

CLAIMS

1. Conjugate for transferring a saponin from outside a cell into said cell, comprising a single-domain antibody (sdAb), capable of binding to said cell, covalently bound to at least one saponin, directly or via
5 a linker, wherein the at least one saponin is a monodesmosidic triterpene glycoside or a bidesmosidic triterpene glycoside.
2. Conjugate of claim 1, wherein the sdAb is a V_H domain derived from a heavy chain of an antibody, preferably of immunoglobulin G origin, preferably of human origin, a V_L domain derived from a light chain
10 of an antibody, preferably of immunoglobulin G origin, preferably of human origin, a V_{HH} domain such as derived from a heavy-chain only antibody (HCAb) such as from *Camelidae* origin or *Ig-NAR* origin such as a variable heavy chain new antigen receptor (V_{NAR}) domain, preferably the HCAb is from *Camelidae* origin, preferably the sdAb is a V_{HH} domain derived from an HCAb from *Camelidae* origin (camelid V_H) such as derived from an HCAb from camel, lama, alpaca, dromedary, vicuna, guanaco and
15 Bactrian camel.
3. Conjugate of claim 1 or 2, wherein the conjugate comprises at least two sdAbs with a single first sdAb covalently linked to the at least one saponin, or with two or more sdAbs linked to at least one saponin, or with all of the at least two sdAbs linked to at least one saponin.
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4. Conjugate of any one of the claims 1-3, wherein the sdAb comprises at least two sdAbs, which are the same sdAbs, preferably two – eight sdAbs, more preferably two – four sdAbs.
5. Conjugate of any one of the claims 1-4, comprising one – eight sdAbs, capable of binding to the same
25 binding site on a cell-surface molecule of the cell, wherein the at least one saponin is linked to a single first sdAb of the one – eight sdAbs or wherein the at least one saponin is linked to two or more of the sdAbs, if present.
6. Conjugate of any one of the claims 1-5, comprising at least two sdAbs which are biparatopic,
30 preferably comprising two sdAbs which are biparatopic.
7. Conjugate of any one of the claims 1-6, wherein the conjugate comprises 1 – 100 saponin moieties of the at least one saponin, preferably 2 – 64 saponin moieties, more preferably 4 – 32 saponin moieties, most preferably 8 – 16 saponin moieties, or any number therein between.
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8. Conjugate of any one of the claims 1-7, wherein the at least one saponin comprises an aglycone core structure selected from any one of:
2alpha-hydroxy oleanolic acid;
16alpha-hydroxy oleanolic acid;
40 hederagenin (23-hydroxy oleanolic acid);

- 16 α ,23-dihydroxy oleanolic acid;
 gypsogenin;
 quillaic acid;
 protoaescigenin-21(2-methylbut-2-enoate)-22-acetate;
- 5 23-oxo-barringtogenol C-21,22-bis(2-methylbut-2-enoate);
 23-oxo-barringtogenol C-21(2-methylbut-2-enoate)-16,22-diacetate;
 digitogenin;
 3,16,28-trihydroxy oleanan-12-en; and
 gypsogenic acid,
- 10 preferably, the at least one saponin comprises an aglycone core structure selected from quillaic acid
 and gypsogenin, more preferably the aglycone core structure of the at least one saponin is quillaic acid.
9. Conjugate of any one of the claims 1-8, wherein the at least one saponin comprises a first saccharide
 chain, which is bound to the C₃ atom or the C₂₈ atom of the aglycone core structure of the at least one
- 15 saponin, preferably to the C₃ atom, and/or wherein the at least one saponin comprises a second
 saccharide chain, which is bound to the C₂₈ atom of the aglycone core structure of the at least one
 saponin, preferably, the at least one saponin comprises the first and second saccharide chain.
10. Conjugate of any one of the claims 1-9, wherein the at least one saponin comprises a first saccharide
 chain selected from:
- 20 GlcA-,
 Glc-,
 Gal-,
 Rha-(1→2)-Ara-,
- 25 Gal-(1→2)-[Xyl-(1→3)]-GlcA-,
 Glc-(1→2)-[Glc-(1→4)]-GlcA-,
 Glc-(1→2)-Ara-(1→3)-[Gal-(1→2)]-GlcA-,
 Xyl-(1→2)-Ara-(1→3)-[Gal-(1→2)]-GlcA-,
 Glc-(1→3)-Gal-(1→2)-[Xyl-(1→3)]-Glc-(1→4)-Gal-,
- 30 Rha-(1→2)-Gal-(1→3)-[Glc-(1→2)]-GlcA-,
 Ara-(1→4)-Rha-(1→2)-Glc-(1→2)-Rha-(1→2)-GlcA-,
 Ara-(1→4)-Fuc-(1→2)-Glc-(1→2)-Rha-(1→2)-GlcA-,
 Ara-(1→4)-Rha-(1→2)-Gal-(1→2)-Rha-(1→2)-GlcA-,
 Ara-(1→4)-Fuc-(1→2)-Gal-(1→2)-Rha-(1→2)-GlcA-,
- 35 Ara-(1→4)-Rha-(1→2)-Glc-(1→2)-Fuc-(1→2)-GlcA-,
 Ara-(1→4)-Fuc-(1→2)-Glc-(1→2)-Fuc-(1→2)-GlcA-,
 Ara-(1→4)-Rha-(1→2)-Gal-(1→2)-Fuc-(1→2)-GlcA-,
 Ara-(1→4)-Fuc-(1→2)-Gal-(1→2)-Fuc-(1→2)-GlcA-,
 Xyl-(1→4)-Rha-(1→2)-Glc-(1→2)-Rha-(1→2)-GlcA-,
- 40 Xyl-(1→4)-Fuc-(1→2)-Glc-(1→2)-Rha-(1→2)-GlcA-,

- Xyl-(1→4)-Rha-(1→2)-Gal-(1→2)-Rha-(1→2)-GlcA-,
 Xyl-(1→4)-Fuc-(1→2)-Gal-(1→2)-Rha-(1→2)-GlcA-,
 Xyl-(1→4)-Rha-(1→2)-Glc-(1→2)-Fuc-(1→2)-GlcA-,
 Xyl-(1→4)-Fuc-(1→2)-Glc-(1→2)-Fuc-(1→2)-GlcA-,
 5 Xyl-(1→4)-Rha-(1→2)-Gal-(1→2)-Fuc-(1→2)-GlcA-, and
 Xyl-(1→4)-Fuc-(1→2)-Gal-(1→2)-Fuc-(1→2)-GlcA-,
 and/or wherein the at least one saponin comprises a second saccharide chain is selected from:
 Glc-,
 Gal-,
 10 Rha-(1→2)-[Xyl-(1→4)]-Rha-,
 Rha-(1→2)-[Ara-(1→3)-Xyl-(1→4)]-Rha-,
 Ara-,
 Xyl-,
 Xyl-(1→4)-Rha-(1→2)-[R1-(→4)]-Fuc- wherein R1 is 4E-Methoxycinnamic acid,
 15 Xyl-(1→4)-Rha-(1→2)-[R2-(→4)]-Fuc- wherein R2 is 4Z-Methoxycinnamic acid,
 Xyl-(1→4)-[Gal-(1→3)]-Rha-(1→2)-4-OAc-Fuc-,
 Xyl-(1→4)-[Glc-(1→3)]-Rha-(1→2)-3,4-di-OAc-Fuc-,
 Xyl-(1→4)-[Glc-(1→3)]-Rha-(1→2)-[R3-(→4)]-3-OAc-Fuc- wherein R3 is 4E-Methoxycinnamic acid,
 Glc-(1→3)-Xyl-(1→4)-[Glc-(1→3)]-Rha-(1→2)-4-OAc-Fuc-,
 20 Glc-(1→3)-Xyl-(1→4)-Rha-(1→2)-4-OAc-Fuc-,
 (Ara- or Xyl)-(1→3)-(Ara- or Xyl)-(1→4)-(Rha- or Fuc)-(1→2)-[4-OAc-(Rha- or Fuc)-(1→4)]-(Rha- or
 Fuc-),
 Xyl-(1→3)-Xyl-(1→4)-Rha-(1→2)-[Qui-(1→4)]-Fuc-,
 Api-(1→3)-Xyl-(1→4)-[Glc-(1→3)]-Rha-(1→2)-Fuc-,
 25 Xyl-(1→4)-[Gal-(1→3)]-Rha-(1→2)-Fuc-,
 Xyl-(1→4)-[Glc-(1→3)]-Rha-(1→2)-Fuc-,
 Ara/Xyl-(1→4)-Rha/Fuc-(1→4)-[Glc/Gal-(1→2)]-Fuc-,
 Api-(1→3)-Xyl-(1→4)-[Glc-(1→3)]-Rha-(1→2)-[R4-(→4)]-Fuc- wherein R4 is 5-O-[5-O-Ara/Api-3,5-
 dihydroxy-6-methyl-octanoyl]-3,5-dihydroxy-6-methyl-octanoic acid),
 30 Api-(1→3)-Xyl-(1→4)-Rha-(1→2)-[R5-(→4)]-Fuc- wherein R5 is 5-O-[5-O-Ara/Api-3,5-dihydroxy-6-
 methyl-octanoyl]-3,5-dihydroxy-6-methyl-octanoic acid),
 Api-(1→3)-Xyl-(1→4)-Rha-(1→2)-[Rha-(1→3)]-4-OAc-Fuc-,
 Api-(1→3)-Xyl-(1→4)-[Glc-(1→3)]-Rha-(1→2)-[Rha-(1→3)]-4-OAc-Fuc-,
 6-OAc-Glc-(1→3)-Xyl-(1→4)-Rha-(1→2)-[3-OAc-Rha-(1→3)]-Fuc-,
 35 Glc-(1→3)-Xyl-(1→4)-Rha-(1→2)-[3-OAc-Rha-(1→3)]-Fuc-,
 Xyl-(1→3)-Xyl-(1→4)-Rha-(1→2)-[Qui-(1→4)]-Fuc-,
 Glc-(1→3)-[Xyl-(1→4)]-Rha-(1→2)-[Qui-(1→4)]-Fuc-,
 Glc-(1→3)-Xyl-(1→4)-Rha-(1→2)-[Xyl-(1→3)-4-OAc-Qui-(1→4)]-Fuc-,
 Xyl-(1→3)-Xyl-(1→4)-Rha-(1→2)-[3,4-di-OAc-Qui-(1→4)]-Fuc-,
 40 Glc-(1→3)-[Xyl-(1→4)]-Rha-(1→2)-Fuc-,

- 6-OAc-Glc-(1→3)-[Xyl-(1→4)]-Rha-(1→2)-Fuc-,
 Glc-(1→3)-[Xyl-(1→3)-Xyl-(1→4)]-Rha-(1→2)-Fuc-,
 Xyl-(1→3)-Xyl-(1→4)-Rha-(1→2)-[Xyl-(1→3)-4-OAc-Qui-(1→4)]-Fuc-,
 Api/Xyl-(1→3)-Xyl-(1→4)-[Glc-(1→3)]-Rha-(1→2)-[Rha-(1→3)]-4OAc-Fuc-,
 5 Api-(1→3)-Xyl-(1→4)-[Glc-(1→3)]-Rha-(1→2)-[Rha-(1→3)]-4OAc-Fuc-,
 Api/Xyl-(1→3)-Xyl-(1→4)-[Glc-(1→3)]-Rha-(1→2)-[R6-(→4)]-Fuc- wherein R6 is 5-O-[5-O-Rha-(1→2)-
 Ara/Api-3,5-dihydroxy-6-methyl-octanoyl]-3,5-dihydroxy-6-methyl-octanoic acid),
 Api/Xyl-(1→3)-Xyl-(1→4)-[Glc-(1→3)]-Rha-(1→2)-[R7-(→4)]-Fuc- wherein R7 is 5-O-[5-O-Ara/Api-3,5-
 dihydroxy-6-methyl-octanoyl]-3,5-dihydroxy-6-methyl-octanoic acid),
 10 Api/Xyl-(1→3)-Xyl-(1→4)-[Glc-(1→3)]-Rha-(1→2)-[R8-(→4)]-Fuc- wherein R8 is 5-O-[5-O-Ara/Api-3,5-
 dihydroxy-6-methyl-octanoyl]-3,5-dihydroxy-6-methyl-octanoic acid),
 Api-(1→3)-Xyl-(1→4)-Rha-(1→2)-[R9-(→4)]-Fuc- wherein R9 is 5-O-[5-O-Ara/Api-3,5-dihydroxy-6-
 methyl-octanoyl]-3,5-dihydroxy-6-methyl-octanoic acid),
 Xyl-(1→3)-Xyl-(1→4)-Rha-(1→2)-[R10-(→4)]-Fuc- wherein R10 is 5-O-[5-O-Ara/Api-3,5-dihydroxy-6-
 15 methyl-octanoyl]-3,5-dihydroxy-6-methyl-octanoic acid),
 Api-(1→3)-Xyl-(1→4)-Rha-(1→2)-[R11-(→3)]-Fuc- wherein R11 is 5-O-[5-O-Ara/Api-3,5-dihydroxy-6-
 methyl-octanoyl]-3,5-dihydroxy-6-methyl-octanoic acid),
 Xyl-(1→3)-Xyl-(1→4)-Rha-(1→2)-[R12-(→3)]-Fuc- wherein R12 is 5-O-[5-O-Ara/Api-3,5-dihydroxy-6-
 methyl-octanoyl]-3,5-dihydroxy-6-methyl-octanoic acid) and
 20 Glc-(1→3)-[Glc-(1→6)]-Gal-,
 preferably the at least one saponin comprises such a selected first saccharide chain and such a selected
 second saccharide chain.

11. Conjugate of any one of the claims 1-10, wherein the at least one saponin is selected from: 3-O-
 25 beta-D-galactopyranosyl-(1→2)-[beta-D-xylopyranosyl-(1→3)]-beta-D-glucuronopyranosyl quillaic
 acid 28-O-beta-D-glucopyranosyl-(1→3)-beta-D-xylopyranosyl-(1→4)- alpha-L-rhamnopyranosyl-
 (1→2)-[beta-D-xylopyranosyl-(1→3)-4OAc-beta-D-quinovopyranosyl-(1→4)]-beta-D-fucopyranoside,
Quillaja bark saponin, dipsacoside B, saikosaponin A, saikosaponin D, macranthoidin A, esculentoside
 A, phytolaccagenin, aescinate, AS6.2, NP-005236, AMA-1, AMR, alpha-Hederin, NP-012672, NP-
 30 017777, NP-017778, NP-017774, NP-018110, NP-017772, NP-018109, NP-017888, NP-017889, NP-
 018108, SA1641, AE X55, NP-017674, NP-017810, AG1, NP-003881, NP-017676, NP-017677, NP-
 017706, NP-017705, NP-017773, NP-017775, SA1657, AG2, SO1861, SO1862, SO1904, GE1741,
 SO1542, SO1584, SO1658, SO1674, SO1832, QS-7, QS1861, QS-7 api, QS1862, QS-17, QS-18, QS-
 21 A-apio, QS-21 A-xylo, QS-21 B-apio, QS-21 B-xylo, beta-Aescin, Aescin Ia, Teaseed saponin I,
 35 Teaseedsaponin J, Assamsaponin F, Digitonin, Primula acid 1 and AS64R, and/or a functional derivative
 thereof, and/or a stereoisomer thereof, and/or any combination thereof, the functional derivative
 optionally without an aldehyde group in the aglycone core structure of the at least one saponin, and/or
 without a glucuronic acid moiety comprising a carboxyl group in a first saccharide chain of the at least
 one saponin, and/or without an acetyl group in a second saccharide chain of the at least one saponin,
 40 preferably the at least one saponin is selected from: QS-21, GE1741, SA1641 and SO1861, and/or a

functional derivative thereof, the functional derivative preferably without an aldehyde group in the aglycone core structure of the at least one saponin, and/or without a glucuronic acid moiety comprising a carboxyl group in a first saccharide chain of the at least one saponin, and/or without an acetyl group in a second saccharide chain of the at least one saponin.

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12. Conjugate of any one of the claims 1-11, wherein the at least one saponin is selected from: SO1861, SA1657, GE1741, SA1641, QS-21, QS-21A, QS-21 A-api, QS-21 A-xyl, QS-21B, QS-21 B-api, QS-21 B-xyl, QS-7-xyl, QS-7-api, QS-17-api, QS-17-xyl, QS1861, QS1862, Quillajasaponin, Saponinum album, QS-18, Quil-A, Gyp1, gypsoside A, AG1, AG2, SO1542, SO1584, SO1658, SO1674, SO1832, SO1862, SO1904, and/or a stereoisomer thereof, and/or a functional derivative thereof, and/or any combination thereof, optionally the functional derivative without an aldehyde group in the aglycone core structure of the at least one saponin, and/or without a glucuronic acid moiety comprising a carboxyl group in a first saccharide chain of the at least one saponin, and/or without an acetyl group in a second saccharide chain of the at least one saponin, preferably the at least one saponin is selected from: SO1861, GE1741, SA1641 and QS-21, preferably a functional derivative thereof without an aldehyde group in the aglycone core structure of the at least one saponin, and/or without a glucuronic acid moiety comprising a carboxyl group in a first saccharide chain of the at least one saponin, and/or without an acetyl group in a second saccharide chain of the at least one saponin.

13. Conjugate of any one of the claims 1-12, wherein the at least one saponin comprises an aglycone core structure comprising an aldehyde group, and/or comprises a first saccharide chain comprising a glucuronic acid moiety comprising a carboxyl group, and/or comprises a second saccharide chain comprising an acetyl group, preferably, the at least one saponin comprises an aglycone core structure comprising an aldehyde group, a first saccharide chain comprising a glucuronic acid moiety comprising a carboxyl group and a second saccharide chain comprising an acetyl group, more preferably, the at least one saponin comprises one or two of: an aglycone core structure comprising an aldehyde group, a first saccharide chain comprising a glucuronic acid moiety comprising a carboxyl group, a second saccharide chain comprising an acetyl group.

14. Conjugate of claim 11 or 12, wherein the at least one saponin is a saponin functional derivative comprising none of an aglycone core structure comprising an aldehyde group, a first saccharide chain comprising a glucuronic acid moiety comprising a carboxyl group and a second saccharide chain comprising an acetyl group.

15. Conjugate of any one of the claims 1-14, wherein the at least one saponin is covalently bound to the sdAb via a linker, preferably a cleavable linker.

16. Conjugate of claim 15, wherein the cleavable linker is subject to cleavage under acidic conditions, reductive conditions, enzymatic conditions and/or light-induced conditions, and preferably the cleavable linker comprises a cleavable bond selected from a hydrazone bond and a hydrazide bond subject to

cleavage under acidic conditions, and/or a bond susceptible to proteolysis, for example proteolysis by Cathepsin B, and/or a bond susceptible for cleavage under reductive conditions such as a disulfide bond.

- 5 17. Conjugate of claim 15 or 16, wherein the cleavable linker is subject to cleavage *in vivo* under acidic conditions such as for example present in endosomes and/or lysosomes of mammalian cells, preferably human cells, preferably the cleavable linker is subject to cleavage *in vivo* at pH 4.0 – 6.5, and more preferably at pH ≤ 5.5 .
- 10 18. Conjugate of any one of the claims 1-17, wherein the at least one saponin is part of a covalent saponin conjugate comprising an oligomeric molecule or a polymeric molecule to which the saponin is covalently bound, and wherein the sdAb is also covalently bound to the same oligomeric molecule or polymeric molecule as to which the saponin is bound.
- 15 19. Conjugate of claim 18, wherein 1-8 of the oligomeric molecules or polymeric molecules comprising the saponin(s) is/are covalently bound to the sdAb, or 2-4 of the oligomeric molecules or polymeric molecules comprising the saponin(s), wherein the oligomeric molecule or the polymeric molecule of the covalent saponin conjugate is optionally a dendron such as a G2 dendron, G3 dendron, G4 dendron or G5 dendron with 4, 8, 16 and 32 binding sites for covalently binding 4, 8, 16 or 32 saponin moieties, respectively, wherein 1-32 saponin moieties, preferably 2, 3, 4, 5, 6, 8, 10, 16, 32 saponin moieties, or
20 any number of saponin moieties therein between, such as 7, 9, 12 saponin moieties, are covalently bound to the oligomeric molecule or to the polymeric molecule of the covalent saponin conjugate.
- 25 20. Conjugate of claim 18 or 19, wherein the at least one saponin is covalently bound to the oligomeric molecule or to the polymeric molecule of the covalent saponin conjugate via any one or more of an imine bond, a hydrazone bond, a hydrazide bond, an oxime bond, a 1,3-dioxolane bond, a disulfide bond, a thio-ether bond, an amide bond, a peptide bond or an ester bond, preferably via a linker.
- 30 21. Conjugate of claim 20, wherein the at least one saponin comprises an aldehyde function in position C₂₃ of the aglycone core structure of the at least one saponin and optionally a glucuronic acid function in a first saccharide chain at the C₃beta-OH group of the aglycone core structure of the at least one saponin, which aldehyde function is involved in the covalent bonding to the oligomeric molecule or to the polymeric molecule of the covalent saponin conjugate, and/or, if present, the glucuronic acid function is involved in the covalent bonding of the at least one saponin to the oligomeric molecule or to the
35 polymeric molecule of the covalent saponin conjugate, the bonding of the at least one saponin either via a direct covalent bond, or via a linker.
- 40 22. Conjugate of claim 21, wherein the aldehyde function in position C₂₃ of the aglycone core structure of the at least one saponin is covalently bound to a linker, preferably to linker N-ε-maleimidocaproic acid hydrazide (EMCH), which linker is covalently bound via a thio-ether bond to a sulfhydryl group in the

oligomeric molecule or in the polymeric molecule of the covalent saponin conjugate, such as a sulfhydryl group of a cysteine.

23. Conjugate of claim 21 or 22, wherein the glucuronic acid function in the first saccharide chain at the C₃β-OH group of the aglycone core structure of the at least one saponin is covalently bound to a linker such as linker 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU), which linker is covalently bound via an amide bond to an amine group in the oligomeric molecule or in the polymeric molecule of the covalent saponin conjugate, such as an amine group of a lysine or an N-terminus of a protein.

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24. Conjugate of any one of the claims 20-23, wherein the polymeric molecule or the oligomeric molecule of the covalent saponin conjugate is bound to the sdAb, preferably to an amino-acid residue of the sdAb, involving a click chemistry group on the polymeric molecule or the oligomeric molecule of the covalent saponin conjugate, the click chemistry group preferably selected from a tetrazine, an azide, an alkene or an alkyne, or a cyclic derivative of these groups, more preferably the click chemistry group is an azide.

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25. Conjugate of any one of the claims 18-24, wherein the polymeric molecule or the oligomeric molecule of the covalent saponin conjugate comprises a polymeric structure and/or an oligomeric structure selected from: a linear polymer, a branched polymer and/or a cyclic polymer, an oligomer, a dendrimer, a dendron, a dendronized polymer, a dendronized oligomer, a DNA, a polypeptide, a poly-lysine, a poly-ethylene glycol, an oligo-ethylene glycol (OEG), such as OEG₃, OEG₄ and OEG₅, or an assembly of these polymeric structures and/or oligomeric structures which assembly is preferably built up by covalent cross-linking, preferably the polymeric molecule or the oligomeric molecule of the covalent saponin conjugate is a dendron such as a poly-amidoamine (PAMAM) dendrimer.

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26. Conjugate of any one of the claims 1-25, wherein the sdAb is a single sdAb or are at least two, preferably two sdAbs, wherein the sdAb(s) can bind to a tumor-cell surface molecule of the cell, preferably a tumor-cell surface receptor such as a tumor-cell specific receptor, more preferably a receptor of the cell selected from any one or more of: CD71, CA125, EpCAM(17-1A), CD52, CEA, CD44v6, FAP, EGF-IR, integrin, syndecan-1, vascular integrin alpha-V beta-3, HER2, EGFR, CD20, CD22, Folate receptor 1, CD146, CD56, CD19, CD138, CD27L receptor, prostate specific membrane antigen (PSMA), CanAg, integrin-alphaV, CA6, CD33, mesothelin, Cripto, CD3, CD30, CD239, CD70, CD123, CD352, DLL3, CD25, ephrinA4, MUC-1, Trop2, CEACAM5, CEACAM6, HER3, CD74, PTK7, Notch3, FGF2, C4.4A, FLT3, CD38, FGFR3, CD7, PD-L1, CTLA-4, CD52, PDGFRA, VEGFR1, VEGFR2, c-Met (HGFR), EGFR1, RANKL, ADAMTS5, CD16, CXCR7 (ACKR3), glucocorticoid-induced TNFR-related protein (GITR), most preferably selected from: HER2, c-Met, VEGFR2, CXCR7, CD71 and EGFR1.

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27. Conjugate of any one of the claims 1-26, wherein the sdAb is a single sdAb or are at least two, preferably two sdAbs, wherein the sdAb(s) is/are selected from: an anti-CD71 sdAb, an anti-HER2 sdAb,

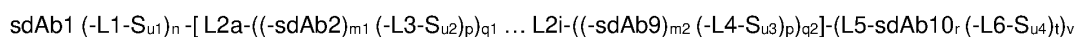
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an anti-CD20 sdAb, an anti-CA125 sdAb, an anti-EpCAM (17-1A) sdAb, an anti-EGFR sdAb, an anti-CD30 sdAb, an anti-CD33 sdAb, an anti-vascular integrin alpha-v beta-3 sdAb, an anti-CD52 sdAb, an anti-CD22 sdAb, an anti-CEA sdAb, an anti-CD44v6 sdAb, an anti-FAP sdAb, an anti-CD19 sdAb, an anti-CanAg sdAb, an anti-CD56 sdAb, an anti-CD38 sdAb, an anti-CA6 sdAb, an anti-IGF-1R sdAb, an anti-integrin sdAb, an anti-syndecan-1 sdAb, an anti-CD79b, an anti-c-Met sdAb, an anti-EGFR1 sdAb, an anti-VEGFR2 sdAb, an anti-CXCR7 sdAb, wherein the sdAb(s) is/are preferably $V_{HH}(s)$, more preferably camelid $V_H(s)$.

28. Conjugate of any one of the claims 1-27, wherein the conjugate comprises an sdAb that can bind to HER2, CD71 or to EGFR, wherein the sdAb is preferably a V_{HH} , more preferably camelid V_H .

29. Conjugate of any one of the claims 1-28, wherein the conjugate comprises an sdAb for binding to HER2 selected from: sdAb produced by clone 11A4, clone 18C3, clone 22G12, clone Q17, clone Q17-C-tag; or an sdAb for binding to EGFR and produced by clone anti-EGFR Q86-C-tag; or an sdAb for binding to CD71 and produced by clone anti-CD71 Q52-C-tag; or an sdAb for binding to HIVgp41 and produced by clone anti-HIVgp41 Q8-C-tag; or an sdAb encoded by a cDNA of any one of the SEQ ID NO: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, 23, 25, 27, 29 and 31; or any one of the sdAbs with an amino-acid sequence of SEQ ID NO: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 36-72, or the biparatopic tandem of sdAbs 7D12 and 9G8 with an amino-acid sequence of SEQ ID NO: 74 or sdAb 7D12 with an amino-acid sequence of SEQ ID NO: 75 or sdAb 9G8 with an amino-acid sequence of SEQ ID NO: 76, wherein optionally the conjugate further comprises an sdAb for binding to albumin, such as any one or more of sdAbs with an amino-acid sequence of SEQ ID NO: 33, 34 and 35.

30. Conjugate of any one of the claims 1-29, wherein the conjugate is represented by the general structure of Molecule I:



(Molecule I),

wherein sdAb1, sdAb2 ... sdAb9, sdAb10 are sdAbs sdAb1, sdAb2, sdAb3, sdAb4, sdAb5, sdAb6, sdAb7, sdAb8, sdAb9 and sdAb10, which sdAbs are the same sdAb;

S is at least one saponin moiety;

L1, L3, L4 and L6 are each independently a covalent bond or a covalent linker linking the at least one saponin to the sdAb, wherein such linkers are the same or different;

L2a – L2i, and L5 are each independently a covalent bond or a covalent linker linking two consecutive sdAbs if more than one sdAb is present, wherein such linkers are the same or different;

n is an integer selected from 0 – 4, preferably n is 1, 2, 3 or 4;

m1, m2 each independently is an integer selected from 0 – 10, preferably m1 and/or m2 is/are 0, 1, 2, 3, 4, 5, 6, 7 or 8, wherein, if m1 or m2 is > 1, consecutive sdAbs are covalently linked, preferably via a linker;

p is an integer selected from 0 – 4, preferably p is 1, 2, 3 or 4;

5 q1, q2 each independently is an integer selected from 0 – 10, preferably q1 and/or q2 is/are 0, 1, 2, 3, 4, 5, 6, 7 or 8;

r is an integer selected from 0 – 10, preferably r is 0, 1, 2, 3, 4, 5, 6, 7, 8 or 9;

t is an integer selected from 0 – 4, preferably t is 1, 2, 3 or 4;

10 u1, u2, u3, u4 are an integer, each independently selected from 0 – 100, preferably u1, u2, u3 and/or u4 is/are 0, 1, 2, 4, 16, 32 or 64, preferably u1, u2, u3 and u4 are the same; and v is 0 or 1.

31. Conjugate of claim 30, wherein L1 and L2a are linkers, u1 is > 0, n is > 0, m1 is any of 1-9, p is 0, q1 is 1, m2 is 0, u2 is 0, u3 is 0, q2 is 0, v is 0, r is 0, u4 is 0 and t is 0, or wherein L1, L2a, L5 and L6
15 are a linker, u1 is 0, n is 0, m1 is any of 1-9, u2 is 0, p is 0, q1 is 1, m2 is 0, u3 is 0, p is 0, q2 is 0, r is 1, u4 is > 1, t is > 1 and v is 1.

32. Pharmaceutical combination comprising:

20 - a first pharmaceutical composition comprising the conjugate of any one of the claims 1-31 and optionally comprising a pharmaceutically acceptable excipient and/or a pharmaceutically acceptable diluent; and

25 - a second pharmaceutical composition comprising an active pharmaceutical ingredient such as selected from any one or more of: a drug molecule, an oligonucleotide such as an mRNA, an anti-sense oligonucleotide, a ligand-drug conjugate such as EGF-dianthin or EGF-saporin, an antibody-drug conjugate (ADC) such as OKT9 monoclonal anti-CD71 antibody, trastuzumab or cetuximab conjugated with saporin, dianthin or a BNA, a ligand-oligonucleotide conjugate such as an antibody-oligonucleotide conjugate (AOC) such as an antibody-BNA conjugate or an antibody-siRNA conjugate, wherein the antibody of the ADC or the AOC optionally comprises or consists of at least one sdAb, wherein the at least one sdAb comprised by the ADC or AOC is/are different from or the same as the sdAb of the
30 conjugate of any one of the claims 1-31, and optionally comprising a pharmaceutically acceptable excipient and/or a pharmaceutically acceptable diluent.

33. Pharmaceutical composition comprising:

35 - the conjugate of any one of the claims 1-31;
- one or more active pharmaceutical ingredients, such as selected from: a drug molecule, an oligonucleotide such as an mRNA, an ASO, a ligand-drug conjugate such as EGF-dianthin or EGF-saporin, an ADC such as OKT9 monoclonal anti-CD71 antibody, trastuzumab or cetuximab conjugated with saporin, dianthin or a BNA, a ligand-oligonucleotide conjugate such as an AOC such as an antibody-BNA conjugate or an antibody-siRNA conjugate, wherein optionally the antibody of the ADC
40 or the AOC comprises or consists of at least one sdAb, wherein the at least one sdAb comprised by the

ADC or AOC is/are different from or the same as the sdAb of the conjugate of any one of the claims 1-31; and

optionally comprising a pharmaceutically acceptable excipient and/or a pharmaceutically acceptable diluent.

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34. Pharmaceutical combination of claim 32 or pharmaceutical composition of claim 33, wherein the antibody of the ADC or the AOC comprises or is a V_{HH}, preferably a camelid V_H.

10 35. Pharmaceutical combination of claim 32 or 34 or pharmaceutical composition of claim 33-34, wherein the conjugate of any one of the claims 1-31 comprises an sdAb that can bind to HER2, CD71 or EGFR, and/or wherein one or more active pharmaceutical ingredient(s) comprise(s) an sdAb that can bind to HER2, CD71 or EGFR, and/or wherein the ADC comprises dianthin or saporin.

15 36. Pharmaceutical combination of any one of the claims 32 or 34-35 or pharmaceutical composition of any one of the claims 33-35, for use as a medicament.

20 37. Pharmaceutical combination of any one of the claims 32 or 34-35 or pharmaceutical composition of any one of the claims 32-34, for use in the treatment or the prophylaxis of a cancer, an auto-immune disease, an infection such as a viral infection, an enzyme deficiency, a disorder or disease relating to an enzyme deficiency, a gene defect, a disorder or disease relating to a gene defect.

38. *In vitro* or *ex vivo* method for transferring a molecule from outside a cell to inside said cell, preferably to the cytosol of said cell, comprising the steps of:

- 25 a) providing a cell which expresses a binding site for the sdAb according to any one of the claims 1-31 on its surface, preferably selected from a liver cell, an aberrant cell such as a virally infected cell, an auto-immune cell and a tumor cell;
- b) providing the molecule for transferring into the cell provided in step a), wherein the molecule is any one or more of the active pharmaceutical ingredient(s) of any one of the claims 32-35;
- 30 c) providing the conjugate of any one of the claims 1-31;
- d) contacting the cell of step a) *in vitro* or *ex vivo* with the molecule of step b) and the conjugate of step c),

therewith establishing the transfer of the molecule from outside the cell into said cell, preferably into the cytosol of said cell.

35 39. Kit of parts, comprising the pharmaceutical combination of any one of the claims 32 or 34-35 or the pharmaceutical composition of any one of the claims 33-35, or the conjugate of any one of the claims 1-31, and instructions for use of said pharmaceutical combination according to any one of the claims 32 or 34-38, for use of said pharmaceutical composition according to any one of the claims 33-38, or for use of said conjugate according to claim 38.

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