Claims:

1. Saponin conjugate comprising at least one saponin covalently linked to a ligand for asialoglycoprotein receptor (ASGPR), wherein the ligand for ASGPR comprises at least one *N*-acetylgalactosamine (GalNAc) moiety, preferably three or four GalNAc moieties, more preferably the ligand for ASGPR comprises or consists of $(GalNAc)_3Tris$, wherein the at least one saponin is selected from monodesmosidic triterpenoid saponins and bidesmosidic triterpenoid saponins.

2. Saponin conjugate of claim 1, wherein the saponin comprises an aglycone core structure selected from the group consisting 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
derivatives thereof,

preferably the saponin comprises an aglycone core structure selected from quillaic acid and gypsogenin or derivatives thereof, more preferably the saponin aglycone core structure is quillaic acid or a derivative thereof.

3. Saponin conjugate of claim 1 or 2, wherein

- the saponin comprises a saccharide chain bound to the aglycone core structure, which is selected from group A:

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
derivatives thereof,
or

- the saponin comprises a saccharide chain bound to the aglycone core structure, which is selected from group B:

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
derivatives thereof,

or

- the saponin is a bidesmosidic triterpene glycoside comprising a first saccharide chain selected from the group A bound to the aglycone core structure and comprising a second saccharide chain selected from the group B bound to the aglycone core structure.

4. Saponin conjugate of any one of the claims 1-3, wherein the saponin is selected from the group consisting 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, stereoisomers thereof, derivatives thereof, and combinations thereof, preferably the saponin is selected from the group consisting of QS-21, a QS-21 derivative, SO1861, a SO1861 derivative, SA1641, a SA1641 derivative, GE1741, a GE1741 derivative and combinations thereof, more preferably the saponin is selected from the group consisting of a QS-21 derivative, a SO1861 derivative and combinations thereof, most preferably the saponin is a SO1861 derivative.

5. Saponin conjugate of claim 3 or 4, wherein the saponin is a saponin derivative wherein

i. the saponin derivative comprises an aglycone core structure comprising an aldehyde group which has been derivatised;

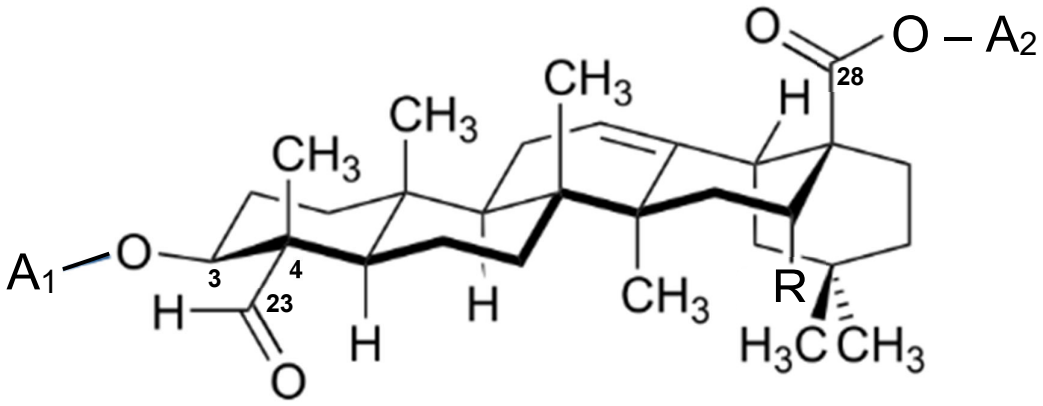
ii. the saponin derivative comprises a saccharide chain, preferably a saccharide chain selected from group A as defined in claim 3, the saccharide chain comprising a carboxyl group which has been derivatised;

iii. the saponin derivative comprises a saccharide chain, preferably a saccharide chain selected from group B as defined in claim 3, the saccharide chain comprising an acetoxy (Me(CO)O-) group which has been derivatised; or

iv. the saponin derivative comprises any combination of derivatisations i., ii. and iii., preferably any combination of two derivatisations of derivatisations i., ii. and iii.

6. Saponin conjugate of any one of the claims 1-5, wherein the 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, SO1904, stereoisomers thereof, derivatives thereof and combinations thereof, preferably the saponin is selected from the group consisting of QS-21, a QS-21 derivative, SO1861, a SO1861 derivative, SA1641, a SA1641 derivative, GE1741, a GE1741 derivative and combinations thereof, more preferably the saponin is selected from the group consisting of a QS-21 derivative, a SO1861 derivative and combinations thereof, most preferably the saponin is a SO1861 derivative.

7. Saponin conjugate of any one of the claims 1-6, wherein the saponin is a saponin derivative of the quillaic acid saponin or the gypsogenin saponin of claim 2 and is represented by Molecule 1:



(Molecule 1)

wherein

A_1 represents hydrogen, a monosaccharide or a linear or branched oligosaccharide, preferably A_1 represents a saccharide chain selected from group A as defined in claim 3, more preferably A_1 represents a saccharide chain selected from group A as defined in claim 3 and A_1 comprises or consists of a glucuronic acid moiety;

A_2 represents hydrogen, a monosaccharide or a linear or branched oligosaccharide, preferably A_2 represents a saccharide chain selected from group B as defined in claim 3, more preferably A_2 represents a saccharide chain selected from group B as defined in claim 3 and A_2 comprises at least one acetoxy (Me(CO)O-) group, such as one, two, three or four acetoxy groups,

wherein at least one of A_1 and A_2 is not hydrogen, preferably both A_1 and A_2 are an oligosaccharide chain;

and R is hydrogen in gypsogenin or hydroxyl in quillaic acid;

wherein the saponin derivative corresponds to the saponin represented by Molecule 1 wherein at least one, preferably one or two, more preferably one, of the following derivatisations is present:

i. the aldehyde group at position C_{23} of the quillaic acid or gypsogenin has been derivatised;
ii. the carboxyl group of a glucuronic acid moiety of A_1, when A_1 represents a saccharide chain selected from group A as defined in claim 3 and A_1 comprises or consists of a glucuronic acid moiety, has been derivatised; and
iii. one or more, preferably all, of acetoxy group(s) of one saccharide moiety or of two or more saccharide moieties of A_2, when A_2 represents a saccharide chain selected from group B as defined in claim 3 and A_2 comprises at least one acetoxy group, has/have been derivatised.

8. Saponin conjugate of claim 7, wherein A_1 represents a saccharide chain selected from group A as defined in claim 3 and comprises or consists of a glucuronic acid moiety and wherein the carboxyl group of a glucuronic acid moiety of A_1 has been derivatised and/or wherein A_2 represents a saccharide chain

selected from group B as defined in claim 3 and A_2 comprises at least one acetoxy group and wherein at least one acetoxy group of A_2 has been derivatised.

9. Saponin conjugate of claim 7 or 8, wherein the saponin represented by Molecule 1 is a bidesmosidic triterpene saponin.

10. Saponin conjugate of any one of the claims 7-9, wherein the saponin derivative corresponds to the saponin represented by Molecule 1 wherein at least one, preferably one or two, more preferably one, of the following derivatisations is present:

i. the aldehyde group at position C_{23} of the quillaic acid or gypsogenin has been derivatised by;

- reduction to an alcohol;
- transformation into a hydrazone bond through reaction with N-ε-maleimidocaproic acid hydrazide (EMCH), therewith providing a saponin-Ald-EMCH such as a SO1861-Ald-EMCH or a QS-21-Ald-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. the carboxyl group of a glucuronic acid moiety of A_1, when A_1 represents a saccharide chain selected from group A as defined in claim 3 and A_1 comprises or consists of a glucuronic acid moiety, 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), therewith providing a saponin-Glu-AMPD such as a QS-21-Glu-AMPD or a SO1861-Glu-AMPD or a saponin-Glu-AEM such as a QS-21-Glu-AEM or a SO1861-Glu-AEM; and

iii. one or more, preferably all, of acetoxy group(s) of one saccharide moiety or of two or more saccharide moieties of A_2, when A_2 represents a saccharide chain selected from group B as defined in claim 3 and A_2 comprises at least one acetoxy group, has/have been derivatised by transformation into a hydroxyl group (HO-) by deacetylation.

11. Saponin conjugate of any one of the claims 7-10, wherein A_1 is Gal-(1→2)-[Xyl-(1→3)]-GlcA and/or A_2 is Glc-(1→3)-Xyl-(1→4)-Rha-(1→2)-[Xyl-(1→3)-4-OAc-Qui-(1→4)]-Fuc, preferably the saponin represented by Molecule 1 is 3-O-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, more preferably the saponin is any one or more of:

SO1861, GE1741, SA1641 and QS-21, or a derivative thereof, most preferably SO1861 or a derivative thereof.

12. Saponin conjugate of any one of the claims 5-11, wherein the saponin is a saponin derivative wherein

i. the saponin derivative comprises 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), therewith providing a saponin-Ald-EMCH such as a SO1861-Ald-EMCH or a QS-21-Ald-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. the saponin derivative comprises a saccharide chain, preferably a saccharide chain selected from group A as defined in claim 3, the 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), therewith providing a saponin-Glu-AMPD such as a QS-21-Glu-AMPD or a SO1861-Glu-AMPD or a saponin-Glu-AEM such as a QS-21-Glu-AEM or a SO1861-Glu-AEM;

iii. the saponin derivative comprises a saccharide chain, preferably a saccharide chain selected from group B as defined in claim 3, the saccharide chain comprising an acetoxy (Me(CO)O-) group which has been derivatised by transformation into a hydroxyl group (HO-) by deacetylation; or

iv. the saponin derivative comprises any combination of derivatisations i., ii. and iii., preferably any combination of two derivatisations of derivatisations i., ii. and iii.;

preferably, the saponin derivative comprises an aglycone core structure wherein the aglycone core structure comprises an aldehyde group which has been derivatised by transformation into a hydrazone bond through reaction with EMCH wherein the maleimide group of the EMCH is optionally derivatised by formation of a thioether bond with mercaptoethanol.

13. Saponin conjugate of claim 12, wherein the saponin is a saponin derivative wherein

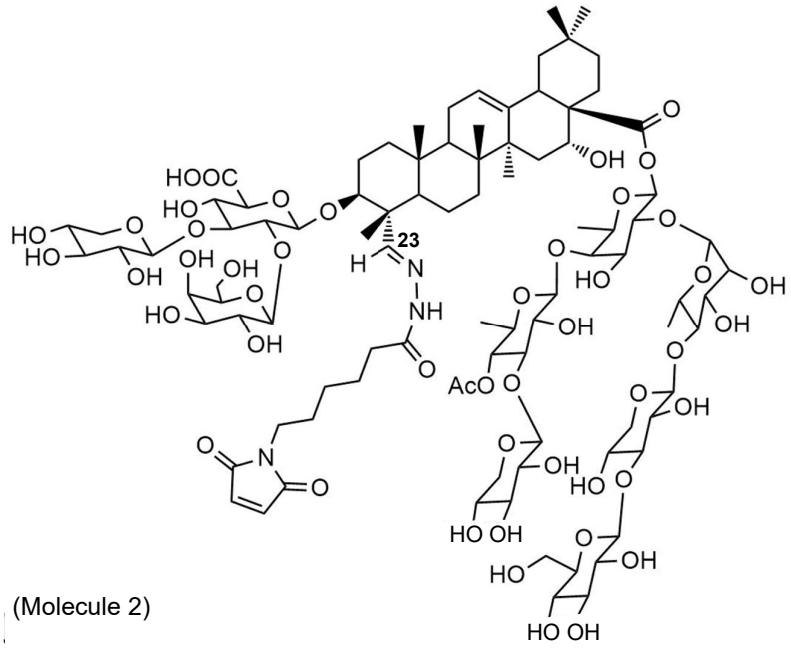
i. the saponin derivative comprises an aglycone core structure comprising an aldehyde group which has been derivatised by transformation into a hydrazone bond through reaction with N-ε-maleimidocaproic acid hydrazide (EMCH), therewith providing a saponin-Ald-EMCH such as a SO1861-Ald-EMCH or a QS-21-Ald-EMCH;

ii. the saponin derivative comprises a saccharide chain, preferably a saccharide chain selected from group A as defined in claim 3, the 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 *N*-(2-aminoethyl)maleimide (AEM), therewith providing a saponin-Glu-AEM such as a QS-21-Glu-AEM or a SO1861-Glu-AEM; or

iii. the saponin derivative comprises a combination of derivatisations i. and ii.

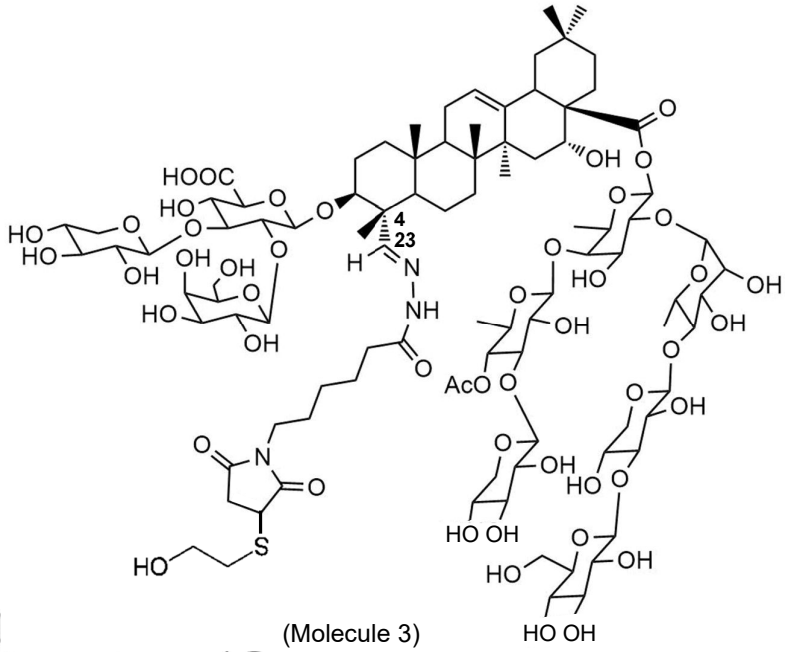
14. Saponin conjugate of claim 12, wherein the saponin derivative comprises an aglycone core structure wherein the aglycone core structure comprises an aldehyde group and wherein the saponin derivative comprises a saccharide chain, preferably a saccharide chain selected from group A as defined in claim 3, the saccharide chain comprising a carboxyl group, preferably a carboxyl group of a glucuronic acid moiety, which glucuronic acid moiety has been derivatised by transformation into an amide bond through reaction with *N*-(2-aminoethyl)maleimide (AEM).

15. Saponin conjugate of any one of the claims 1-12, wherein the saponin is a saponin derivative represented by Molecule 2:



(Molecule 2)

or wherein the saponin is a saponin derivative represented by Molecule 3:

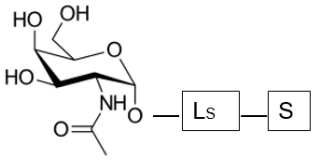


(Molecule 3)

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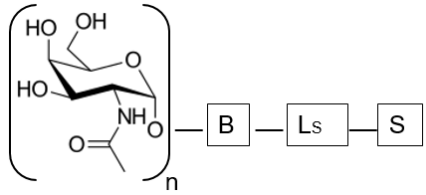
16. Saponin conjugate of any one of the claims 1-15, wherein the at least one saponin and the ligand for ASGPR are covalently linked directly or via at least one linker.

17. Saponin conjugate of any one of the claims 1-16, wherein the GalNAc moiety is bound to the saponin S, preferably via a saponin linker L_S, as shown in formula $(II)_S$:



$(II)_S$.

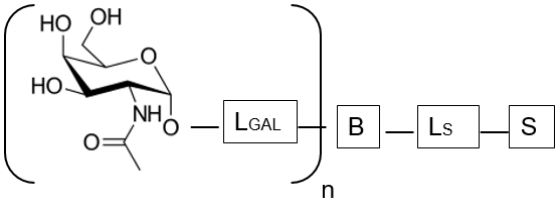
18. Saponin conjugate of any one of the claims 1-16, wherein the GalNAc moieties are each separately covalently bound via the oxygen on position “1” of the GalNAc moiety to a central bridging moiety B, which effectively forms a bridge between the GalNAc moieties and the saponin moiety, preferably via a saponin moiety linker L_S, as shown in formula $(III)_S$:



$(III)_S$

wherein n is an integer larger than or equal to 2, preferably n is 3, L_S is a saponin moiety linker and S is the saponin moiety.

19. Saponin conjugate of claim 18, wherein the GalNAc moieties are bound to the bridging moiety B via GalNAc linkers L_{GAL} as shown in formula $(IV)_S$:



$(IV)_S$

wherein n is an integer larger than or equal to 2, preferably n is 3, L_S is a saponin moiety linker and S is the saponin moiety.

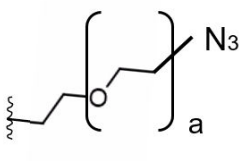
20. Saponin conjugate of any one of claims 17-19, wherein the saponin moiety linker Ls represents any chemical moiety suitable for covalently binding a saponin to GalNAc as in formula $(II)_S$ or to the bridging moiety B as in formula $(III)_S$ and $(IV)_S$.

21. Saponin conjugate of any one of claims 17-20, wherein the saponin moiety linker L_S is the result of a coupling reaction between at least a first precursor L_{S1} covalently bound to GalNAc or the bridging moiety B and a second precursor L_{S2} covalently bound to the saponin moiety, wherein L_{S1} is a precursor of the saponin moiety linker L_S which is covalently bound to GalNAc or to the bridging moiety B and L_{S2} is a precursor of the saponin moiety linker L_S which is covalently bound to the saponin moiety.

22. Saponin conjugate of any one of claims 17-21, wherein the saponin moiety linker L_S is the result of a coupling reaction between at least a first precursor L_{S1} covalently bound to GalNAc or the bridging moiety B and a second precursor L_{S2} covalently bound to the saponin moiety, wherein the coupling reaction is selected from the group consisting of an azide-alkyne cycloaddition, a thiol maleimide coupling, a Staudinger reaction, a nucleophilic ring-opening of strained heterocyclic electrophiles, a carbonyl reaction of the non-aldol type and an addition to a carbon-carbon double bond, preferably wherein the coupling reaction is an azide-alkyne cycloaddition, a thiol maleimide coupling, a Staudinger reaction, a nucleophilic ring-opening of strained heterocyclic electrophiles, more preferably wherein the coupling reaction is an azide-alkyne cycloaddition or a thiol maleimide coupling.

23. Saponin conjugate of any one of claims 17-22, wherein the saponin moiety linker L_S is the result of a coupling reaction between a first precursor L_{S1} covalently bound to GalNAc or the bridging moiety B, the first precursor L_{S1} comprising an azide; and a second precursor L_{S2} covalently bound to the saponin moiety, the second precursor L_{S2} comprising an alkyne and preferably comprising a hydrazon resulting from a hydrazide/aldehyde coupling to an aldehyde of the saponin moiety.

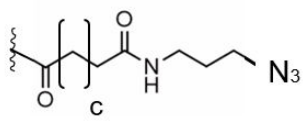
24. Saponin conjugate of any one of claims 21-23, wherein the structure for the precursor L_{S1} is the following azide of formula (XVII):



(XVII)

wherein a represents an integer larger than or equal to 0, preferably a represents an integer selected from 1, 2, and 3, more preferably a represents 2, or

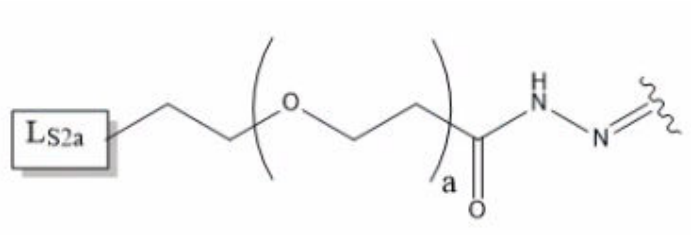
wherein the structure for the precursor L_{S1} comprises the following azide of formula (XVIII):



(XVIII)

wherein c represents an integer larger than or equal to 0, preferably c represents an integer in the range of 5-15, more preferably c represents 9.

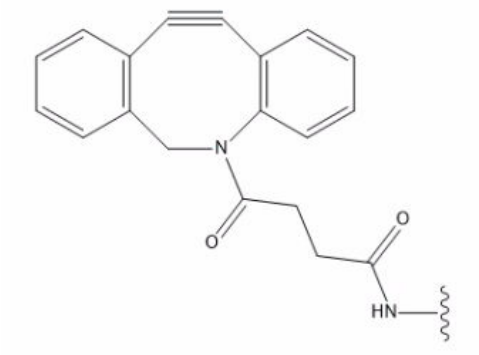
25. Saponin conjugate of any one of claims 21-24, wherein the structure for the precursor L_{S2} comprises the following hydrazone with formula (XIX):



(XIX)

wherein a represents an integer larger than or equal to 0, preferably a represents an integer in the range of 2-6, more preferably a represents 4, and wherein L_{S2a} represents an alkyne-containing moiety.

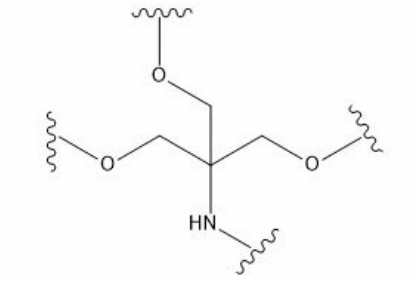
26. Saponin conjugate of claim 25, wherein L_{S2a} comprises less than 20 carbon atoms, preferably L_{S2a} represents a moiety according to formula (XX):



(XX)

.

27. Saponin conjugate of any one of claims 18-26, wherein the bridging moiety is a compound of formula (XV):



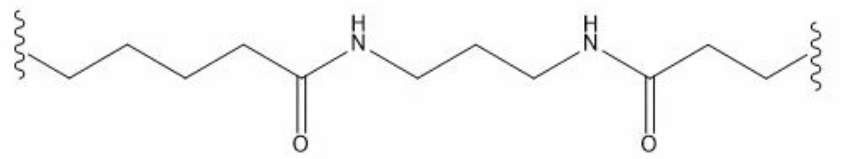
(XV)

wherein the oxygen atoms of the compound of formula (XV) are bound to GalNAc or to the GalNAc linkers L_{GAL}, and the nitrogen atom of the compound of formula (XV) is bound to the saponin moiety linker L_S.

28. Saponin conjugate of any one of claims 19-27, wherein L_{GAL} represents any chemical moiety suitable for covalently binding GalNAc to the bridging moiety B.

29. Saponin conjugate of any one of claims 19-28, wherein L_{GAL} comprises 2-25 carbon atoms, preferably 7-15 carbon atoms, more preferably 11 carbon atoms and wherein L_{GAL} comprises at least one, preferably two amide moieties.

30. Saponin conjugate of any one of claims 19-29, wherein L_{GAL} is a compound according to formula (XVI):

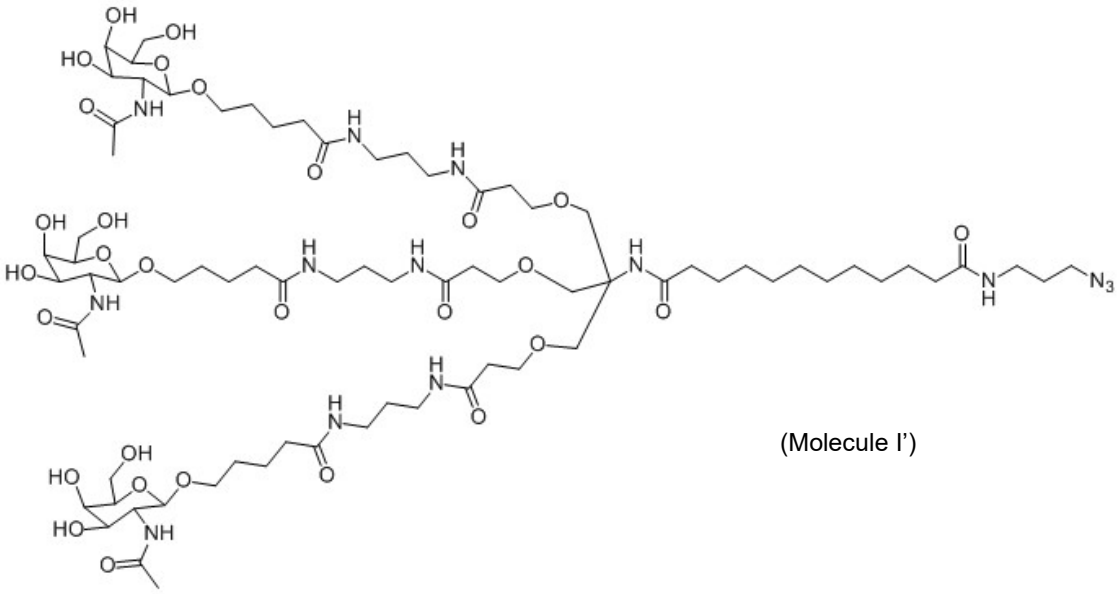


(XVI)

.

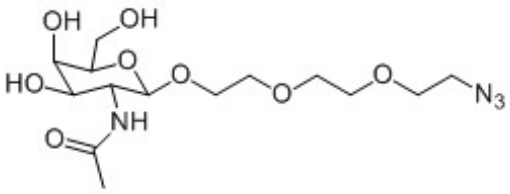
31. Saponin conjugate of any one of the claims 17-30, wherein the ligand for ASGPR is the $(GalNAc)_3$Tris represented by Molecule I':

,



(Molecule I')

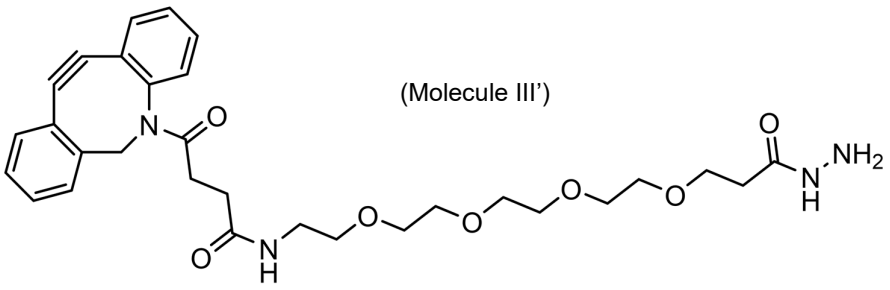
or wherein the ligand for ASGPR is mono-GalNAc represented by Molecule II':



(Molecule II')

.

32. Saponin conjugate of any one of the claims 1-31, wherein the at least one saponin is covalently bound to Molecule I' or Molecule II' of claim 31 via a linker represented by Molecule III':



(Molecule III')

,

wherein the hydrazide moiety of Molecule III' formed a covalent hydrazone bond with an aldehyde group in the saponin, and wherein the dibenzocyclooctyne group formed a covalent bond with the azide group of Molecule I' or Molecule II'.

33. Saponin conjugate of any one of the claims 1-32, wherein the at least one saponin is covalently bound to the ligand for ASGPR via at least one cleavable linker.

34. Saponin conjugate of claim 33, 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.

35. Saponin conjugate of claim 33 or 34, 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 $\leq$ 5.5.

36. Saponin conjugate of any one of the claims 1-35, wherein the conjugate comprises 1, 2, 3, 4, 5, 6, 8, 10, 16, 32, 64, 128 or 1-100 saponin moieties, or any number of saponin moieties therein between, such as 7, 9, 12 saponin moieties.

37. Pharmaceutical combination comprising:

- a first pharmaceutical composition comprising the saponin conjugate of any one of the claims 1-36 and optionally comprising a pharmaceutically acceptable excipient and/or a pharmaceutically acceptable diluent; and

- a second pharmaceutical composition comprising a second conjugate of an effector molecule and a ligand for ASGPR, wherein the ligand for ASGPR preferably comprises at least one GalNAc moiety, preferably three or four GalNAc moieties, more preferably the ligand for ASGPR comprises or consists of $(GalNAc)_3Tris$, or a third conjugate of an effector molecule and a binding molecule comprising a binding site for a cell-surface molecule, and optionally comprising a pharmaceutically acceptable excipient and/or pharmaceutically acceptable diluent.

38. Pharmaceutical composition comprising:

- the saponin conjugate of any one of the claims 1-36;

- a second conjugate of an effector molecule and a ligand for ASGPR wherein the ligand for ASGPR preferably comprises at least one GalNAc moiety, preferably three or four GalNAc moieties, more preferably the ligand for ASGPR comprises or consists of $(GalNAc)_3Tris$, or a third conjugate of an effector molecule and a binding molecule comprising a binding site for a cell-surface molecule, and

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

39. Pharmaceutical combination of claim 37 or pharmaceutical composition of claim 38, 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.

40. Pharmaceutical combination of claim 37 or 39, or pharmaceutical composition of claim 38 or 39, wherein the ligand for ASGPR comprises or is $(GalNAc)_3$Tris, and/or wherein the ligand for ASGPR and the effector molecule are conjugated via a covalent bond, preferably via at least one linker.

41. Pharmaceutical combination of any one of the claims 37 or 39-40 or pharmaceutical composition of any one of the claims 38-40, wherein the effector molecule is an oligonucleotide selected from any one or more of a(n): short interfering RNA (siRNA), short hairpin RNA (shRNA), anti-hairpin-shaped microRNA (miRNA), single-stranded RNA, aptamer RNA, double-stranded RNA (dsRNA), anti-microRNA (anti-miRNA, anti-miR), antisense oligonucleotide (ASO), DNA, antisense DNA, locked nucleic acid (LNA), bridged nucleic acid (BNA), 2'-O,4'-aminoethylene bridged nucleic Acid (BNA^{NC}), BNA-based siRNA, and BNA-based antisense oligonucleotide (BNA-AON).

42. Pharmaceutical combination of any one of the claims 37 or 39-41 or pharmaceutical composition of any one of the claims 38-41, wherein the effector molecule is an oligonucleotide selected from any one or more of a(n): anti-miRNA, a BNA-AON or an siRNA, such as BNA-based siRNA, selected from chemically modified siRNA, metabolically stable siRNA and chemically modified, metabolically stable siRNA.

43. Pharmaceutical combination of any one of the claims 37 or 39-42 or pharmaceutical composition of any one of the claims 38-42, wherein the effector molecule is an oligonucleotide capable of, for example when present inside a mammalian cell, silencing any one of genes: apolipoprotein B (apoB), HSP27, transthyretin (TTR), proprotein convertase subtilisin/kexin type 9 (PCSK9), delta-aminolevulinate synthase 1 (ALAS1), antithrombin 3 (AT3), glycolate oxidase (GO), complement component C5 (CC5), X gene of hepatitis B virus (HBV), S gene of HBV, alpha-1 antitrypsin (AAT) and lactate dehydrogenase (LDH), and/or is an oligonucleotide capable of, for example when present inside a mammalian cell, targeting an aberrant miRNA.

44. Pharmaceutical combination of any one of the claims 37 or 39-43 or pharmaceutical composition of any one of the claims 38-43, wherein the effector molecule is an oligonucleotide, preferably an siRNA such as a BNA-based siRNA, or an antisense oligonucleotide such as a BNA-based antisense

oligonucleotide, for example an AON based on 2'-O,4'-aminoethylene bridged nucleic acid, capable of, preferably when present inside a mammalian cell, silencing gene apolipoprotein B (apoB).

45. Pharmaceutical combination of any one of the claims 37 or 39-44 or pharmaceutical composition of any one of the claims 38-44, wherein the effector molecule is an oligonucleotide capable of, for example when present inside a mammalian cell, targeting an mRNA involved in expression of any one of proteins: apoB, HSP27, TTR, PCSK9, ALAS1, AT3, GO, CC5, expression product of X gene of HBV, expression product of S gene of HBV, AAT and LDH, or is capable of, for example when present inside a mammalian cell, antagonizing or restoring an miRNA function such as inhibiting an oncogenic miRNA (onco-miR) or suppression of expression of an onco-miR.

46. Pharmaceutical combination of any one of the claims 37 or 39-45 or pharmaceutical composition of any one of the claims 38-45, wherein the effector molecule is an oligonucleotide, preferably an siRNA such as a BNA-based siRNA, or an antisense oligonucleotide such as a BNA-based antisense oligonucleotide, for example an AON based on 2'-O,4'-aminoethylene bridged nucleic acid, capable of, preferably when present inside a mammalian cell, targeting an mRNA involved in expression of protein apoB.

47. Pharmaceutical combination of any one of the claims 37 or 39-46 or pharmaceutical composition of any one of the claims 38-46, wherein the effector molecule is or comprises a toxin which toxin comprises or consists of at least one molecule selected from any one or more of a peptide, a protein, an enzyme such as urease and Cre-recombinase, a proteinaceous toxin, a ribosome-inactivating protein, and/or 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 angiogenin from humans, or any fragment or derivative thereof; preferably the protein toxin is dianthin and/or saporin, and/or comprises or consists of at least one of a toxin targeting ribosome, a toxin targeting elongation factor, 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.

48. Pharmaceutical combination of any one of the claims 37 or 39-47 or pharmaceutical composition of any one of the claims 38-47, wherein the binding molecule comprising a binding site for a cell-surface molecule, comprised by the third conjugate, is a ligand for a cell-surface molecule or an antibody comprising a binding site for a cell-surface molecule or at least one domain or fragment thereof comprising the binding site.

49. Pharmaceutical combination of any one of the claims 37 or 39-48 or pharmaceutical composition of any one of the claims 38-48, wherein the third conjugate is any one or more of: an antibody-toxin conjugate, a receptor-ligand – toxin conjugate, an antibody-drug conjugate, a receptor-ligand – drug conjugate, an antibody-nucleic acid conjugate or a receptor-ligand – nucleic acid conjugate.

50. Pharmaceutical combination of any one of the claims 37 or 39-49 or pharmaceutical composition of any one of the claims 38-49, wherein the binding molecule comprising a binding site for a cell-surface molecule, comprised by the third conjugate, is capable of binding to any one of cell-surface molecules: 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, asialoglycoprotein receptor (ASGPR), preferably any one of: HER2, CD71, ASGPR and EGFR, more preferably CD71.

51. Pharmaceutical combination of any one of the claims 37 or 39-50 or pharmaceutical composition of any one of the claims 38-50, wherein the binding molecule comprising a binding site for a cell-surface molecule, comprised by the third conjugate, is or comprises any one of: an antibody, preferably a monoclonal antibody such as a human monoclonal antibody, an IgG, a molecule comprising or consisting of a single-domain antibody, at least one V_{HH} domain, preferable a camelid V_H, a variable heavy chain new antigen receptor (V_{NAR}) domain, a Fab, an scFv, an Fv, a dAb, an F(ab)2 and a Fcab fragment.

52. Pharmaceutical combination of any one of the claims 37, 39-51 or pharmaceutical composition of any one of the claims 38-51, for use as a medicament.

53. Use of the ~~P~~pharmaceutical combination of any one of the claims 37, 39-51 or pharmaceutical composition of any one of the claims 38-51, ~~for use~~ in the manufacture of a medicament for the treatment or prophylaxis of a disease or health problem in which an expression product is involved of any one or

more of genes: apoB, TTR, PCSK9, ALAS1, AT3, GO, CC5, X gene of HBV, S gene of HBV, AAT and LDH.

54. Use of the ~~P~~pharmaceutical combination of any one of the claims 37, 39-51 or 53 or pharmaceutical composition of any one of the claims 38-51 or 53, ~~for use~~ in the manufacture of a medicament for the treatment or prophylaxis of a disease or health problem in which an expression product is involved of gene apoB.

55. Use of the ~~P~~pharmaceutical combination of any one of the claims 37, 39-51 or pharmaceutical composition of any one of the claims 38-51, or pharmaceutical combination or use of pharmaceutical composition ~~for use~~ of claim 53, ~~for use~~in the manufacture of a medicament ~~in~~for the treatment or prophylaxis of a cancer, an infectious disease, a viral infection, hypercholesterolemia, primary hyperoxaluria, haemophilia A, haemophilia B, AAT related liver disease, acute hepatic porphyria, TTR-mediated amyloidosis, hereditary TTR amyloidosis (hATTR), complement-mediated disease, hepatitis B infection, or an auto-immune disease.

56. Use of the ~~P~~pharmaceutical combination ~~for use~~ of claim 53, 54 or 55 or use of pharmaceutical composition ~~for use~~ of claim 53, 54 or 55, wherein the saponin is a saponin derivative, preferably a QS-21 derivative or an SO1861 derivative of any one of the claims 4-15.

57. *In vitro* or *ex vivo* method for transferring the second conjugate or the third conjugate of any one of the claims 37-51 from outside a cell to inside said cell, preferably subsequently transferring the effector molecule comprised by the second conjugate or the third conjugate of any one of the claims 37-51 into the cytosol of said cell, comprising the steps of:

a) providing a cell which expresses ASGPR on its surface, and, when the third conjugate is to be transferred into the cell, which expresses the cell-surface molecule for which the third conjugate comprises a binding molecule for binding to said cell-surface molecule, the cell preferably selected from a liver cell, a virally infected cell and a tumor cell;
b) providing the second conjugate or the third conjugate of any one of the claims 37-51 for transferring into the cell provided in step a);
c) providing the saponin conjugate of any one of the claims 1-36;
d) contacting the cell of step a) *in vitro* or *ex vivo* with the second conjugate or the third conjugate of step b) and the saponin conjugate of step c), therewith effecting the transfer of the second conjugate or the third conjugate from outside the cell into said cell, and preferably therewith subsequently effecting the transfer of the second conjugate or the third conjugate into the cytosol of said cell, or preferably therewith subsequently effecting the transfer of at least the effector molecule comprised by the second conjugate or the third conjugate into the cytosol of said cell.