CLAIMS

1. Oligonucleotide 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 three GalNAc moieties, more preferably the ligand for ASGPR comprises or consists of $(GalNAc)_3$Tris, and further covalently linked to an oligonucleotide, wherein the at least one saponin is a monodesmosidic or bidesmosidic penta-cyclic triterpene saponin of the 12,13-dehydrooleanane type, with an aldehyde function in position C-23 of the aglycone core structure of the saponin.

2. Oligonucleotide 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. Oligonucleotide 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. Oligonucleotide 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, SO1832, a SO1832 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, SO1861 and combinations thereof, most preferably the saponin is a SO1861 derivative or SO1861, or SO1832 derivative or SO1832.

5. Oligonucleotide 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;

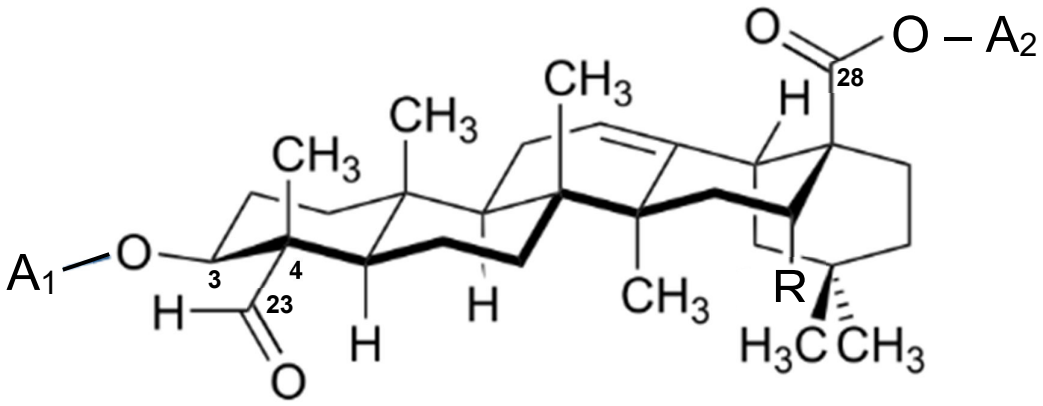
iii. the saponin derivative comprises a saccharide chain, preferably a saccharide chain selected from group B as defined in claim 3, the saccharide chain comprising an acetoxy (Me(CO)O-) group which has been derivatised; or

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. Oligonucleotide 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, SO1832, a SO1832 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, SO1861 and combinations thereof, most preferably the saponin is a SO1861 derivative or SO1861, or a SO1832 derivative or SO1832.

7. Oligonucleotide conjugate of any one of the claims 1-6, wherein the saponin 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. Oligonucleotide 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. Oligonucleotide conjugate of claim 7 or 8, wherein the saponin represented by Molecule 1 is a bidesmosidic triterpene saponin.

10. Oligonucleotide 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 thio-ether 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 thio-ether 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 thio-ether 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. Oligonucleotide 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, SO1832, GE1741, SA1641 and QS-21, or a derivative thereof, most preferably SO1861 or a derivative thereof, or a SO1832 derivative or SO1832.

12. Oligonucleotide 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 thio-ether 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 thio-ether 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 thio-ether 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 thio-ether bond with mercaptoethanol.

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

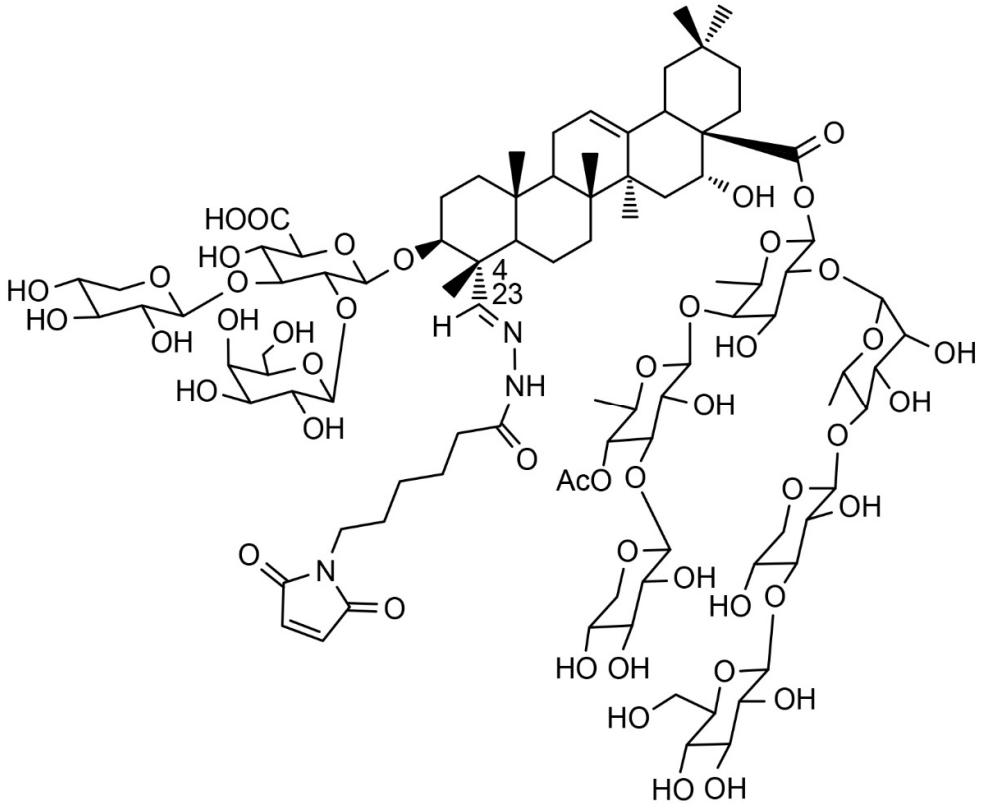
i. the saponin derivative comprises an aglycone core structure comprising an aldehyde group which has been derivatised by transformation into a hydrazone bond through reaction with N-ε-maleimidocaproic acid hydrazide (EMCH), therewith providing a saponin-Ald-EMCH such as a SO1861-Ald-EMCH or a QS-21-Ald-EMCH;

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.

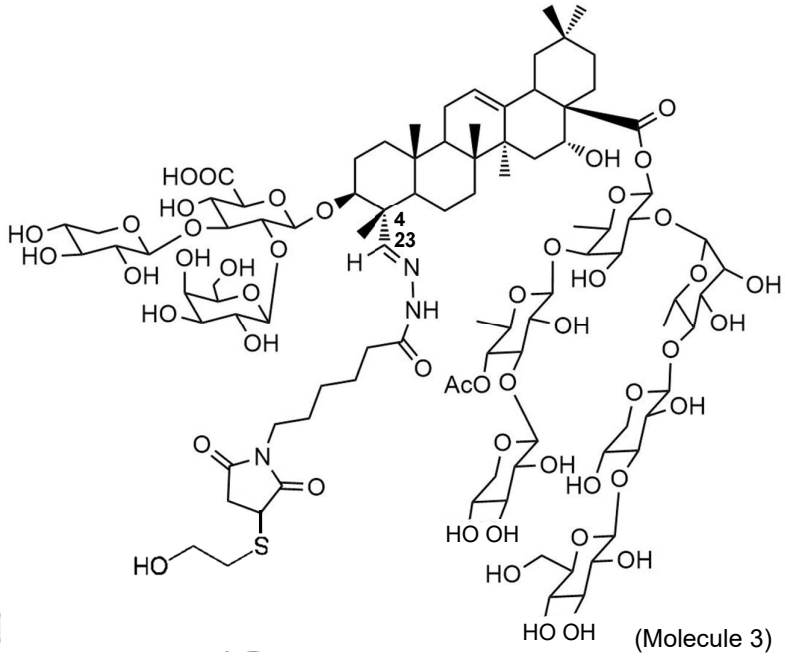
14. Oligonucleotide conjugate of claim 12, wherein the saponin derivative comprises an aglycone core structure wherein the aglycone core structure comprises an aldehyde group and wherein the saponin derivative comprises a saccharide chain, preferably a saccharide chain selected from group A as defined 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. Oligonucleotide 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:

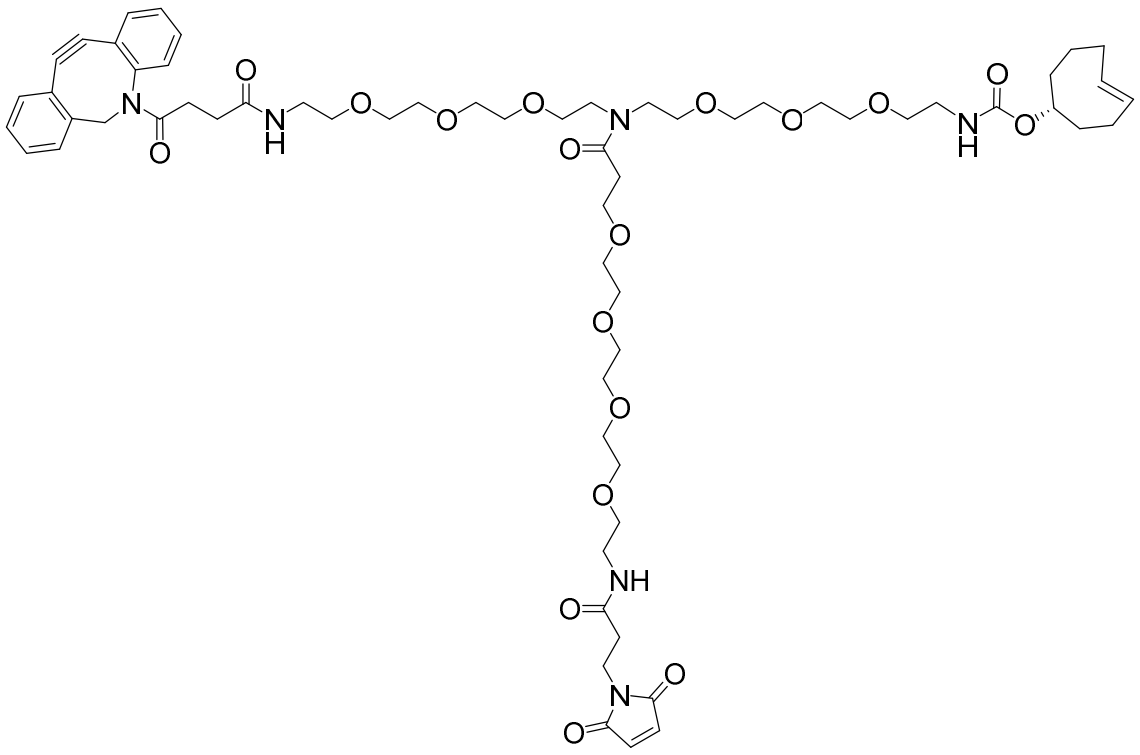


(Molecule 3)

16. Oligonucleotide 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, and/or wherein the at least one saponin and the oligonucleotide are covalently linked directly or via at least one linker, and/or wherein the ligand for ASGPR and the oligonucleotide are covalently linked directly or via at least one linker, preferably, the at least one saponin, the ligand for ASGPR and the oligonucleotide are linked via at least one linker.

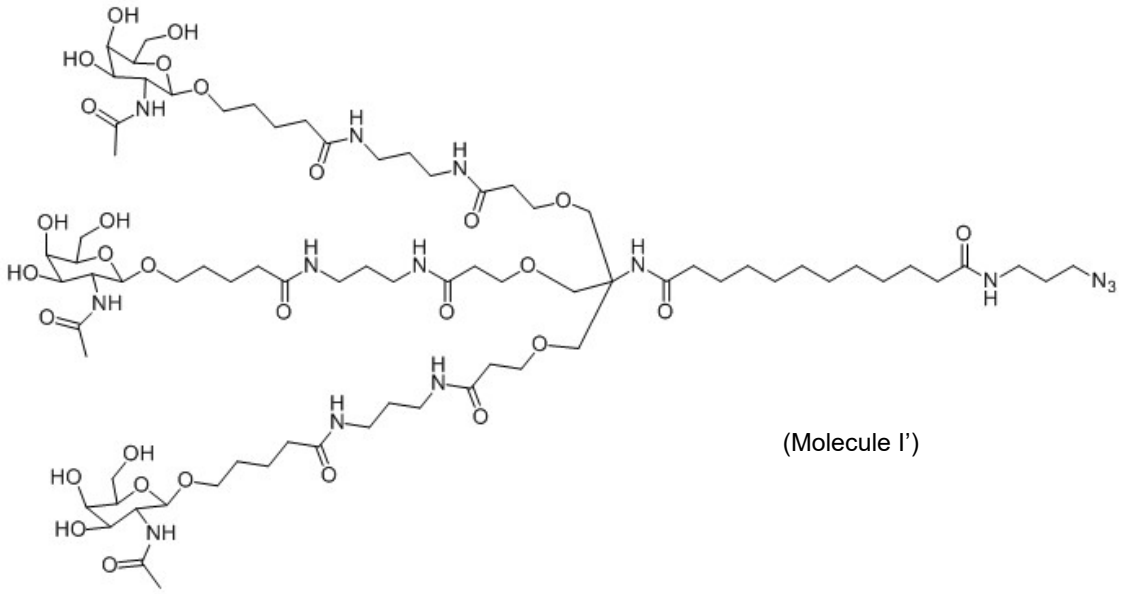
17. Oligonucleotide conjugate of any one of the claims 1-16, wherein the at least one GalNAc moiety, preferably three GalNAc moieties, the at least one saponin, preferably 1-16 saponin moieties, more preferably 1-8 saponin moieties such as 1, 4 or 8 saponin moieties, and the oligonucleotide are covalently bound via a tri-functional linker, preferably with each of the GalNAc moiety/moieties, the saponin/saponin moieties and the oligonucleotide covalently bound to a separate arm of the tri-functional linker.

18. Oligonucleotide conjugate of claim 17, wherein the tri-functional linker is the tri-functional linker represented by formula (XXI):



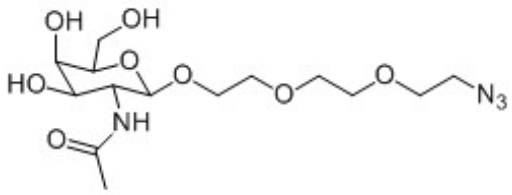
(XXI).

19. Oligonucleotide conjugate of any one of the claims 1-18, 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') .

20. Oligonucleotide conjugate of any one of the claims 1-19, wherein the at least one saponin is covalently bound to the ligand for ASGPR via at least one cleavable linker, and/or wherein the at least one saponin is covalently bound to the oligonucleotide via at least one cleavable linker.

21. Oligonucleotide conjugate of claim 17 or 18, wherein the at least one saponin is covalently bound to an arm of the tri-functional linker via at least one cleavable linker.

22. Oligonucleotide conjugate of claim 20 or 21, 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.

23. Oligonucleotide conjugate of any one of the claims 20-22, 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.

24. Oligonucleotide conjugate of any one of the claims 1-23, wherein the oligonucleotide 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, and preferably 1, 4 or 8 saponin moieties.

25. Oligonucleotide conjugate of any one of the claims 1-23, wherein the oligonucleotide conjugate comprises 1 saponin moiety or 4 saponin moieties or 8 saponin moieties.

26. Oligonucleotide conjugate of any one of the claims 1-25, wherein the saponin is SO1861, SO1832 or QS-21, preferably SO1861 or SO1832.

27. Oligonucleotide conjugate of any one of the claims 1-26, wherein the oligonucleotide conjugate comprises 1 or 3 GalNAc moieties, preferably 3 GalNAc moieties.

28. Oligonucleotide conjugate of any one of the claims 1-27, wherein the oligonucleotide is any one of a BNA, a xeno nucleic acid, an siRNA, an antisense oligonucleotide.

29. Oligonucleotide conjugate of any one of the claims 1-27, wherein the oligonucleotide is 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).

30. Oligonucleotide conjugate of any one of the claims 1-27, wherein the oligonucleotide is 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.

31. Oligonucleotide conjugate of any one of the claims 1-30, wherein the oligonucleotide is an oligonucleotide capable of, for example when present inside a mammalian cell and preferably when present inside a human cell, silencing any one of genes: apolipoprotein B (apoB), HSP27, transthyretin (TTR), proprotein convertase subtilisin/kexin type 9 (PCSK9), TMPRSS6, delta-aminolevulinate synthase 1 (ALAS1), anti-thrombin 3 (AT3), glycolate oxidase (GO), complement component C5 (CC5), X gene of hepatitis B virus (HBV), S gene of HBV, alpha-1 antitrypsin (AAT), miR-122, hepatitis B virus HbsAg, LDHA, CEBPA and lactate dehydrogenase (LDH), and/or is an oligonucleotide capable of, for example when present inside a mammalian cell, targeting an aberrant miRNA.

32. Oligonucleotide conjugate of any one of the claims 1-30, wherein the oligonucleotide is an oligonucleotide capable of, for example when present inside a mammalian cell and preferably when present inside a human cell, silencing any one of genes: apolipoprotein B (apoB) and HSP27.

33. Oligonucleotide conjugate of any one of the claims 1-32, wherein the oligonucleotide is an oligonucleotide capable of, for example when present inside a mammalian cell and preferably when present inside a human cell, targeting an mRNA involved in expression of any one of proteins: apoB, HSP27, TTR, PCSK9, TMPRSS6, ALAS1, AT3, GO, CC5, expression product of X gene of HBV, expression product of S gene of HBV, AAT, miR-122, hepatitis B virus HbsAg, LDHA, CEBPA and LDH, or is capable of, for example when present inside a mammalian cell and preferably when present inside a human cell, antagonizing or restoring an miRNA function such as inhibiting an oncogenic miRNA (onco-miR) or suppression of expression of an onco-miR.

34. Oligonucleotide conjugate of any one of the claims 1-32, wherein the oligonucleotide is an oligonucleotide capable of, for example when present inside a mammalian cell and preferably when present inside a human cell, targeting an mRNA involved in expression of any one of proteins: HSP27, apoB, TTR, PCSK9, TMPRSS6, ALAS1, AAT, miR-122, hepatitis B virus HbsAg, LDHA and CEBPA.

35. Oligonucleotide conjugate of any one of the claims 1-32, wherein the oligonucleotide is an oligonucleotide capable of, for example when present inside a mammalian cell and preferably when present inside a human cell, targeting an mRNA involved in expression of any one of proteins: apoB and HSP27.

36. Pharmaceutical composition comprising the oligonucleotide conjugate of any one of the claims 1-35, and optionally a pharmaceutically acceptable excipient and/or optionally a pharmaceutically acceptable diluent.

37. Pharmaceutical composition of claim 36 or oligonucleotide conjugate of any one of the claims 1-35, for use as a medicament.

~~39~~38. Use of the ~~P~~pharmaceutical composition of claim 36 or oligonucleotide conjugate of any one of the claims 1-35, ~~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: HSP27, apoB, TTR, PCSK9, TMPRSS6, ALAS1, AT3, GO, CC5, X gene of HBV, S gene of HBV, AAT, miR-122, hepatitis B virus HbsAg, LDHA, CEBPA and LDH, and/or for ~~use in~~ the treatment or prophylaxis of a disease or health problem which involves any one or more of genes: HSP27, apoB, TTR, PCSK9, TMPRSS6, ALAS1, AT3, GO, CC5, X gene of HBV, S gene of HBV, AAT, miR-122, hepatitis B virus HbsAg, LDHA, CEBPA and LDH.

39. Use of the Ppharmaceutical composition of claim 36 or oligonucleotide conjugate of any one of the claims 1-35, 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: HSP27, apoB, TTR, PCSK9, TMPRSS6, ALAS1, AAT, miR-122, hepatitis B virus HbsAg, LDHA and CEBPA, and/or for use in the treatment or prophylaxis of a disease or health problem which involves any one or more of genes: HSP27, apoB, TTR, PCSK9, TMPRSS6, ALAS1, AAT, miR-122, hepatitis B virus HbsAg, LDHA and CEBPA.

40. Use of the Ppharmaceutical composition of claim 35 or oligonucleotide conjugate of any one of the claims 1-35 for use according to claim 38 or 39, wherein said use is 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: HSP27 and apoB, preferably apoB, and/or for use in the treatment or prophylaxis of a disease or health problem which involves any one or more of genes: HSP27 and apoB, preferably apoB.

41. Use of the Ppharmaceutical composition or oligonucleotide conjugate for use of any one of the claims 37-40, for use in the manufacture of a medicament for the treatment or prophylaxis of a cancer, an infectious disease, a viral infection, hypercholesterolemia, cardiovascular disease, 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, hepatitis C infection, α1-antitrypsin deficiency, β-thalassaemia, or an auto-immune disease.

42. Use of the Ppharmaceutical composition or oligonucleotide conjugate for use of any one of the claims 37-40, for use in the manufacture of a medicament for the treatment or prophylaxis of a cancer such as endometrial carcinoma, breast cancer, lung cancer or hepatocellular carcinoma, and/or a cardiovascular disease such as hypercholesterolemia, preferably hypercholesterolemia.

43. Use of the Ppharmaceutical composition of claim 35 or oligonucleotide conjugate of any one of the claims 1-35 for use in the manufacture of a medicament for lowering of LDL-cholesterol in a subject.

44. *In vitro* or *ex vivo* method for transferring the oligonucleotide conjugate of any one of the claims 1-35 from outside a cell to inside said cell, preferably for subsequently transferring the oligonucleotide comprised by the oligonucleotide conjugate of any one of the claims 1-35 into the cytosol and/or into the nucleus of said cell, comprising the steps of:

a) providing a cell which expresses ASGPR, preferably ASGPR1, on its surface, the cell preferably selected from a liver cell, a virally infected mammalian cell and a mammalian tumor cell, wherein preferably said cell is a human cell;
b) providing the oligonucleotide conjugate of any one of the claims 1-35 for transferring into the cell provided in step a);

c) contacting the cell of step a) *in vitro* or *ex vivo* with the oligonucleotide conjugate of step b), preferably in a liquid medium, therewith effecting the transfer of the oligonucleotide conjugate from outside the cell into said cell, and optionally and preferably therewith subsequently effecting the transfer of the oligonucleotide comprised by the oligonucleotide conjugate into the cytosol and/or nucleus of said cell.

45. Method for providing the oligonucleotide conjugate of any one of the claims 1-35, comprising the steps of:

(a) providing at least one saponin moiety comprising a covalently bound first linker, wherein the first linker comprises at least one first reactive group for covalent binding to a second reactive group on a second linker or to a seventh reactive group on a seventh linker;

(b) providing an oligonucleotide comprising a covalently bound third linker, wherein the third linker comprises a third reactive group for covalent binding to a fourth reactive group on a fourth linker or to an eighth reactive group on the seventh linker;

(c) providing at least one GalNAc moiety comprising a covalently bound fifth linker, wherein the fifth linker comprises a fifth reactive group for covalent binding to a sixth reactive group on a sixth linker or to a ninth reactive group on the seventh linker; and

either

(d1) linking the first linker to the second linker through formation of a covalent bond between the first reactive group and the second reactive group, linking the third linker to the fourth linker through formation of a covalent bond between the third reactive group and the fourth reactive group, linking the fifth linker to the sixth linker through formation of a covalent bond between the fifth reactive group and the sixth reactive group, and covalently linking the second linker, fourth linker and sixth linker together, therewith providing the oligonucleotide,

or

(d2) linking the first linker to the seventh linker through formation of a covalent bond between the first reactive group and the seventh reactive group, linking the third linker to the seventh linker through formation of a covalent bond between the third reactive group and the eighth reactive group, linking the fifth linker to the seventh linker through formation of a covalent bond between the fifth reactive group and the ninth reactive group, therewith providing the oligonucleotide conjugate.

46. Method according to claim 45, wherein the seventh linker is a tri-functional linker, such as the tri-functional linker of claim 18.

47. Method according to claim 45 or 46, wherein the at least one saponin moiety are 1-16 saponin moieties, preferably 1-8 saponin moieties, such as 1, 4 or 8 saponin moieties.

48. Method according to any one of the claims 45-47, wherein the saponin is SO1861, SO1832, QS-21, or any functional derivative thereof, preferably SO1861 or SO1832.

49. Method according to any one of the claims 45-48, wherein the saponin moiety or the saponin moieties is/are covalently linked via a hydrazone bond or a semicarbazone bond.

50. Method according to any one of the claims 45-49, wherein the at least one GalNAc moiety are 1-4 GalNAc moieties, preferably 1 or 3 GalNAc moieties.