CLAIMS

1. Therapeutic combination comprising:

(a) a first pharmaceutical composition comprising a conjugate comprising a first binding molecule comprising a first binding region for binding to a first binding site of a cell-surface molecule and the conjugate comprising at least one saponin covalently bound to said first binding molecule, wherein the saponin is a monodesmosidic triterpene glycoside or a bidesmosidic triterpene glycoside; and

(b) a second pharmaceutical composition comprising a conjugate comprising a second binding molecule different from the first binding molecule, the second binding molecule comprising a second binding region different from the first binding region, the second binding region for binding to a second binding site of said cell-surface molecule different from the first binding site of said cell-surface molecule, and the conjugate comprising an effector molecule covalently bound to said second binding molecule,

the first pharmaceutical composition and the second pharmaceutical composition optionally further comprising a pharmaceutically acceptable excipient and optionally further comprising a pharmaceutically acceptable diluent.

2. Pharmaceutical composition comprising:

- a conjugate comprising a first binding molecule comprising a first binding region for binding to a first binding site of a cell-surface molecule and the conjugate comprising at least one saponin covalently bound to said first binding molecule, wherein the saponin is a triterpenoid saponin of the monodesmosidic type or the bidesmosidic type; and

- a conjugate comprising a second binding molecule different from said first binding molecule, the second binding molecule comprising a second binding region different from said first binding region, the second binding region for binding to a second binding site of said cell-surface molecule different from said first binding site of said cell-surface molecule, and the conjugate comprising an effector molecule covalently bound to said second binding molecule,

and optionally further comprising a pharmaceutically acceptable excipient and optionally further comprising a pharmaceutically acceptable diluent.

3. The therapeutic combination of claim 1 or the pharmaceutical composition of claim 2, wherein the first binding molecule is a first proteinaceous binding molecule or a first non-proteinaceous ligand comprising the first binding region for binding to the first binding site of the cell-surface molecule, and/or wherein the second binding molecule is a second proteinaceous binding molecule or a second non-proteinaceous ligand comprising the second binding region for binding to the second binding site of the cell-surface molecule.

4. The therapeutic combination of claim 1 or 3 or the pharmaceutical composition of claim 2 or 3, wherein the first binding molecule is a first proteinaceous binding molecule and wherein the saponin is covalently bound to an amino acid residue of the first binding molecule, preferably via a linker.

5. The therapeutic combination of claim 1, 3 or 4 or the pharmaceutical composition of any one of the claims 2-4, wherein the first binding site is a first epitope of said cell-surface molecule such as a cell-surface receptor and wherein the second binding site is a second epitope of said, same, cell-surface molecule, wherein the second epitope is different from the first epitope.

6. The therapeutic combination of any one of the claims 1 or 3-5 or the pharmaceutical composition of any one of the claims 2-5, wherein the saponin is a bidesmosidic triterpene saponin.

7. The therapeutic combination of any one of the claims 1 or 3-6 or the pharmaceutical composition of any one of the claims 2-6, wherein the cell-surface molecule is a tumor-cell surface molecule, preferably a tumor cell-specific cell-surface molecule.

8. The therapeutic combination of any one of the claims 1 or 3-7 or the pharmaceutical composition of any one of the claims 2-7, wherein the first binding region of the first binding molecule comprises or consists of a ligand for binding to the first binding site of the cell-surface molecule such as EGF, or wherein the first binding region of the first binding molecule comprises or consists of an immunoglobulin or at least one binding fragment or binding domain of said immunoglobulin comprising the first binding region for binding to the first binding site of the cell-surface molecule, and/or wherein the second binding region of the second binding molecule comprises or consists of a ligand for binding to the second binding site of the cell-surface molecule such as EGF or a cytokine, or wherein the second binding region of the second binding molecule comprises or consists of an immunoglobulin or at least one binding fragment or binding domain of said immunoglobulin comprising the second binding region for binding to the second binding site of the cell-surface molecule,

wherein the immunoglobulin is preferably any one or more of an antibody such as a monoclonal antibody, preferably a human antibody, an IgG, a molecule comprising or consisting of a single-domain antibody, at least one V_{HH} domain or at least one V_H domain, a variable heavy chain new antigen receptor (V_{NAR}) domain, a Fab, an scFv, an Fv, a dAb, an F(ab)2, a Fcab fragment.

9. The therapeutic combination of any one of the claims 1 or 3-8 or the pharmaceutical composition of any one of the claims 2-8, wherein the first binding region of the first binding molecule comprises or consists of a monoclonal antibody, a single-domain antibody, at least one V_{HH} domain, at least one V_H domain, a variable heavy chain new antigen receptor (VNAR) domain, a Fab, an scFv, an Fv, a dAb, an $F(ab)_2$, or a Fcab fragment, preferably a monoclonal antibody or a single-domain antibody, such as at least one V_{HH} domain, and/or wherein the second binding region of the second binding molecule comprises or consists of a monoclonal antibody, a single-domain antibody, at least one V_{HH} domain, at least one V_H domain, a variable heavy chain new antigen receptor (VNAR) domain, a Fab, an scFv, an

Fv, a dAb, an $F(ab)_2$, or a Fcab fragment, preferably a monoclonal antibody or a single-domain antibody, such as at least one V_{HH} domain.

10. The therapeutic combination of claim 8 or the pharmaceutical composition of claim 8, wherein the at least one binding fragment or binding domain of said immunoglobulin comprising the first binding region for binding to the first binding site of the cell-surface molecule and/or the at least one binding fragment or binding domain of said immunoglobulin comprising the second binding region for binding to the second binding site of the cell-surface molecule is a single-domain antibody, preferably at least one V_{HH} domain.

11. The therapeutic combination of any one of the claims 1 or 3-10 or the pharmaceutical composition of any one of the claims 2-10, wherein the first binding region and the second binding region are selected to simultaneously bind the same cell-surface molecule at the first binding site and at the second binding site.

12. The therapeutic combination of any one of the claims 1 or 3-11 or the pharmaceutical composition of any one of the claims 2-11, wherein the first binding region is selected to bind to the first binding site of the cell-surface molecule without competing for the binding of the second binding region to the second binding site of the same cell-surface molecule, and wherein the second binding region is selected to bind to the second binding site of the cell-surface molecule without competing for the binding of the first binding region to the first binding site of the same cell-surface molecule.

13. The therapeutic combination of any one of the claims 1 or 3-12 or the pharmaceutical composition of any one of the claims 2-12, wherein the at least one saponin is a bidesmosidic triterpene saponin belonging to the type of a 12,13-dehydrooleanane with an aldehyde function in position C_{23}, the saponin comprising a first saccharide chain at the C_3beta-OH group of the saponin, the first saccharide chain optionally comprising a glucuronic acid moiety, and the saponin comprising a second saccharide chain linked to C_{28} of the saponin and comprising or consisting of a monosaccharide or a linear or branched oligosaccharide wherein optionally at least one saccharide moiety of the second saccharide chain comprises at least one acetyl group, for example 1, 2, 3 or 4 acetyl groups.

14. The therapeutic combination of any one of the claims 1 or 3-13 or the pharmaceutical composition of any one of the claims 2-13, wherein the at least one saponin is a saponin isolated from any one or more of a *Gypsophila* species, a *Saponaria* species, an *Agrostemma* species and a *Quillaja* species such as *Quillaja saponaria*.

15. The therapeutic combination of any one of the claims 1 or 3-14 or the pharmaceutical composition of any one of the claims 2-14, wherein the at least one saponin comprises an aglycone core structure selected from any one or more of:

2alpha-hydroxy oleanolic acid;

16alpha-hydroxy oleanolic acid;
hederagenin (23-hydroxy oleanolic acid);
16alpha,23-dihydroxy oleanolic acid;
gypsogenin;
quillaic acid;
protoaescigenin-21(2-methylbut-2-enoate)-22-acetate;
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;
gypsogenic acid; and
a derivative thereof,

preferably, the aglycone core structure is selected from quillaic acid and gypsogenin or a derivative thereof, most preferably the aglycone core structure is quillaic acid or a derivative thereof.

16. Pharmaceutical combination of any one of the claims 1, 3-15 or pharmaceutical composition of any one of the claims 2-15, wherein the at least one saponin comprises a first saccharide chain bound to its aglycone core structure, selected from:

GlcA-,
Glc-,
Gal-,
Rha-(1→2)-Ara-,
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-,
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-,
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-,
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-,
Xyl-(1→4)-Rha-(1→2)-Gal-(1→2)-Fuc-(1→2)-GlcA-,
Xyl-(1→4)-Fuc-(1→2)-Gal-(1→2)-Fuc-(1→2)-GlcA-, and
any derivative thereof,
and/or wherein the at least one saponin optionally comprises a second saccharide chain bound to its aglycone core structure, selected from:
Glc-,
Gal-,
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,
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-,
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-,
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),
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-,
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-,
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-,
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),
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-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),
Glc-(1→3)-[Glc-(1→6)]-Gal-, and
a derivative thereof,
preferably the at least one saponin comprises such a first saccharide chain and comprises such a second saccharide chain bound to the aglycone core structure of the saponin of claim 13 or 15.

17. Pharmaceutical combination of any one of the claims 1, 3-16 or pharmaceutical composition of any one of the claims 2-16, wherein the at least one saponin is any one or more of: *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-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, GE1741, SO1542, SO1584, SO1658, SO1674, SO1832, SO1862, SO1904, 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, Teaseedsaponin J, Assamsaponin F, Digitonin, Primula acid 1 and AS64R, or a saponin derivative based thereon, or any of their stereoisomers and/or any combinations thereof, preferably any one or more of QS-21, a QS-21 derivative, SO1861, a SO1861 derivative, SA1641, a SA1641 derivative, GE1741 and a GE1741 derivative, more preferably QS-21, a QS-21 derivative, SO1861 or a SO1861 derivative, most preferably SO1861 or a SO1861 derivative.

18. Pharmaceutical combination of any one of the claims 1, 3-17 or pharmaceutical composition of any one of the claims 2-17, wherein the saponin moiety or the saponin derivative moiety in the first conjugate comprises the first saccharide chain and comprises the second saccharide chain, wherein the first saccharide chain comprises more than one saccharide moiety and the second saccharide chain comprises more than one saccharide moiety, and wherein the aglycone core structure of the saponin is, or is a derivative of, quillaic acid or gypsogenin, wherein one, two or three, preferably one or two, of:

i. an aldehyde group in the aglycone core structure of the saponin has been derivatised,
ii. a carboxyl group of a glucuronic acid moiety in the first saccharide chain has been derivatised, and
iii. at least one acetoxy (Me(CO)O-) group in the second saccharide chain has been derivatised.

19. Pharmaceutical combination of any one of the claims 1, 3-18 or pharmaceutical composition of any one of the claims 2-18, wherein the saponin moiety or the saponin derivative moiety in the first conjugate comprises:

i. an aglycone core structure comprising an aldehyde group which has been derivatised by:
- reduction to an alcohol;
- transformation into a hydrazone bond through reaction with N-ε-maleimidocaproic acid hydrazide (EMCH), wherein the maleimide group of the EMCH is optionally derivatised by formation of a thioether bond with mercaptoethanol;
- transformation into a hydrazone bond through reaction with N-[ß-maleimidopropionic acid] hydrazide (BMPH), wherein the maleimide group of the BMPH is optionally derivatised by formation of a thioether bond with mercaptoethanol; or
- transformation into a hydrazone bond through reaction with N-[κ-maleimidoundecanoic acid] hydrazide (KMUH), wherein the maleimide group of the KMUH is optionally derivatised by formation of a thioether bond with mercaptoethanol;
ii. a first saccharide chain comprising a carboxyl group, preferably a carboxyl group of a glucuronic acid moiety, which has been derivatised by transformation into an amide bond through reaction with 2-amino-2-methyl-1,3-propanediol (AMPD) or *N*-(2-aminoethyl)maleimide (AEM);
iii. a second saccharide chain comprising an acetoxy group (Me(CO)O-) which has been derivatised by transformation into a hydroxyl group (HO-) by deacetylation; or
iv. any combination of two or three, preferably two, derivatisations of derivatisations i., ii. and iii.

20. Pharmaceutical combination of any one of the claims 1, 3-19 or pharmaceutical composition of any one of the claims 2-19, wherein the at least one saponin is any one or more of: 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, or a saponin derivative thereof, or a stereoisomer thereof and/or any combination thereof, preferably any one or more of QS-21 or a QS-21 derivative, SO1861 or a SO1861 derivative, SA1641 or a SA1641 derivative and

GE1741 or a GE1741 derivative, more preferably a QS-21 derivative or a SO1861 derivative, most preferably SO1861 or a SO1861 derivative.

21. Pharmaceutical combination of any one of the claims 1, 3-20 or pharmaceutical composition of any one of the claims 2-20, wherein the at least one saponin is a bidesmosidic triterpene glycoside belonging to the type of a 12,13-dehydrooleanane with an aldehyde function in position C_{23} of the aglycone core structure of the saponin, wherein the saponin is covalently bound to the first binding molecule, preferably covalently bound to an amino-acid residue of the first binding molecule, via an aldehyde function in the saponin, preferably said aldehyde function in position C_{23} of the aglycone core structure, preferably via at least one linker, and/or via at least one cleavable linker, wherein the amino-acid residue preferably is selected from cysteine and lysine.

22. Pharmaceutical combination of claim 21 or pharmaceutical composition of claim 21, wherein the aldehyde function in position C_{23} of the aglycone core structure of the at least one saponin is covalently bound to linker EMCH, which linker is covalently bound via a thio-ether bond to a sulfhydryl group in the first binding molecule, such as a sulfhydryl group of a cysteine.

23. Pharmaceutical combination of any one of the claims 1, 3-22 or pharmaceutical composition of any one of the claims 2-22, wherein the at least one saponin is a bidesmosidic triterpene glycoside belonging to the type of a 12,13-dehydrooleanane with an aldehyde function in position C_{23} of the aglycone core structure of the saponin and comprising a glucuronic acid unit in a first saccharide chain at the C_3beta-OH group of the aglycone core structure of the saponin, wherein the saponin is covalently bound to an amino-acid residue of the first binding molecule via the carboxyl group of the glucuronic acid unit in the first saccharide chain, preferably via a linker, wherein the amino-acid residue preferably is selected from cysteine and lysine.

24. Pharmaceutical combination of claim 23 or pharmaceutical composition of claim 23, wherein the at least one saponin comprises a glucuronic acid unit in its first saccharide chain at the C_3beta-OH group of the aglycone core structure of the at least one saponin, which glucuronic acid unit is covalently bound to linker 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU), which linker is preferably covalently bound via an amide bond to an amine group in the first binding molecule, such as an amine group of a lysine or an N-terminus of the first binding molecule if the first binding molecule is a first proteinaceous binding molecule.

25. Pharmaceutical combination of any one of the claims 1, 3-24 or pharmaceutical composition of any one of the claims 2-24, wherein the cell-surface molecule is a cell-surface receptor, preferably a tumor-cell specific cell-surface receptor, more preferably a receptor 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, PSMA, CanAg, integrin-alphaV, CA6, CD33, mesothelin, Cripto, CD3, CD30, CD239, CD70,

CD123, CD352, DLL3, CD25, ephrinA4, MUC1, Trop2, CEACAM5, CEACAM6, HER3, CD74, PTK7, Notch3, FGF2, C4.4A, FLT3, CD38, FGFR3, CD7, PD-L1, CTLA4, CD52, PDGFRA, VEGFR1, VEGFR2, most preferably selected from: HER2, CD71 and EGFR.

26. Pharmaceutical combination of any one of the claims 1, 3-25 or pharmaceutical composition of any one of the claims 2-25, wherein the first binding region of the first binding molecule and the second binding region of the second binding molecule comprise or consist of an antibody or a cell-surface molecule binding fragment thereof or cell-surface molecule binding domain(s) thereof and/or comprise or consist of a ligand for binding to the cell-surface molecule, preferably selected from: an anti-CD71 monoclonal antibody such as IgG type OKT-9 and a second anti-CD71antibody; an anti-HER2 monoclonal antibody such as trastuzumab (Herceptin), pertuzumab and a third anti-HER2 monoclonal antibody; an anti-CD20 monoclonal antibody such as rituximab, ofatumumab, tositumomab, obinutuzumab ibritumomab and a fifth anti-CD20 monoclonal antibody; an anti-CA125 monoclonal antibody such as oregovomab and a second anti-CA125 monoclonal antibody; an anti-EpCAM (17-1A) monoclonal antibody such as edrecolomab and a second anti-EpCAM (17-1A) monoclonal antibody; an anti-EGFR monoclonal antibody such as cetuximab, matuzumab, panitumumab, nimotuzumab and a fifth anti-EGFR monoclonal antibody or EGF; an anti-CD30 monoclonal antibody such as brentuximab and a second anti-CD30 antibody; an anti-CD33 monoclonal antibody such as gemtuzumab, huMy9-6 and a third anti-CD33 monoclonal antibody; an anti-vascular integrin alpha-v beta-3 monoclonal antibody such as etaracizumab and a second anti-vascular integrin alpha-v beta-3 antibody; an anti-CD52 monoclonal antibody such as alemtuzumab and a second anti-CD52 antibody; an anti-CD22 monoclonal antibody such as epratuzumab, pinatuzumab, binding fragment (Fv) of anti-CD22 antibody moxetumomab, humanized monoclonal antibody inotuzumab and a fifth anti-CD22 monoclonal antibody; an anti-CEA monoclonal antibody such as labetuzumab and a second anti-CEA monoclonal antibody; an anti-CD44v6 monoclonal antibody such as bivatuzumab and a second anti-CD44v6 monoclonal antibody; an anti-FAP monoclonal antibody such as sibrotuzumab and a second anti-FAB monoclonal antibody; an anti-CD19 monoclonal antibody such as huB4 and a second anti-CD19 monoclonal antibody; an anti-CanAg monoclonal antibody such as huC242 and a second anti-CanAg monoclonal antibody; an anti-CD56 monoclonal antibody such as huN901 and a second anti-CD56 monoclonal antibody; an anti-CD38 monoclonal antibody such as daratumumab, OKT-10 anti-CD38 monoclonal antibody and a third anti-CD38 monoclonal antibody; an anti-CA6 monoclonal antibody such as DS6 and a second anti-CA6 monoclonal antibody; an anti-IGF-1R monoclonal antibody such as cixutumumab, 3B7 and a third anti-CA6 monoclonal antibody; an anti-integrin monoclonal antibody such as CNTO 95 and a second anti-integrin monoclonal antibody; an anti-syndecan-1 monoclonal antibody such as B-B4 and a second anti-syndecan-1 monoclonal antibody; an anti-CD79b monoclonal antibody such as polatuzumab and a second anti-CD79b monoclonal antibody, preferably any one of: trastuzumab and pertuzumab; cetuximab and matuzumab; matuzumab and V_{HH} 7D12 with amino-acid sequence of SEQ ID NO: 1; cetuximab and V_{HH} 9G8 with amino-acid sequence of SEQ ID NO: 2; and EGF and matuzumab,

with the proviso that the first binding region and the second binding region are different and with the proviso that the first binding site and the second binding site are different.

27. Pharmaceutical combination of claim 26 or pharmaceutical composition of claim 26, wherein binding of the first binding region to the first binding site does not compete with binding of the second binding region to the second binding site on the same cell-surface molecule, and *vice versa*.

28. Pharmaceutical combination of any one of the claims 1, 3-27 or pharmaceutical composition of any one of the claims 2-27, wherein the first binding region of the first binding molecule is capable of binding to the first binding site of the cell-surface receptor and the second binding region of the second binding molecule is capable of binding to the second binding site of the cell-surface receptor, simultaneously.

29. Pharmaceutical combination of any one of the claims 1, 3-28 or pharmaceutical composition of any one of the claims 2-28, wherein the first binding region of the first binding molecule is capable of binding to the first binding site of the cell-surface receptor without blocking the capacity of the second binding region of the second binding molecule to bind to the second binding site of the cell-surface receptor simultaneously, and/or wherein the second binding region of the second binding molecule is capable of binding to the second binding site of the cell-surface receptor without blocking the capacity of the first binding region of the first binding molecule to bind to the first binding site of the cell-surface receptor simultaneously.

30. Pharmaceutical combination of any one of the claims 1, 3-29 or pharmaceutical composition of any one of the claims 2-29, wherein the conjugate comprising the first binding molecule and the conjugate comprising the second molecule can bind to the same cell-surface molecule, simultaneously.

31. Pharmaceutical combination of any one of the claims 1, 3-30 or pharmaceutical composition of any one of the claims 2-30, wherein the effector molecule comprises or consists of at least one of a small molecule such as a drug molecule, a toxin such as a protein toxin, an oligonucleotide such as a BNA, a xeno nucleic acid or an siRNA, an enzyme, a peptide, a protein, or any combination thereof, preferably, the effector molecule is a toxin, an enzyme or an oligonucleotide, more preferably, the effector molecule comprises or consists of at least one of an oligonucleotide, a nucleic acid and a xeno nucleic acid.

32. Pharmaceutical combination of any one of the claims 1, 3-32 or pharmaceutical composition of any one of the claims 2-32, wherein the effector molecule is selected from any one or more of a vector, a gene, a cell suicide inducing transgene, deoxyribonucleic acid (DNA), ribonucleic acid (RNA), anti-sense oligonucleotide (ASO, AON), short interfering RNA (siRNA), anti-microRNA (anti-miRNA), DNA aptamer, RNA aptamer, mRNA, mini-circle DNA, peptide nucleic acid (PNA), phosphoramidate morpholino oligomer (PMO), locked nucleic acid (LNA), bridged nucleic acid (BNA), 2'-deoxy-2'-fluoroarabino nucleic acid (FANA), 2'-O-methoxyethyl-RNA (MOE), 2'-O,4'-aminoethylene bridged nucleic acid, 3'-fluoro hexitol nucleic acid (FHNA), a plasmid, glycol nucleic acid (GNA) and threose

nucleic acid (TNA), or a derivative thereof, more preferably a BNA, for example a BNA for silencing HSP27 protein expression or a BNA for silencing apolipoprotein B expression.

33. Pharmaceutical combination of any one of the claims 1, 3-33 or pharmaceutical composition of any one of the claims 2-33, wherein the effector molecule comprises or, when dependent on any one of the claims 1, 3-30, consists of at least one proteinaceous molecule, preferably selected from any one or more of a peptide, a protein, an enzyme and a protein toxin.

34. Pharmaceutical combination of any one of the claims 1, 3-33 or pharmaceutical composition of any one of the claims 2-33, wherein the effector molecule comprises or, when dependent on any one of the claims 1, 3-30, consists of at least one of: urease and Cre-recombinase, a proteinaceous toxin, a ribosome-inactivating protein, a protein toxin, a bacterial toxin, a plant toxin, more preferably selected from any one or more of a viral toxin such as apoptin; a bacterial toxin such as Shiga toxin, Shiga-like toxin, Pseudomonas aeruginosa exotoxin (PE) or exotoxin A of PE, full-length or truncated diphtheria toxin (DT), cholera toxin; a fungal toxin such as alpha-sarcin; a plant toxin including ribosome-inactivating proteins and the A chain of type 2 ribosome-inactivating proteins such as dianthin *e.g.* dianthin-30 or dianthin-32, saporin *e.g.* saporin-S3 or saporin-S6, bouganin or de-immunized derivative debouganin of bouganin, shiga-like toxin A, pokeweed antiviral protein, ricin, ricin A chain, modeccin, modeccin A chain, abrin, abrin A chain, volkensin, volkensin A chain, viscumin, viscumin A chain; or an animal or human toxin such as frog RNase, or granzyme B or human angiogenin, or any toxic fragment or toxic derivative thereof; preferably the protein toxin is dianthin and/or saporin.

35. Pharmaceutical combination of any one of the claims 1, 3-34 or pharmaceutical composition of any one of the claims 2-34, wherein the effector molecule comprises or, when dependent on any one of the claims 1, 3-30, consists of at least one payload.

36. Pharmaceutical combination of any one of the claims 1, 3-35 or pharmaceutical composition of any one of the claims 2-35, wherein the effector molecule comprises or, when dependent on any one of the claims 1, 3-30, consists of at least one of: a toxin targeting ribosomes, a toxin targeting elongation factors, a toxin targeting tubulin, a toxin targeting DNA and a toxin targeting RNA, more preferably any one or more of emtansine, pasudotox, maytansinoid derivative DM1, maytansinoid derivative DM4, monomethyl auristatin E (MMAE, vedotin), monomethyl auristatin F (MMAF, mafodotin), a Calicheamicin, N-Acetyl-γ-calicheamicin, a pyrrolobenzodiazepine (PBD) dimer, a benzodiazepine, a CC-1065 analogue, a duocarmycin, Doxorubicin, paclitaxel, docetaxel, cisplatin, cyclophosphamide, etoposide, docetaxel, 5-fluorouracyl (5-FU), mitoxantrone, a tubulysin, an indolinobenzodiazepine, AZ13599185, a cryptophycin, rhizoxin, methotrexate, an anthracycline, a camptothecin analogue, SN-38, DX-8951f, exatecan mesylate, truncated form of *Pseudomonas aeruginosa* exotoxin (PE38), a Duocarmycin derivative, an amanitin, α-amanitin, a spliceostatin, a thailanstatin, ozogamicin, tesirine, Amberstatin269 and soravtansine, or a derivative thereof.

37. Pharmaceutical combination of any one of the claims 1, 3-36 or pharmaceutical composition of any one of the claims 2-36, wherein the conjugate comprising the second binding molecule and the effector molecule comprises or, when dependent on any one of the claims 1, 3-30, consists of an antibody-drug conjugate, such as any one of antibody-drug conjugates: gemtuzumab ozogamicin, brentuximab vedotin, trastuzumab emtansine, inotuzumab ozogamicin, moxetumomab pasudotox and polatuzumab vedotin, or comprises or consists of at least the drug and one cell-surface molecule binding-domain of the antibody, and/or comprises or consists of at least the drug and one cell-surface molecule binding-fragment of the antibody.

38. Pharmaceutical combination of any one of the claims 1, 3-37 or pharmaceutical composition of any one of the claims 2-37, wherein the conjugate comprising the first binding molecule and the at least one saponin comprises more than one covalently bound saponin, preferably 2, 3, 4, 5, 6, 8, 10, 16, 32, 64, 128 or 1-100 saponins, or any number of saponins therein between, such as 7, 9, 12 saponins.

39. Pharmaceutical combination of claim 38 or pharmaceutical composition of claim 38, wherein the more than one covalently bound saponins are covalently bound directly to an amino-acid residue of the first binding molecule, preferably to a cysteine and/or to a lysine, and/or are covalently bound via a linker and/or via a cleavable linker and/or are part of a covalent saponin conjugate comprising at least one oligomeric molecule or polymeric molecule and the more than one saponin covalently bound thereto, wherein the covalent saponin conjugate is covalently bound to the first binding molecule, preferably 1-8 of such covalent saponin conjugates are bound to the first binding molecule, more preferably 2-4 of such of such covalent saponin conjugates, wherein the at least one covalent saponin conjugate is optionally based on a dendron, wherein optionally 1-32 saponins, preferably 2, 3, 4, 5, 6, 8, 10, 16, 32 saponins, or any number of saponins therein between, such as 7, 9, 12 saponins, are covalently bound to the oligomeric molecule or to the polymeric molecule of the at least one covalent saponin conjugate, either directly or via a linker.

40. Pharmaceutical combination of any one of the claims 1, 3-39 or pharmaceutical composition of any one of the claims 2-39, wherein the at least one saponin is covalently bound to the first binding molecule via a cleavable linker.

41. Pharmaceutical combination of claim 40 or pharmaceutical composition of claim 40, 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.

42. Pharmaceutical combination of claim 40 or 41 or pharmaceutical composition of claim 40 or 41, wherein the cleavable linker is subject to cleavage *in vivo* under acidic conditions as present in

endosomes and/or lysosomes of mammalian cells, preferably human cells, preferably at pH 4.0 – 6.5, and more preferably at pH ≤ 5.5.

43. Pharmaceutical combination of claim 39 or any one of claims 40-42 when dependent on claim 39, or pharmaceutical composition of claim 39 or any one of claims 40-42 when dependent on claim 39, wherein the oligomeric molecule or the polymeric molecule of the covalent saponin conjugate is covalently bound to the first binding molecule, preferably to an amino-acid residue of the binding molecule.

44. Pharmaceutical combination of claim 42 or 43, or pharmaceutical composition of claim 42 or 43, wherein the at least one saponin is covalently bound to the oligomeric molecule or to the polymeric molecule of the covalent saponin conjugate via a cleavable linker according to any one of the claims 39-42.

45. Pharmaceutical combination of any one of the claims 42-44, or pharmaceutical composition of any one of the claims 42-44, 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.

46. Pharmaceutical combination of any one of the claims 39-45, or pharmaceutical composition of any one of the claims 39-45, wherein the at least one saponin comprises an aglycone core structure comprising an aldehyde function in position C_{23} and the at least one saponin comprising optionally a glucuronic acid function in a first saccharide chain at the C_3beta-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 polymeric molecule of the covalent saponin conjugate, and/or, if present, the glucuronic acid function is involved in the covalent bonding to the oligomeric molecule or to the polymeric molecule of the covalent saponin conjugate, the bonding of the saponin either via a direct covalent bond, or via a linker.

47. Pharmaceutical combination of claim 46 or pharmaceutical composition of claim 46, wherein the aldehyde function in position C_{23} of the aglycone core structure of the at least one saponin is covalently bound to linker EMCH, which EMCH 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.

48. Pharmaceutical combination of claim 46 or 47 or pharmaceutical composition of claim 46 or 47, wherein the glucuronic acid function in the first saccharide chain at the C_3beta-OH group of the aglycone core structure of the at least one saponin is covalently bound to linker 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU), which HATU 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.

49. Pharmaceutical combination of any one of the claims 43-48, or pharmaceutical composition of any one of the claims 43-48, wherein the polymeric molecule or the oligomeric molecule of the covalent saponin conjugate is bound to the first binding molecule, preferably to an amino-acid residue of the first binding molecule, 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.

50. Pharmaceutical combination of any one of the claims 43-49, or pharmaceutical composition of any one of the claims 43-49, 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 OEG_3, OEG_4 and OEG_5, 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.

51. Pharmaceutical combination of any one of the claims 1-50, or pharmaceutical composition of any one of the claims 1-50, for use as a medicament.

52. Pharmaceutical combination of any one of the claims 1-50, or pharmaceutical composition of any one of the claims 1-50, for use in the treatment or prevention of a cancer, an autoimmune disease, a disease relating to (over)expression of a protein, a disease relating to an aberrant cell such as a tumor cell or a diseased liver cell, a disease relating to a mutant gene, a disease relating to a gene defect, a disease relating to a mutant protein, a disease relating to absence of a (functional) protein, a disease relating to a (functional) protein deficiency.

53. Pharmaceutical combination for use of claim 52, or pharmaceutical composition for use of claim 52, wherein:

- said use is in the treatment or prevention of cancer in a human subject; and/or
- said use is in the treatment or prophylaxis of cancer in a patient in need thereof, wherein the cell-surface molecule is a tumor-cell surface molecule, preferably a tumor cell-specific surface molecule; and/or
- the pharmaceutical combination or the pharmaceutical composition, preferably a therapeutically effective amount of the pharmaceutical combination or the pharmaceutical composition, is administered to a patient in need thereof, preferably a human patient.

54. Kit of parts, comprising the pharmaceutical combination of any one of the claims 1, 3-50 or the pharmaceutical composition of any one of the claims 2-50, and optionally instructions for use of said pharmaceutical combination or said pharmaceutical composition.