CLAIMS

~~1. Therapeutic molecule with chemical structure of COMPOUND I:~~

~~$A1_m ((\text{-}L9_w) ((\text{–} L1_q \text{–} B1_n)_u ((\text{–} L2_r \text{–} L3_s) (\text{–} L4_v \text{–} C)_p)_t))_x$~~

~~(compound I),~~

~~wherein~~

~~A1 is a first ligand and B1 is a first effector moiety;~~

~~C is a saponin, wherein the saponin C is a bisdesmosidic triterpene saponin, belonging to the type of a 12,13-dehydrooleanane with an aldehyde function in position C-23 and optionally comprising a glucuronic acid function in a carbohydrate substituent at the C-3beta-OH group of the saponin;~~

~~m = 1;~~

~~n = 0;~~

~~p = any of 1-128;~~

~~L1 is at least one linker for covalently coupling two chemical groups;~~

~~L2 is at least one linker for covalently coupling two chemical groups;~~

~~L3 is at least one oligomeric or polymeric scaffold for covalently coupling two chemical groups;~~

~~L4 is at least one linker for covalently coupling two chemical groups;~~

~~L9 is a tri-functional linker for covalently coupling three chemical groups;~~

~~q = 0;~~

~~r = 0;~~

~~s = 0;~~

~~t = 1 or 2 if s = 0;~~

~~u = 0 if A1 is the first ligand and B1 is the first effector moiety;~~

~~v = 1;~~

~~w = 0; and~~

~~x = 1-16;~~

~~wherein the therapeutic molecule comprises a first ligand and at least one saponin; wherein said at least one saponin is covalently bound via at least one linker to an amino-acid residue of said first ligand; wherein said first ligand consists of an immunoglobulin, a binding domain of an immunoglobulin or a binding fragment of an immunoglobulin, such as an antibody, an IgG, a molecule comprising or consisting of a Vhh domain or Vh domain, a Fab, an scFv, an Fv, a dAb, an $F(ab)_2$, Fcab fragment.~~

~~2~~1. Therapeutic molecule with chemical structure of COMPOUND I:

$$A1_m ((\text{-}L9_w) ((\text{–} L1_q \text{–} B1_n)_u ((\text{–} L2_r \text{–} L3_s) (\text{–} L4_v \text{–} C)_p)_t))_x$$

(compound I),

wherein

A1 is a first ligand and B1 is a first effector moiety;

C is a saponin, wherein the saponin C is a bisdesmosidic triterpene saponin, belonging to the type of a 12,13-dehydrooleanane with an aldehyde function in position C-23 and optionally comprising a glucuronic acid function in a carbohydrate substituent at the C-3beta-OH group of the saponin;

m = 1;

n = 1;

p = any of 1-128;

L1 is at least one linker for covalently coupling two chemical groups;

L2 is at least one linker for covalently coupling two chemical groups;

L3 is at least one oligomeric or polymeric scaffold for covalently coupling two chemical groups;

L4 is at least one linker for covalently coupling two chemical groups;

L9 is a tri-functional linker for covalently coupling three chemical groups;

q = 0 or 1;

r = 0;

s = 0;

t = 1 or 2;

u = any of 0 – 32 if A1 is the first ligand and B1 is the first effector moiety;

v = 0 or 1;

w = 1 or 0; and

x = 1-16;

wherein said therapeutic molecule comprises a first ligand and at least one first effector moiety and further comprises at least one covalently bound saponin, wherein the first effector moiety is a pharmaceutically active substance and consists of at least one proteinaceous molecule, wherein said first ligand consists of an immunoglobulin, a binding domain of an immunoglobulin or a binding fragment of an immunoglobulin, such as an antibody, an IgG, a molecule comprising or consisting of a Vhh domain or Vh domain, a Fab, an scFv, an Fv, a dAb, an $F(ab)_2$, Fcab fragment.

~~3. Therapeutic combination comprising the therapeutic molecule according to claim 1 and a second therapeutic molecule with chemical structure of COMPOUND II:~~

~~$A2_a\text{-}((\text{-}L10_j)\ ((\text{-}L5_d\text{-}B2_b)_h\ ((\text{-}L6_e\text{-}L7_f)\ (\text{-}L8_i\text{-}C)_c)_g))_k$~~

~~(compound II),~~

~~wherein~~

~~A2 is a second ligand and B2 is a second effector moiety;~~

~~C is a saponin;~~

~~a = 1;~~

~~b = 1;~~

~~c = any of 1-128;~~

~~L5 is at least one linker for covalently coupling two chemical groups;~~

~~L6 is at least one linker for covalently coupling two chemical groups;~~

~~L7 is at least one oligomeric or polymeric scaffold for covalently coupling two chemical groups;~~

~~L8 is at least one linker for covalently coupling two chemical groups;~~

~~L10 is a tri-functional linker for covalently coupling three chemical groups;~~

~~d = 0 or 1;~~

~~e = 0;~~

~~f = 0;~~

~~g = 0 if f = 0;~~

~~h = any of 1 – 32 if A2 is the second ligand and B2 is the second effector moiety;~~

~~i = 0;~~

~~j = 0 and;~~

~~k = 1-16;~~

~~wherein said second therapeutic molecule comprises a second ligand and at least one second effector moiety, wherein the second effector moiety is a pharmaceutically active substance and consists of at least one proteinaceous molecule, wherein said second ligand consists of an immunoglobulin, a binding domain of an immunoglobulin or a binding fragment of an immunoglobulin, such as an antibody, an IgG, a molecule comprising or consisting of a Vhh domain or Vh domain, a Fab, an scFv, an Fv, a dAb, an $F(ab)_2$, Fcab fragment, or consists of at least one proteinaceous ligand for binding to a cell-surface molecule such as EGF or a cytokine, wherein the first ligand and the second ligand are the same or are different.~~

~~4~~2. Therapeutic molecule of ~~any one of the~~ claim~~s~~ 1~~-3 or the therapeutic combination of claim 3~~, wherein the first ligand ~~and/or the second ligand~~ bind~~(~~s~~)~~ to a tumor-cell epitope, preferably a tumor-cell specific epitope, of a tumor-cell receptor, preferably a tumor-cell specific receptor, preferably selected from 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, more preferably selected from CD71, EGFR and HER2~~, with the proviso that the first ligand and the second ligand bind to the same or to a different tumor-cell epitope, preferably a tumor-cell specific epitope, and/or wherein the tumor-cell receptor, preferably the tumor-cell specific receptor, to which the first ligand can bind is the same as, or is different from the tumor-cell receptor, preferably the tumor-cell specific receptor, to which the second ligand can bind~~.

~~5~~3. Therapeutic molecule of any one of the claims 1-~~4~~ 2~~or the therapeutic combination of claim 3 or 4~~, wherein the first ligand ~~and/or the second ligand~~ comprise~~(s)~~ or consist~~(s)~~ of cetuximab, daratumumab, gemtuzumab, trastuzumab, panitumumab, brentuximab, inotuzumab, moxetumomab, polatuzumab, obinutuzumab, OKT-9 anti-CD71 monoclonal antibody of the IgG type, pertuzumab, rituximab, ofatumumab, Herceptin, alemtuzumab, pinatuzumab, OKT-10 anti-CD38 monoclonal antibody, an antibody of Table A2 or Table A3 or Table A4, preferably cetuximab or trastuzumab or OKT-9, or at least one tumor-cell receptor binding-domain thereof and/or at least one tumor-cell receptor binding-fragment thereof which are preferably (a) tumor-cell specific receptor binding-domain(s) and/or (a) tumor-cell specific receptor binding-fragment(s), ~~with the proviso that the first ligand is the same or different from the second ligand~~.

~~6~~4. Therapeutic molecule of any one of the claims ~~2~~1-~~5~~ 3~~or the therapeutic combination of any one of the claims 3-5~~, wherein the first effector moiety ~~and/or the second effector moiety~~ consists of at least one of any one or more of an oligonucleotide, a nucleic acid and a xeno nucleic acid, preferably selected from any one or more of a vector, a gene, a cell suicide inducing transgene, deoxyribonucleic acid (DNA), ribonucleic acid (RNA), anti-sense oligonucleotide (ASO, AON), short interfering RNA (siRNA), microRNA (miRNA), DNA aptamer, RNA aptamer, mRNA, mini-circle DNA, peptide nucleic acid (PNA), phosphoramidate morpholino oligomer (PMO), locked nucleic acid (LNA), bridged nucleic acid (BNA), 2'-deoxy-2'-fluoroarabino nucleic acid (FANA), 2'-O-methoxyethyl-RNA (MOE), 2'-O,4'-aminoethylene bridged nucleic acid, 3'-fluoro hexitol nucleic acid (FHNA), a plasmid, glycol nucleic acid (GNA) and threose nucleic acid (TNA), or a derivative thereof, more preferably a BNA, for example a BNA for silencing HSP27 protein expression.

~~7~~5. Therapeutic molecule of any one of the claims 1~~2~~-~~5~~ 4~~or the therapeutic combination of any one of the claims 3-5~~, wherein the first effector moiety ~~and/or the second effector moiety~~ is 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, at least one protein toxin selected from Table A5 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~~, with the proviso that the first effector moiety/moieties and the second effector moiety/moieties are the same or are different~~.

~~8~~6. Therapeutic molecule of any one of the claims ~~2~~1-~~7 5or the therapeutic combination of any one of the claims 3-7~~, wherein the therapeutic molecule comprises and/or ~~the second therapeutic molecule~~ consists of any one of Gemtuzumab ozogamicin, Brentuximab vedotin, Trastuzumab emtansine, Inotuzumab ozogamicin, Moxetumomab pasudotox and Polatuzumab vedotin and an antibody-drug conjugate of Table A2 and Table A3, or at least one tumor-cell specific receptor binding-domain thereof and/or at least one tumor-cell specific receptor binding-fragment thereof which are preferably (a) tumor-cell specific receptor binding-domain(s) and/or (a) tumor-cell specific receptor binding-fragment(s)~~, with the proviso that the therapeutic molecule and the second therapeutic molecule are the same or are different~~.

~~9~~7. Therapeutic molecule of any one of the claims 1-~~8~~6, wherein the saponin is a saponin isolated from *a Gypsophila* species and/or a *Saponaria* species and/or an *Agrostemma* species and/or a *Quillaja* species such as *Quillaja saponaria*.

~~10~~8. Therapeutic molecule of any one of the claims 1-~~9~~7, wherein the saponin is a single specific saponin or is a mixture of two or more different saponins, such as one or more of the saponins 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, AE X55, NP-017674, NP-017810, NP-003881, NP-017676, NP-017677, NP-017706, NP-017705, NP-017773, NP-017775, QS-17, 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, AS64R, AS6.2, SO1861, SA1657, GE1741, SA1641, QS-21, QS-21A, QS-21 A-api, QS-21 A-xyl, QS-21B, QS-21 B-api, QS-21 B-xyl, QS-7-xyl, QS-7-api, QS-17-api, QS-17-xyl, QS1861, QS1862, Quillajasaponin, Saponinum album, QS-18, Quil-A, Gyp1, gypsoside A, AG1, AG2, SO1542, SO1584, SO1658, SO1674, SO1832, or any of their stereomers and/or any combinations thereof, preferably the saponin is SO1861 and/or GE1741 and/or SA1641 and/or QS-21 and/or saponin with a quillaic acid aglycon core, a Gal-(1→2)-[Xyl-(1→3)]-GlcA carbohydrate substituent at the C-3beta-OH group and a Glc-(1→3)-Xyl-(1→4)-Rha-(1→2)-[Xyl-(1→3)-4-OAc-Qui-(1→4)]-Fuc carbohydrate substituent at the C-28-OH group, and/or 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)-4-OAc-beta-D-quinovopyranosyl-(1→4)]-beta-D-fucopyranoside, more preferably the saponin is SO1861 and/or QS-21.

~~11~~9. Therapeutic molecule of any one of the claims 1-~~10~~8, wherein the saponin is a bisdesmosidic saponin having a molecular mass of at least 1.500 Dalton and comprising an oleanan-type triterpene containing an aldehyde group at the C-23 position and optionally a hydroxyl group at the C-16 position, with a first branched carbohydrate side chain at the C-3 position which first branched carbohydrate side chain optionally contains glucuronic acid, wherein the saponin contains an ester group with a second branched carbohydrate side chain at the C-28 position which second branched carbohydrate chain preferably comprises at least four carbohydrate units, optionally containing at least one acetyl residue

such as two acetyl residues and/or at least one deoxy carbohydrates and/or a quinovose and/or a glucose and/or 4-methoxycinnamic acid and/or optionally comprising 5-O-[5-O-Ara/Api-3,5-dihydroxy-6-methyl-octanoyl]-3,5-dihydroxy-6-methyl-octanoic acid and/or optionally comprising 5-O-[5-O-Rha-(1→2)-Ara/Api-3,5-dihydroxy-6-methyl-octanoyl]-3,5-dihydroxy-6-methyl-octanoic acid bound to a carbohydrate via an ester bond, or wherein the at least one saponin is QS-21 or any one or more of 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, QS-18, QS1861, protonated QS1861 (QS1862), Quil-A.

~~12~~10. Therapeutic molecule of any one of the claims 1-~~11~~9, wherein the saponin is a bisdesmosidic triterpene saponin belonging to the type of a 12,13-dehydrooleanane with an aldehyde function in position C-23, wherein the saponin is covalently coupled to an amino-acid residue of the first ligand via the aldehyde function in the saponin, preferably said aldehyde function in position C-23, wherein the amino-acid residue preferably is selected from cysteine and lysine.

~~13~~11. Therapeutic molecule of any one of the claims 1-~~12~~10, wherein the saponin is a bisdesmosidic triterpene saponin belonging to the type of a 12,13-dehydrooleanane with an aldehyde function in position C-23, wherein the aldehyde function in position C-23 of the at least one saponin is covalently coupled to linker N-ε-maleimidocaproic acid hydrazide, which linker is covalently coupled via a thio-ether bond to a sulfhydryl group in the first ligand , such as a sulfhydryl group of a cysteine.

~~14~~12. Therapeutic molecule of any one of the claims 1-~~13~~11, wherein the saponin is a bisdesmosidic triterpene saponin belonging to the type of a 12,13-dehydrooleanane with an aldehyde function in position C-23 and comprising a glucuronic acid function in a carbohydrate substituent at the C-3beta-OH group of the saponin, wherein the saponin is covalently coupled to the amino-acid residue of the first ligand via the glucuronic acid function in the saponin, wherein the amino-acid residue preferably is selected from cysteine and lysine, more preferably the amino-acid residue is lysine.

~~15~~13. Therapeutic molecule of any one of the claims 1-~~14~~12, wherein the saponin is a bisdesmosidic triterpene saponin belonging to the type of a 12,13-dehydrooleanane with an aldehyde function in position C-23 and comprising a glucuronic acid function in a carbohydrate substituent at the C-3beta-OH group of the saponin, wherein the glucuronic acid function in the carbohydrate substituent at the C-3beta-OH group of the at least one saponin is covalently coupled to linker 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate, which linker is covalently coupled via an amide bond to an amine group in the first ligand , such as an amine group of a lysine or an N-terminus of the first ligand .

~~16~~14. Therapeutic molecule of any one of the claims 1-~~15~~13, wherein the first ligand comprise~~(s)~~ one or more than one covalently bound saponin, preferably 2, 3, 4, 5, 6, 8, 10, 16, 32, 64, 128 or 1-100 saponins, or any number of saponins therein between, such as 7, 9, 12 saponins.

~~17~~15. Therapeutic molecule of any one of claims 1-~~16~~14, wherein the linker L4, L6, L8 and/or L9 is subject to cleavage under acidic conditions, reductive conditions, enzymatic conditions or light-induced conditions, and preferably the cleavable linker comprises a hydrazone bond or a hydrazide bond subject to cleavage under acidic conditions when bound to saponin, and/or comprises a bond susceptible to proteolysis, for example proteolysis by Cathepsin B, when bound to saponin, and/or the cleavable linker comprises a disulphide bond susceptible to cleavage under reductive conditions.

~~18~~16. Therapeutic molecule of any one of claims 1-~~15~~13, wherein the cleavable linker L4, L6, L8 and/or L9 is subject to cleavage *in vivo* under acidic conditions as present in endosomes and/or lysosomes of mammalian cells, preferably human cells, preferably at pH 4.0 – 6.5, and more preferably at pH ≤ 5.5.

~~19~~17. Therapeutic molecule of any one of the claims ~~17~~15-~~18~~16, wherein the at least one saponin is covalently bound to the first ligand via at least one linker such as a bi-functional linker, for example based on N-ε-maleimidocaproic acid hydrazide and/or based on 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate.

~~20. Therapeutic combination of any one of the claims 17-19, wherein the second ligand is covalently bound to the second effector moiety via at least one linker L5.~~

~~21. Therapeutic combination, wherein the therapeutic combination comprises:~~

~~(a) a first pharmaceutical composition comprising the therapeutic molecule with chemical structure of COMPOUND I according to any one of the claims 1, 3-20, the first pharmaceutical composition optionally further comprising a pharmaceutically acceptable excipient; and~~

~~(b) a second pharmaceutical composition comprising the second therapeutic molecule with chemical structure of COMPOUND II according to any one of the claims 3-20, the second pharmaceutical composition optionally further comprising a pharmaceutically acceptable excipient.~~22. ~~The first pharmaceutical composition of claim 21 for use as a medicament.~~

~~23. Use of therapeutic combination in the preparation of a medicament for the treatment or prevention of cancer in a human subject, wherein the therapeutic combination comprises:~~

~~(a) the first pharmaceutical composition of claim 21; and~~

~~(b) the second pharmaceutical composition of claim 21,~~

~~wherein the first ligand and the second ligand can bind to a tumor-cell epitope, preferably to a tumor-cell specific epitope, on a tumor-cell surface molecule, preferably on a tumor cell-specific surface molecule, with the proviso that the tumor-cell epitope or tumor-cell specific epitope to which the first ligand can bind is the same as, or is different from the tumor-cell epitope or the tumor-cell specific epitope to which the second ligand can bind.~~

~~24. Use of the first pharmaceutical composition of any one of the claims 21-23 in the preparation of a medicament for the treatment or prophylaxis of cancer in a patient in need thereof, wherein the first ligand can bind to a tumor-cell epitope, preferably a tumor-cell specific epitope, on a tumor-cell surface molecule, preferably a tumor cell-specific surface molecule.~~

~~25. Use of the first pharmaceutical composition according to claim 22 or 24 or use of the therapeutic combination according to claim 23, wherein the second pharmaceutical composition of claim 23 and the first pharmaceutical composition of claim 22 or 24 are administered to the patient in need thereof.~~

~~26. The first pharmaceutical composition of claim 21 further comprising the second therapeutic molecule of any one of the claims 3-20.~~

~~27. The first pharmaceutical composition of claim 26, for use as a medicament.~~

~~28. Use of the first pharmaceutical composition of claim 26 in the preparation of a medicament for the treatment or prevention of a cancer in a human subject.~~

~~29~~18. Pharmaceutical composition comprising the therapeutic molecule with chemical structure of COMPOUND I according to any one of the claims ~~2 and 4-19~~1-17 ~~when dependent on claim 2~~, for use as a medicament.