CLAIMS:

1. Pharmaceutical composition comprising a saponin derivative, wherein the saponin derivative is based on a *Quillaja saponaria* (QS) saponin comprising a triterpene aglycone core structure, a first saccharide chain and a second saccharide chain linked to the aglycone core structure, wherein the aglycone core structure is quillaic acid,
wherein the saponin derivative comprises the aglycone core structure, which is quillaic acid, the first saccharide chain and the second saccharide chain, which are independently selected from a linear oligosaccharide and a branched oligosaccharide, wherein the first saccharide chain is Gal-(1→2)-[Xyl-(1→3)]-GlcA- and the second saccharide chain is any one selected of (List S3):
Api/Xyl-(1→3)-Xyl-(1→4)-[Glc-(1→3)]-Rha-(1→2)-[Rha-(5 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-3,5-10 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),
15 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), and
Xyl-(1→3)-Xyl-(1→4)-Rha-(1→2)-[R12-(→3)]-Fuc- wherein R12 is 5-O-[5-O-Ara/Api-3,5-dihydroxy-6-20 methyl-octanoyl]-3,5-dihydroxy-6-methyl-octanoic acid),
wherein the saponin derivative comprises said aglycone core structure comprising an aldehyde group which has been derivatised by:

- hydrazone formation with a hydrazide, or
- imine formation with an amine, or
- chemoselective reversible oxime formation with a hydroxylamine.

2. Pharmaceutical composition according to claim 1, wherein the saponin comprises a hydrazone bond which is formed between the carbonyl group of the aldehyde and a hydrazide moiety.

3. Pharmaceutical composition according to claim 2, wherein the hydrazide is N-ε-maleimidocaproic acid hydrazide (EMCH), N-[ß-maleimidopropionic acid] hydrazide (BMPH), or N-[κ-maleimidoundecanoic acid] hydrazide (KMUH).

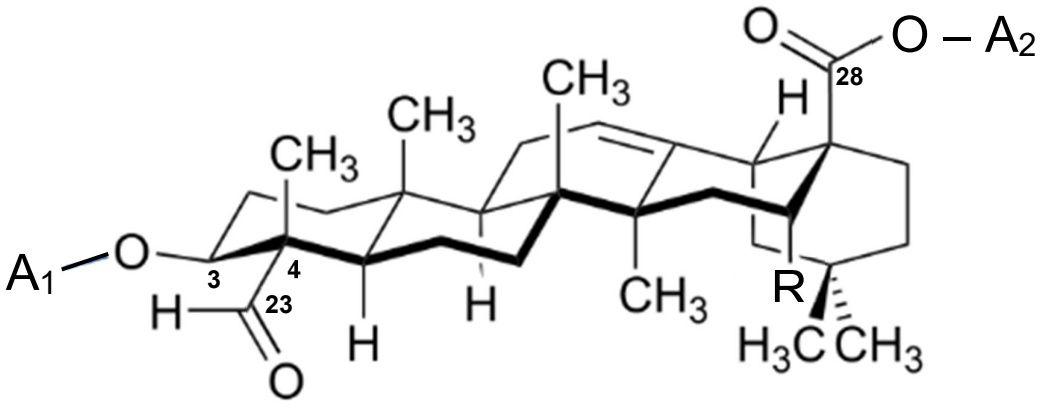
4. Pharmaceutical composition according to according to claim 2, wherein the saponin is a naturally occurring saponin.

5. Pharmaceutical composition according any one of claims 1-4, wherein the saponin derivative comprises the first saccharide chain wherein the first saccharide chain comprises a carboxyl group, or a carboxyl group of a glucuronic acid moiety, which has been derivatised.

6. Pharmaceutical composition according to any one of the claims 1-5, wherein the first saccharide chain is linked to the C_3 atom of the aglycone core structure and wherein the second saccharide chain is linked to the C_{28} atom of the aglycone core structure.

7. Pharmaceutical composition according to any one of the claims 1-6, wherein the saponin derivative is a derivative of a saponin selected from the group of saponins consisting of: *Quillaja* bark saponin, QS-7, QS1861, QS-7 api, QS1862, QS-17, QS-18, QS-21, QS-21 A-apio, QS-21 A-xylo, QS-21 B-apio, QS-21 B-xylo, stereoisomers thereof and combinations thereof, or the saponin derivative is selected from the group consisting of a QS-21 derivative.

8. Pharmaceutical composition according to any one of the claims 1-7, wherein the saponin derivative is a saponin derivative of the quillaic acid saponin represented by Molecule 1:



(Molecule 1)

wherein
the first saccharide chain is A_1;
the second saccharide chain is A_2,
and R is hydroxyl.

9. Pharmaceutical composition according to claim 8, wherein the carboxyl group of the glucuronic acid moiety of A_1 has been derivatised.

10. Pharmaceutical composition according to any one of the claims 8 - 9, wherein the saponin derivative corresponds to the saponin represented by Molecule 1 wherein the aldehyde group at position C_{23} of the quillaic acid has been derivatised by;
- transformation into a hydrazone bond through reaction with N-ε-maleimidocaproic acid hydrazide (EMCH), therewith providing a saponin-Ald-EMCH; or
- transformation into a hydrazone bond through reaction with N-[ß-maleimidopropionic acid] hydrazide (BMPH); or
- transformation into a hydrazone bond through reaction with N-[κ-maleimidoundecanoic acid] hydrazide (KMUH).

11. Pharmaceutical composition according to claim 10, wherein the maleimide group of the EMCH of the saponin-Ald-EMCH is derivatised by formation of a thioether bond with mercaptoethanol.

12. Pharmaceutical composition according to claim 10, wherein the maleimide group of the BMPH is derivatised by formation of a thioether bond with mercaptoethanol.

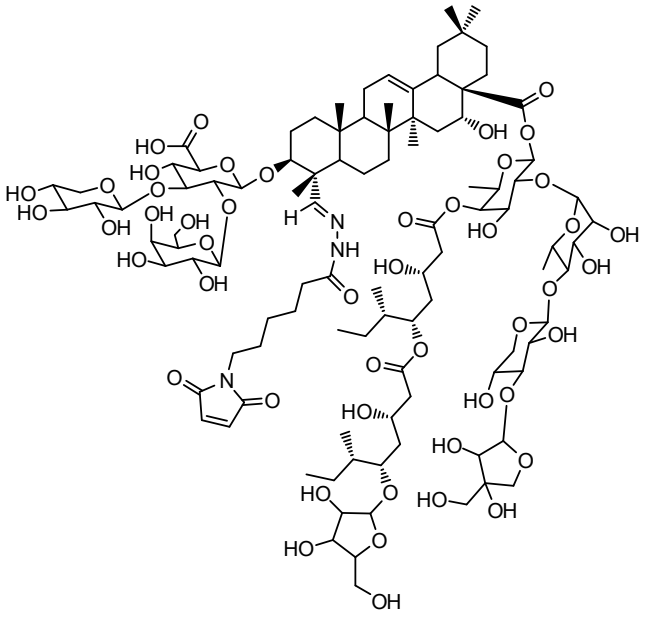
13. Pharmaceutical composition according to claim 10, wherein the maleimide group of the KMUH is derivatised by formation of a thioether bond with mercaptoethanol.

14. Pharmaceutical composition according to claim 13, wherein the carboxyl group of a glucuronic acid moiety of A_1, 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 saponin-Glu-AEM such as a QS-21-Glu-AEM

15. Pharmaceutical composition according to any one of the claims 8 - 14, wherein A_2 is Glc-(1→3)-Xyl-(1→4)-Rha-(1→2)-[Xyl-(1→3)-4-OAc-Qui-(1→4)]-Fuc, or A_2 is Glc-(1→3)-Xyl-(1→4)-Rha-(1→2)-[Xyl-(1→3)-4-OAc-Qui-(1→4)]-Fuc.

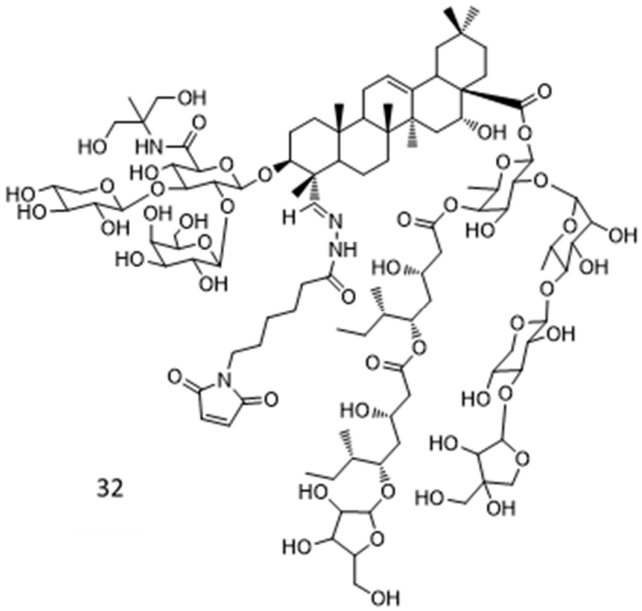
16. Pharmaceutical composition of any one of the preceding claims, wherein the saponin derivative is selected from the group consisting of derivatives of: QS-21, QS-21A, QS-21 A-api, QS-21 A-xyl, QS-21B, QS-21 B-api, QS-21 B-xyl, QS-7-xyl, QS-7-api, QS-17-api, QS-17-xyl, QS1861, QS1862, Quillajasaponin, QS-18, Quil-A, stereoisomers thereof and combinations thereof.

17. Saponin derivative of any one of the preceding claims, wherein the saponin derivative is a QS-21 derivative comprising a single derivatisation, wherein the saponin derivative is a QS-21 derivative represented by Molecule 30, which represents a QS-21 derivative comprising an aldehyde group at indicated position C_{23} of the quillaic acid aglycone core structure which has been derivatised by transformation into a hydrazone bond through reaction with N-ε-maleimidocaproic acid hydrazide (EMCH):



(30),

or wherein the saponin derivative is a QS-21 derivative, which QS-21 derivative comprises an aldehyde group at indicated position C_{23} of the quillaic acid aglycone core structure which has been derivatised by transformation into a hydrazone bond through reaction with N-ε-maleimidocaproic acid hydrazide (EMCH) wherein the maleimide group of the EMCH is derivatised with mercaptoethanol therewith forming a thioether bond, or the saponin derivative has a formula according to the following:



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18. Pharmaceutical composition according to any one of the preceding claims, wherein the aglycone core structure comprises an aldehyde group which has been derivatised by:
- transformation into a hydrazone bond through reaction with N-ε-maleimidocaproic acid hydrazide (EMCH); or
- transformation into a hydrazone bond through reaction with N-[ß-maleimidopropionic acid] hydrazide (BMPH); or
- transformation into a hydrazone bond through reaction with N-[κ-maleimidoundecanoic acid] hydrazide (KMUH).

19. Pharmaceutical composition according to claim 18, wherein the first saccharide chain comprises a carboxyl group, or 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);
or, the aglycone core structure comprises an aldehyde group which has been derivatised by transformation into a hydrazone bond through reaction with EMCH.

20. Pharmaceutical composition according to claim 18 or 19, wherein the maleimide group of the EMCH, BMPH or KMUH is derivatised by formation of a thioether bond with mercaptoethanol.

21. Pharmaceutical composition according to claim 18 or 19, wherein the first saccharide chain comprises a carboxyl group, or 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).

22. Pharmaceutical composition according to any one of the claims 18-21, with the proviso that when the aldehyde group in the aglycone core structure is derivatised by transformation into a hydrazone bond through reaction with N-ε-maleimidocaproic acid hydrazide (EMCH) and the saponin is QS-21, the glucuronic acid is also derivatised, and with the proviso that when the saponin is QS-21 and the carboxyl group of the glucuronic acid moiety of QS-21 is derivatised by reaction of 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU) with the carboxyl group of the glucuronic acid moiety of QS-21, the aldehyde group is also modified.

23. Pharmaceutical composition as defined in any one of claims 1-22 and a pharmaceutically acceptable excipient and/or diluent.

24. Pharmaceutical combination comprising:

- pharmaceutical composition as defined in any one of claims 1-22 ; and
- a second pharmaceutical composition comprising 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-oligonucleotide conjugate or a receptor-ligand – oligonucleotide conjugate.

25. Pharmaceutical combination according to claim 24, wherein the second pharmaceutical composition comprises a pharmaceutically acceptable excipient and/or diluent.

26. Pharmaceutical composition according to any one of the claims 2-22 and further comprising 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.

27. Pharmaceutical composition according to claim 26, comprising a pharmaceutically acceptable excipient and/or diluent.

28. Pharmaceutical combination of claim 24 or 25 or the pharmaceutical composition of claim 26 or 27, wherein the second pharmaceutical composition or the pharmaceutical composition of claim 26 or 27 comprises any one or more of an antibody-drug conjugate, a receptor-ligand – drug conjugate, an antibody-oligonucleotide conjugate or a receptor-ligand – oligonucleotide conjugate, wherein the drug is for example a toxin such as saporin and dianthin, and wherein the oligonucleotide is for example an siRNA or a BNA, for example for gene silencing of apolipoprotein B or HSP27.

29. Pharmaceutical combination of claim 24, 25 or claim 28 or the pharmaceutical composition of claim 26, 27 or 28, wherein the saponin derivative is a saponin derivative according to claim 17.

30. Use of the pharmaceutical composition of any one of claims 1 - 22, pharmaceutical combination of any one of the claims 24, 25 or 28-29 or the pharmaceutical composition of any one of the claims 26-29, in the manufacture of a medicament for use as endosomal escape enhancer for and in combination with an antibody-toxin conjugate, a receptor-ligand – toxin conjugate, an antibody-drug conjugate, a receptor-ligand – drug conjugate, an antibody-oligonucleotide conjugate or a receptor-ligand – oligonucleotide conjugate.

31. Pharmaceutical composition of any one of claims 1-22, pharmaceutical combination of any one of the claims 24, 25 or 27-29 or the pharmaceutical composition of any one of the claims 26-29, for use as a medicament.

32. Use of the pharmaceutical composition of any one of claims 1-22, pharmaceutical combination of any one of the claims 24, 25 or 27-29 or the pharmaceutical composition of any one of the claims 26-29, in the manufacture of a medicament for the treatment or prophylaxis of a cancer, an infectious disease, viral infection, hypercholesterolemia, primary hyperoxaluria, haemophilia A, haemophilia B, alpha-1 antitrypsin related liver disease, acute hepatic porphyria, transthyretin-mediated amyloidosis, or an auto-immune disease.

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

a) providing a cell;

b) providing the molecule for transferring from outside the cell into the cell provided in step a);

c) providing a saponin derivative according to any one of the claims 1-22;

d) contacting the cell of step a) *in vitro* or *ex vivo* with the molecule of step b) and the saponin derivative of step c), therewith establishing the transfer of the molecule from outside the cell into said cell.

34. The method of claim 33, wherein the cell is a human cell such as a T-cell, an NK-cell, a tumor cell and/or wherein the saponin derivative is the saponin derivative of any one of the claims 15-22, and/or wherein the molecule of step b) is any one of: an antibody-drug conjugate, a receptor-ligand – drug conjugate, an antibody-oligonucleotide conjugate or a receptor-ligand – oligonucleotide conjugate, wherein the drug is for example a toxin and wherein the oligonucleotide is for example an siRNA or a BNA.