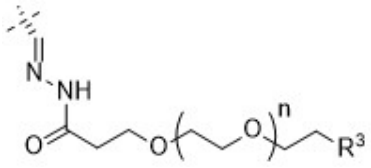
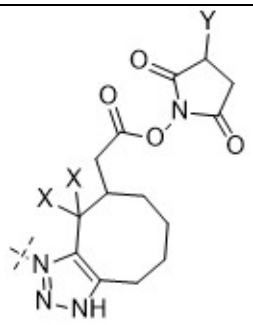
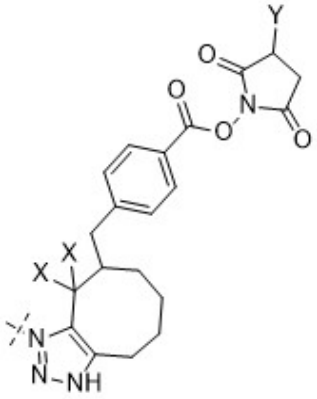
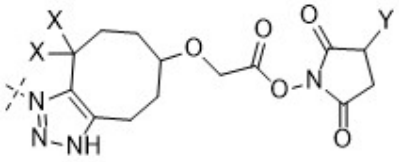
Claims

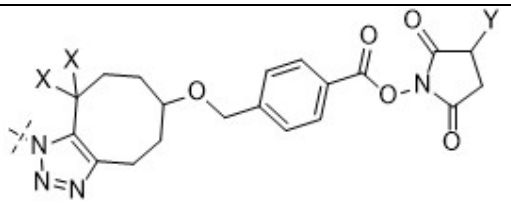
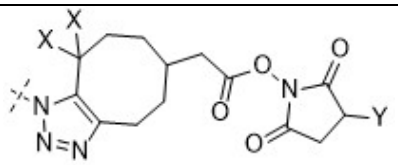
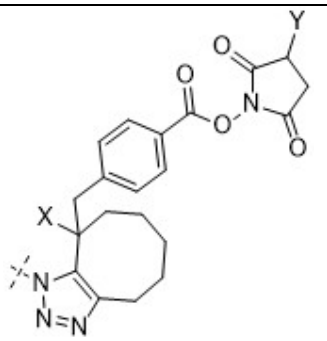
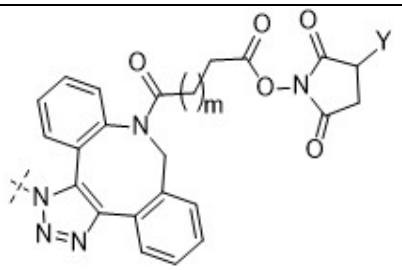
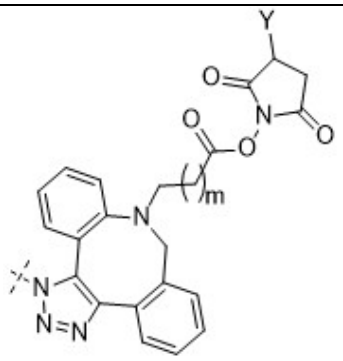
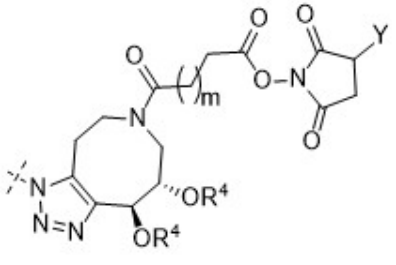
1. Saponin derivative based on a saponin comprising a triterpene aglycone core structure and at least one of a first saccharide chain 'R^1' and a second saccharide chain 'R^2' linked to the aglycone core structure, wherein the saponin derivative comprises an aglycone core structure comprising an aldehyde functional group which
is transformed to a hydrazone functional group according to formula (I)

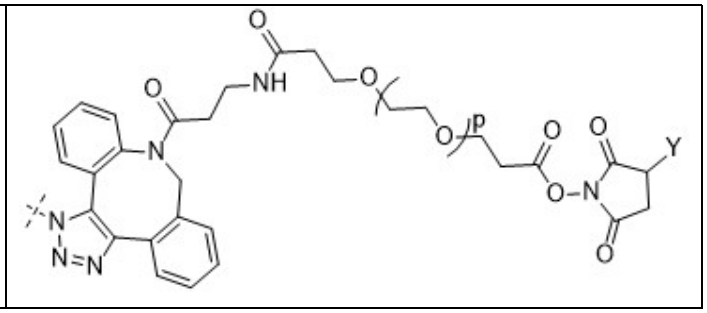


(I),

wherein n is an integer selected from 0-15,
R^3 is selected from the group consisting of linkers (IV)a-j:

(IV)a	
(IV)b	
(IV)c	

(IV)d	
(IV)e	
(IV)f	
(IV)g	
(IV)h	
(IV)i	

(IV)j	

wherein X is H or F, preferably F;

wherein Y is H or SO_2ONa;

m is 1 or 2;

p is an integer selected from 0-5, preferably 1-4, more preferably 2-3; and

R^4 is a C1-C3 alkyl chain, preferably a C1 alkyl chain.

2. Saponin derivative according to claim 1, wherein the saponin on which the saponin derivative is based is a mono-desmosidic or bi-desmosidic triterpene saponin belonging to the type of a 12,13-dehydrooleanane with the aldehyde group in position C-23 and optionally comprising a glucuronic acid group in a carbohydrate substituent at the C-3beta-OH group of the saponin, preferably a bi-desmosidic triterpene saponin belonging to the type of a 12,13-dehydrooleanane with the aldehyde group in position C-23 and comprising a glucuronic acid group in a carbohydrate substituent at the C-3beta-OH group of the saponin.

3. Saponin derivative according to claim 1 or 2, wherein n is an integer selected from 1-12, preferably 2-9, more preferably 3-6, most preferably n is 3.

4. Saponin derivative according to any one of the claims 1-3, wherein

R^1 is 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
derivatives thereof, and

R^2 is 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)-[R^5-(→4)]-3-OAc-Fuc- wherein R^5 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)-[R^6-(→4)]-Fuc- wherein R^6 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)-[R^7-(→4)]-Fuc- wherein R^7 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)-[R^8-(→4)]-Fuc- wherein R^8 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)-[R^9-(→4)]-Fuc- wherein R^9 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)-[R^{10}-(→4)]-Fuc- wherein R^{10} 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)-[R^{11}-(→4)]-Fuc- wherein R^{11} 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)-[R^{12}-(→4)]-Fuc- wherein R^{12} 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)-[R^{13}-(→3)]-Fuc- wherein R^{13} 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)-[R^{14}-(→3)]-Fuc- wherein R^{14} 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.

5. Saponin derivative according to any one of the claims 1-4, wherein
R^1 is selected from:
Gal-(1→2)-[Xyl-(1→3)]-GlcA-; and
R^2 is selected from:
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-,
Api-(1→3)-Xyl-(1→4)-Rha-(1→2)-[R^{11}-(→4)]-Fuc- wherein R^{11} 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)-[R^{12}-(→4)]-Fuc- wherein R^{12} 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)-[R^{13}-(→3)]-Fuc- wherein R^{13} 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)-[R^{14}-(→3)]-Fuc- wherein R^{14} is 5-O-[5-O-Ara/Api-3,5-dihydroxy-6-methyl-octanoyl]-3,5-dihydroxy-6-methyl-octanoic acid,
preferably R^1 is Gal-(1→2)-[Xyl-(1→3)]-GlcA- and R^2 is Glc-(1→3)-Xyl-(1→4)-Rha-(1→2)-[Xyl-(1→3)-4-OAc-Qui-(1→4)]-Fuc-.

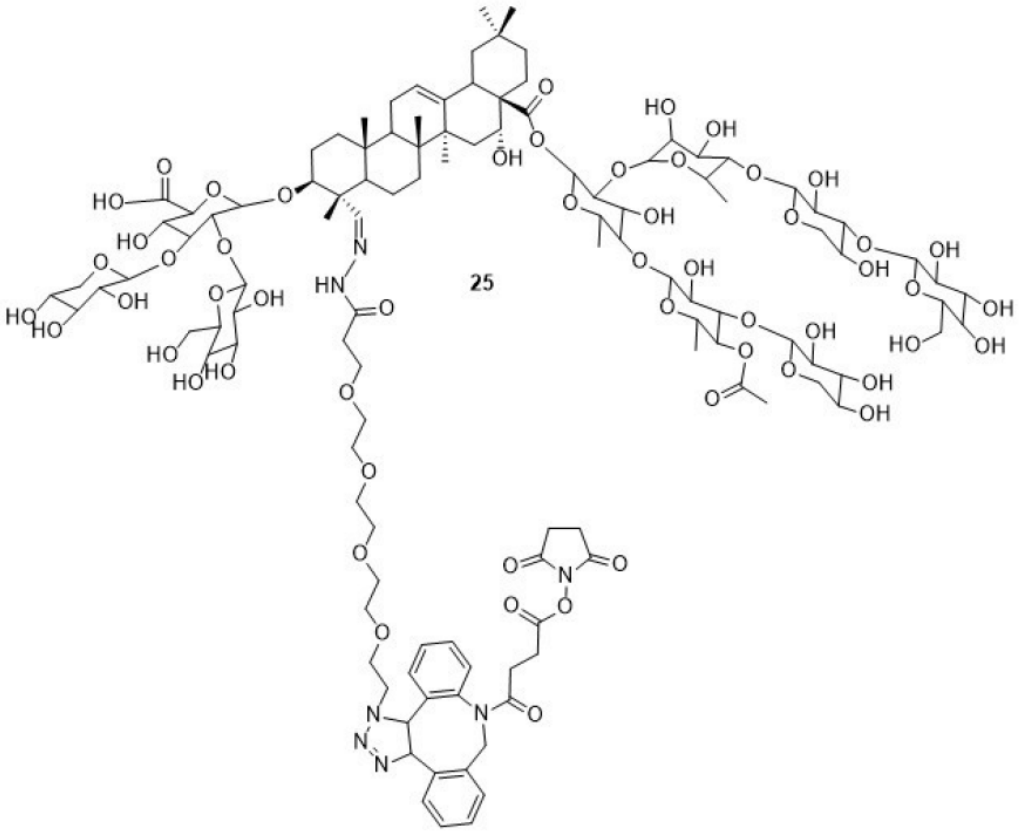
6. Saponin derivative according to any one of the claims 1-5, wherein the saponin derivative is a derivative of a saponin selected from the group of saponins consisting of: *Quillaja* bark saponin, NP-017777, NP-017778, NP-017774, NP-018110, NP-017772, NP-018109, NP-017888, NP-017889, NP-018108, SA1641, 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, SO1904, SO1862, 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 and Agrostemmoside E (AG1856), preferably the saponin derivative is selected from the group consisting of a QS-21 derivative, an SO1861 derivative, an SA1641 derivative and a GE1741 derivative, more preferably the saponin derivative is selected from the group consisting of a QS-21 derivative and an SO1861 derivative, most preferably the saponin derivative is an SO1861 derivative.

7. Saponin derivative according to any one of the claims 1-6, wherein Y = H.

8. Saponin derivative according to any one of claims 1-7, wherein the linker is selected from the group consisting of linkers (IV)g-(IV)j, preferably the linker is linker (IV)g or (IV)h, more preferably the linker is linker (IV)g.

9. Saponin derivative according to any one of claims 1-8, wherein m = 1.

10. Saponin derivative according to any one of claims 1-9, wherein the saponin derivative is a compound according to formula (VIII)



(VIII).

11. First pharmaceutical composition comprising the saponin derivative according to any one of claims 1-10 and optionally a pharmaceutically acceptable excipient and/or diluent.

12. First pharmaceutical combination comprising:
    (a) the first pharmaceutical composition of claim 11; and
    (b) a second pharmaceutical composition comprising any one or more of: a conjugate of a cell-surface molecule binding-molecule and an effector moiety, an antibody-effector moiety conjugate, a receptor-ligand – effector moiety conjugate, an antibody-toxin conjugate, a receptor-ligand – toxin conjugate, an antibody-drug conjugate, a receptor-ligand – drug conjugate, an antibody-oligonucleotide conjugate and a receptor-ligand – oligonucleotide conjugate, and optionally comprising a pharmaceutically acceptable excipient and/or diluent.

13. Third pharmaceutical composition comprising the saponin derivative of any one of the claims 1-10 and further comprising any one or more of: a conjugate of a cell-surface molecule binding-

molecule and an effector moiety, such as an antibody-effector moiety conjugate, a receptor-ligand – effector moiety conjugate, an antibody-toxin conjugate, a receptor-ligand – toxin conjugate, an antibody-drug conjugate, a receptor-ligand – drug conjugate, an antibody-nucleic acid conjugate and a receptor-ligand – nucleic acid conjugate, and optionally comprising a pharmaceutically acceptable excipient and/or diluent.

14. First pharmaceutical combination of claim 12 or the third pharmaceutical composition of claim 13, wherein the second pharmaceutical composition or the third pharmaceutical composition comprises any one or more of an antibody-toxin conjugate, a receptor-ligand – toxin conjugate, an antibody-oligonucleotide conjugate or a receptor-ligand – oligonucleotide conjugate, wherein preferably the toxin is a protein toxin.

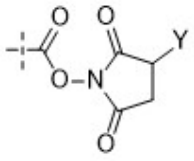
15. First pharmaceutical combination of claim 12 or 14 or the third pharmaceutical composition of claim 13 or 14, wherein the saponin derivative is the saponin derivative according to claim 10.

16. First pharmaceutical composition of claim 11, first pharmaceutical combination of any one of the claims 12, 14 and 15 or the third pharmaceutical composition of any one of the claims 13-15, for use as a medicament.

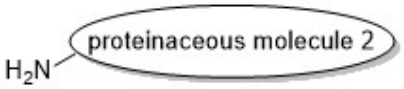
17. Use of the first pharmaceutical composition of claim 14, use of the first pharmaceutical combination of any one of the claims 12, 14 and 15 or use of the third pharmaceutical composition of any one of the claims 13-15, in the manufacture of a medicament for the treatment or prophylaxis of a cancer or an auto-immune disease.

18. *In vitro* or *ex vivo* method for transferring a molecule from outside a cell to inside said cell, preferably 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 1-10;
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.

19. Saponin conjugate based on a saponin derivative according to any one of the claims 1-6,



wherein the *N*-hydroxy succinimide active ester functional group ( ) is transformed to an amide functional group (-C(O)-N(H)-) through reaction with a second proteinaceous molecule (‘proteinaceous molecule 2’) comprising an amine functional group according to formula (XI)



(XI).

20. Saponin conjugate according to claim 19, wherein n is an integer selected from 1-14, preferably 2-12, more preferably 3-9.

21. Saponin conjugate according to any one of claims 19-20, wherein m = 1.

22. Saponin conjugate according to any one of the claims 19-21, wherein the proteinaceous molecule 2 comprise a first binding site for binding to a first epitope of a first cell-surface molecule.

23. Saponin conjugate according to claim 22, wherein the first binding site is selected from any one or more of: an amino acid, a peptide, a protein, an antibody or a derivative or fragment thereof such as a Fab or an scFv, a single-domain antibody (sdAb), a ligand.

24. Saponin conjugate according to claim 22 or 23, wherein the first binding site is or comprise(s) a single-domain antibody (sdAb), preferably V_H domain derived from a heavy chain of an antibody, preferably of immunoglobulin G origin, preferably of human origin, a V_L domain derived from a light chain of an antibody, preferably of immunoglobulin G origin, preferably of human origin, a V_{HH} domain such as derived from a heavy-chain only antibody (HCAb) such as from *Camelidae* origin or *Ig-NAR* origin such as a variable heavy chain new antigen receptor (VNAR) domain, preferably the HCAb is from *Camelidae* origin, preferably the sdAb is a V_{HH} domain derived from an HCAb from *Camelidae* origin (camelid V_H) such as derived from an HCAb from camel, lama, alpaca, dromedary, vicuna, guanaco and Bactrian camel.

25. Saponin conjugate according to any one of the claims 22-24, wherein the first epitope of the first cell-surface molecule to which the first binding site can bind is a tumor-cell specific first epitope of a first tumor-cell surface molecule, more preferably a tumor-cell specific first epitope of a first tumor-cell surface receptor specifically present on a tumor cell.

26. Second pharmaceutical combination, comprising:

(a) a fourth pharmaceutical composition comprising the saponin conjugate of any one of the claims 22-25 and optionally a pharmaceutically acceptable excipient and/or diluent; and

(b) a fifth pharmaceutical composition comprising a conjugate comprising a cell-surface molecule binding-molecule, such as a third proteinaceous molecule ('proteinaceous molecule 3'), and an effector moiety, wherein the proteinaceous molecule 3 is the same or different from the proteinaceous molecule 2 present in the saponin conjugate, the

proteinaceous molecule 3 comprising a third binding site for binding to a third epitope of a third cell-surface molecule, wherein the third cell-surface molecule, if different from the first cell surface molecule and/or the second cell surface molecule, is present on the same cell as the first cell surface,

the fifth pharmaceutical composition optionally further comprising a pharmaceutically acceptable excipient and/or diluent.

27. Second pharmaceutical combination of claim 26, comprising:

(a) the fourth pharmaceutical composition of claim 26 comprising the saponin conjugate of any one of the claims 22-25, wherein the first epitope on the first cell-surface molecule is a tumor-cell specific first epitope on a first tumor cell-specific surface molecule, preferably a tumor-cell specific first epitope on a first cell-surface receptor specifically present at a tumor cell; and

(b) the fifth pharmaceutical composition of claim 26, wherein the third cell-surface molecule is a third tumor cell-specific surface molecule which is the same or different from the first tumor cell-specific surface molecule, preferably a third cell-surface receptor specifically present at a tumor cell which is the same or different from the first cell-surface receptor specifically present at said tumor cell, and wherein the third epitope is a tumor-cell specific third epitope, wherein the first epitope and the third epitope, which is the same as or different from the first epitope, are exposed at the same cell.

28. Third pharmaceutical combination, comprising:

(a) the fourth pharmaceutical composition of claim 26 or 27 comprising the saponin conjugate according to of any one of the claims 2225 which comprises the first binding site for binding to the first epitope on the first cell-surface molecule, the fourth pharmaceutical composition optionally further comprising a pharmaceutically acceptable excipient and/or diluent; and

(b) a sixth pharmaceutical composition comprising a conjugate comprising a cell-surface molecule binding-molecule, such as a fourth proteinaceous molecule (‘proteinaceous molecule 4’), and an effector moiety, wherein the proteinaceous molecule 4 comprises the first binding site for binding to the first epitope on the cell-surface molecule of (a), the sixth pharmaceutical composition optionally further comprising a pharmaceutically acceptable excipient and/or diluent,

wherein the first binding site of the proteinaceous molecule 2 and the first binding site of the proteinaceous molecule 4 are the same, and wherein the first cell-surface molecule and the first epitope on the first cell-surface molecule, to which the proteinaceous molecule 2 can bind, and the first cell-surface molecule and the first epitope on the first cell-surface molecule, to which the proteinaceous molecule 4 can bind, are the same.

29. Fourth pharmaceutical combination, comprising:

(a) the fourth pharmaceutical composition of claim 28; and

(b) the sixth pharmaceutical composition of claim 28,

wherein the first cell-surface molecule is expressed on a tumor cell surface, and preferably the first cell-surface molecule is a tumor cell-specific surface molecule, and wherein preferably the first epitope is a first tumor-cell specific epitope.

30. Second pharmaceutical combination or third pharmaceutical combination or fourth pharmaceutical combination according to any one of the claims 26-29, wherein the third binding site of the proteinaceous molecule 3 and/or the first binding site of the proteinaceous molecule 4 comprises or consists of an antibody or a binding derivative or binding fragment or binding domain thereof such as a F(ab')2 fragment, Fab' fragment, Fab fragment, scFv, dsFv, scFv-Fc, reduced IgG (rIgG), minibody, diabody, triabody, tetrabody, Fc fusion protein, nanobody, variable V domain, a single-domain antibody (sdAb), preferably a V_{HH}, for example camelid V_H, or a ligand for a cell-surface molecule such as a receptor such as EGF and a cytokine, preferably a V_H domain derived from a heavy chain of an antibody, preferably of immunoglobulin G origin, preferably of human origin, a V_L domain derived from a light chain of an antibody, preferably of immunoglobulin G origin, preferably of human origin, a V_{HH} domain such as derived from a heavy-chain only antibody (HCAb) such as from *Camelidae* origin or *Ig-NAR* origin such as a variable heavy chain new antigen receptor (VNAR) domain, preferably the HCAb is from *Camelidae* origin, preferably the sdAb is a V_{HH} domain derived from an HCAb from *Camelidae* origin (camelid V_H) such as derived from an HCAb from camel, lama, alpaca, dromedary, vicuna, guanaco and Bactrian camel.

31. A seventh pharmaceutical composition comprising the saponin conjugate of any one of the claims 19-25, and the conjugate comprising proteinaceous molecule 3 and an effector moiety of claim 26 or 27, or the conjugate comprising proteinaceous molecule 4 and an effector moiety of claim 28 or 29, and optionally further comprising a pharmaceutically acceptable excipient and/or diluent.

32. The second pharmaceutical combination or third pharmaceutical combination or fourth pharmaceutical combination of any one the claims 26-30, or the seventh pharmaceutical composition of claim 40, for use as a medicament.

33. Use of the second pharmaceutical combination or use of the third pharmaceutical combination or use of the fourth pharmaceutical combination of any one the claims 26-30, or use of the seventh pharmaceutical composition of claim 31, in the manufacture of a medicament for the treatment or prevention of a cancer or of an autoimmune disease such as rheumatoid arthritis.