 454 to 456, 462 to 464, 470 to 472, 478 to 480, 486 to 488, 494 to 496, 502 to 504, 510 to 512, 518 to 520, 526 to 528, 534 to 536, 542 to 544, 550 to 552, 558 to 560, 566 to 568, 574 to 576, 582 to 584, 590 to 592, 598 to 600, 606 to 608, 614 to 616, 622 to 624, 630 to 632, 638 to 640, 646 to 648, 654 to 656, 662 to 664, 670 to 672, 678 to 680, 686 to 688, 694 to 696, 702 to 704, 710 to 712, 718 to 720, 726 to 728, 734 to 736, 742 to 744, 750 to 752, 758 to 760, 766 to 768, 774 to 776, 782 to 784, 790 to 792, 798 to 800, 806 to 808, 814 to 816, 822 to 826, 830 to 832, 838 to 840, 846 to 848, 854 to 856, 862 to 864, 870 to 872, 878 to 880, 886 to 888, 894 to 896, 902 to 904, 910 to 912, 918 to 920, 926 to 928, 934 to 936, 942 to 944, 950 to 952, 958 to 960, 966 to 968, 974 to 976, 982 to 984, 990 to 992, 998 to 1000, 1006 to 1008, 1014 to 1016, 1022 to 1024, 1030 to 1032, 1038 to 1040, 1046 to 1048, 1054 to 1056, and 1062 to 1064, or [preferably any combination of CDR-H 1, CDR-H2 and CDR-H3 as disclosed together in the sequence table Tab. 52, preferably](#) 86 to 88 and 194, 432 and 196 for the first and the third binding domain, respectively, ~~or more preferably~~ 194, 432 and 196 for the first and 86 to 88 for the third binding domain.

34. The antigen-binding molecule according to any of the preceding claims, wherein the first and/or third [\(target\)](#) binding domain comprise a VL region comprising CDR-L1, CDR-L2 and CDR-L3 selected from SEQ ID NO: 80 to 82, 89 to 91, 98 to 100, 106 to 108, 114 to 116, 122 to 124, 130 to 132, 138 to 140, 146 to 148, 154 to 156, 162 to 164, 171 to 173, 180 to 182, 188 to 190, 197 to 199, 206 to 208, 215 to 217, 224 to 226, 233 to 235, 241 to 243, 337 to 339, 359 to 361, 368 to 370, 379 to 381, 388 to 390, 449 to 451, 457 to 459, 465 to 467, 473 to 475, 481 to 483, 489 to 491, 497 to 499, 505 to 507, 513 to 515, 521 to 523, 529 to 531, 537 to 539, 545 to 547, 553 to 555, 561 to 563, 569 to 571, 577 to 579, 585 to 587, 593 to 595, 601 to 603, 609 to 611, 617 to 619, 625 to 627, 633 to 635, 641 to 643, 649 to 651, 657 to 659, 665 to 667, 673 to 675, 681 to 683, 689 to 691, 697 to 699, 705 to 707, 713 to 715, 721 to 723, 729 to 731, 737 to 739, 745 to 747, 753 to 755, 761 to 763, 769 to 771, 777 to 779, 785 to 787, 793 to 795, 801 to 803, 809 to 811, 817 to 819, 825 to 829, 833 to 835, 841 to 843, 849 to 851, 857 to 859, 865 to 867, 873 to 875, 881 to 883, 889 to 891, 897 to 899, 905 to 907, 913 to 915, 921 to 923, 929 to 931, 937 to 939, 945 to 947, 953 to 955, 961 to 963, 969 to 971, 977 to 979, 985 to 987, 993 to 995, 1001 to 1003, 1009 to 1011, 1017 to 1019, 1025 to 1027, 1033 to 1035, 1041 to 1043, 1049 to 1051, 1057 to 1059, and 1065 to 1067 or [preferably any combination of CDR-L 1, CDR-L2 and CDR-L3 as disclosed together in the sequence table Tab. 52, preferably](#) 89 to 91 and

197 to 199 for the first and the third binding domain, respectively, ~~or~~ more preferably 197 to 199 for the first and 89 to 91 for the third binding domain.

35. The antigen-binding molecule according to any of the preceding claims, wherein the first and/or third (target) binding domain comprise a VH region selected from SEQ ID NO: 83, 92, 101, 109, 117, 125, 133, 141, 149, 157, 165, 174, 183, 191, 200, 209, 218, 227, 236, 244, 340, 362, 371, 382, 391, and 433, 452, 460, 468, 476, 484, 492, 500, 508, 516, 524, 532, 540, 548, 556, 564, 572, 580, 588, 596, 604, 612, 620, 628, 636, 644, 652, 660, 668, 676, 684, 692, 700, 708, 716, 724, 732, 740, 748, 756, 764, 772, 780, 788, 796, 804, 812, 820, 828, 836, 844, 852, 860, 868, 876, 884, 892, 900, 908, 916, 924, 932, 940, 948, 956, 964, 972, 980, 988, 996, 1004, 1012, 1020, 1028, 1036, 1044, 1052, 1060, and 1068 or preferably any VH as disclosed together in the sequence table Tab. 52, preferably 433 and 92 for the first and the third binding domain, respectively, ~~or~~ more preferably 433 for the first and 92 for the third binding domain.

~~36. The antigen-binding molecule according to any of the preceding claims, and/or~~ wherein the first and/or third (target) binding domain comprises a VL region selected from SEQ ID NO: 84, 93, 102, 110, 118, 126, 134, 142, 150, 158, 166, 175, 184, 192, 201, 210, 219, 228, 237, 245, 341, 363, 372, 383, 392, 453, 461, 469, 477, 485, 493, 501, 509, 517, 525, 533, 541, 549, 557, 565, 573, 581, 589, 597, 605, 613, 621, 629, 637, 645, 653, 661, 669, 677, 685, 693, 701, 709, 717, 725, 733, 741, 749, 757, 765, 773, 781, 789, 797, 805, 813, 821, 829, 837, 845, 853, 861, 869, 877, 885, 893, 901, 909, 917, 925, 933, 941, 949, 957, 965, 973, 981, 989, 997, 1005, 1013, 1021, 1029, 1037, 1045, 1053, 1061, and 1069 or preferably any VL as disclosed together in the sequence table Tab. 52, preferably 200 and 93 for the first and the third binding domain, respectively, ~~or~~ more preferably 200 for the first and 93 for the third binding domain.

~~37~~36. The antigen-binding molecule according to any of the preceding claims, wherein the first and/or third (target) binding domain comprises a VL region of increased stability by a single amino acid exchange (E to I), selected from SEQ ID NO: 85, 94, 193, 202, 211, 220, 229, 364, 384, ~~and~~ 393, ~~or~~ preferably 94 and 202.

~~38~~37. The antigen-binding molecule according to any of the preceding claims, wherein an amino acid sequence is selected from the group consisting of SEQ ID NOs: 246 to 323 or 330 to 332, 351 to

355, 373 to 375, 394 to 410, 434, 1073, ~~and 1075 to 1080, or 1075 to 1080 or any other full length~~
~~multitargeting bispecific antigen—binding molecule as disclosed in the sequence table Tab. 52,~~
~~preferably~~ 434.

~~39~~38. A polynucleotide encoding an antigen-binding molecule of any of claims 1 to 38~~7~~.

~~40. —A vector comprising a polynucleotide of claim 39.~~

~~41. —A host cell transformed or transfected with the polynucleotide of claim 39 or with the vector of claim 40.~~

~~42. —A process for the production of an antigen binding molecule of any of claims 1 to 38, said process comprising culturing a host cell of the present invention under conditions allowing the expression of the antigen binding molecule and recovering the produced antigen binding molecule from the culture.~~

~~43~~39. A pharmaceutical composition comprising an antigen-binding molecule of any of claims 1 to 33 or produced according to the process of claim 42.

~~44. —The pharmaceutical composition of claim 43~~32, which is ~~preferably~~ stable for at least four weeks at ~~about~~ -20°C.

~~45~~40. ~~An Use of the~~ antigen-binding molecule of claims 1 to 38 or produced according to the process of claim 44~~37 in the manufacture of a medicament, for use in the~~ preventing~~on~~, treating~~ment~~ or ameliorating~~on of~~ a disease selected from a proliferative disease, a tumorous disease, cancer or an immunological disorder.

~~46~~41. The ~~antigen binding molecule use~~ according to claim 45~~0~~, wherein the disease is acute myeloid leukemia (AML), Non-Hodgkin lymphoma (NHL), Non-small-cell lung carcinoma (NSCLC), pancreatic cancer and Colorectal cancer (CRC).

~~47. —A method for the treatment or amelioration of a proliferative disease, the method comprising administering to a subject in need thereof an antigen binding molecule comprising one polypeptide chain, wherein the molecule comprises~~

~~(i.) — a first binding domain which specifically binds to a first target cell surface antigen (e.g. TAA1);~~

~~(ii.) — a second binding domain which specifically binds to an extracellular epitope of the human and/or the Macaca CD3c chain;~~

~~(iii.) — a third binding domain which specifically binds to a second target cell surface antigen (e.g. TAA2), and~~

~~(iv.) — a fourth binding domain which specifically binds to an extracellular epitope of the human and/or the Macaca CD3c chain;~~

~~wherein the antigen binding molecule is characterized by the first and third domain comprise two antibody derived variable domains and the second and the fourth domain comprises two antibody derived variable domains; and wherein the structure of the binding domains are based on the structure of an antibody, and are drawn from the variable heavy chain (VH) and/or variable light chain (VL) domains of an antibody;~~

~~wherein the first binding domain is capable of binding to the first target cell surface antigen and the third binding domain is capable of binding to the second target cell surface antigen simultaneously; wherein the first target cell surface antigen and the second target cell surface antigen are on the same target cell;~~

~~wherein the antigen binding molecule is a single polypeptide chain, wherein the first target cell surface antigen and the second target cell surface antigen are not identical;~~

~~wherein the first binding domain and the second binding domain form a first bispecific entity and the third and the fourth binding domain form a second bispecific entity, and~~

~~wherein the molecule comprises a spacer entity having a molecular weight of at least 5 kDa and/or having a length of more than 50 amino acids, wherein the spacer entity spaces apart the first and the second bispecific entity, wherein the spacer entity is a globular protein, and is selected from a group consisting of ubiquitin, beta 2 microglobulin, VHH antibody lama domain, PD-1 binding domain from human Programmed cell death 1 ligand 1 (PDL1), a programmed cell death protein 1 (PD1)~~

domain, human serum albumin (HSA), and a Fc domain or dimer or trimer thereof, each Fc domain comprising two polypeptide monomers comprising each a hinge, a CH2 and a CH3 domain a hinge and a further CH2 and a CH3 domain, wherein said two polypeptide monomers are fused to each other via a peptide linker, and which spacer entity is positioned between the first and the second bispecific entity, comprising the step of administering to a subject in need thereof the antigen-binding molecule of the present invention, or produced according to the process of the present invention.

4842. The method-use of claim 4740, wherein the method-use comprises addressing a disease-associated target being significantly co-expressed on a pathophysiological and one or more physiological tissues by providing a multitargeting bispecific antigen-binding molecule of the format described herein, wherein the molecule addresses (i.) the target expressed both on the disease-associated and the physiological tissue and (ii.) a further target which is disease associated but not expressed on the physiological tissue under (i.), wherein the method preferably avoids the formation of intra-abdominal adhesions and/or fibrosis where such target is MSLN.

49. ~~The method of claim 47, wherein the disease is a tumorous disease, a cancer, or an immunological disorder.~~

50. ~~The method of claim 49, wherein the disease is acute myeloid leukemia, Non-Hodgkin lymphoma, Non-small cell lung carcinoma, pancreatic cancer and/or Colorectal cancer.~~

5143. ~~The method of claim 47~~The use of claim 40, wherein the TAA1 and TAA2 are selected from EpCAM and MSLN, MSLN and EpCAM, MSLN and CDH3, CDH3 and MSLN, FLT3 and CLL1, and CLL1 and FLT3.

52. ~~—A kit comprising an antigen-binding molecule of any of claims 1 to 38, or produced according to the process of claim 42, a polynucleotide of claim 39, a vector of claim 40, and/or a host cell of claim 41.~~