CLAIMS

1. Therapeutic combination for use as a medicament, wherein the therapeutic combination comprises:

(a) a first pharmaceutical composition comprising a first proteinaceous molecule comprising a binding site for binding to an epitope on a cell-surface molecule and at least one saponin covalently bound to said first proteinaceous molecule preferably to an amino-acid residue of said first proteinaceous molecule, the first pharmaceutical composition optionally further comprising a pharmaceutically acceptable excipient; and

(b) a second pharmaceutical composition comprising a second proteinaceous molecule, the second proteinaceous molecule comprising a binding site for binding to the epitope on the cell-surface molecule of (a) and an effector moiety, the second pharmaceutical composition optionally further comprising a pharmaceutically acceptable excipient,

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

and wherein the binding site of the first proteinaceous molecule and the second proteinaceous molecule comprises or consists of an immunoglobulin or a binding fragment or binding domain of said immunoglobulin, such as any one or more of 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, and/or comprises or consists of at least one ligand, wherein the ligand is epidermal growth factor (EGF);

and wherein the at least one saponin is a triterpenoid saponin and/or a bisdesmosidic triterpene saponin belonging to the type of a 12,13-dehydrooleanane with an aldehyde function in position C-23;

and wherein the effector moiety comprises or consists of any one or more of a oligonucleotide, a nucleic acid and a xeno nucleic acid; or comprises or consists of at least one proteinaceous molecule, selected from any one or more of a viral toxin, a bacterial toxin, a fungal toxin, a plant toxin including ribosome-inactivating proteins and the A chain of type 2 ribosome-inactivating proteins, an animal toxin or a human toxin.

2. The therapeutic combination for use of claim 1, wherein the binding site of the first proteinaceous molecule and the second proteinaceous molecule comprises or consists of an immunoglobulin or a binding fragment or binding domain of said immunoglobulin, such as any one or more of 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. The therapeutic combination for use of any one of the claims 1-2, wherein the tumor-cell surface molecule is a cell-surface receptor specifically present at a tumor cell, and wherein preferably the epitope is a tumor-cell specific epitope.

4. The therapeutic combination for use of any one of the claims 1-3, wherein the at least one saponin comprises a glucuronic acid function in a carbohydrate substituent at the C-3beta-OH group of the saponin.

5. The therapeutic combination for use of any one of the claims 1-4, wherein the saponin is SO1861 and/or QS-21.

6. The therapeutic combination for use of any one of the claims 1-5, wherein the saponin is SO1861.

7. The therapeutic combination for use of any one of the claims 1-6, wherein the at least one 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 the first proteinaceous molecule, preferably covalently coupled to an amino-acid residue of the first proteinaceous molecule, via an aldehyde function in the saponin, preferably said aldehyde function in position C-23, preferably via at least one linker, and/or via at least one cleavable linker, wherein the amino-acid residue preferably is selected from cysteine and lysine.

8. The therapeutic combination for use of claim 7 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 proteinaceous molecule, such as a sulfhydryl group of a cysteine.

9. The therapeutic combination for use of any one of the claims 1-8, wherein the at least one 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 an amino-acid residue of the first proteinaceous molecule via the glucuronic acid function in the carbohydrate substituent at the C-3beta-OH group of the saponin, preferably via at least one linker, wherein the amino-acid residue preferably is selected from cysteine and lysine.

10. The therapeutic combination for use of claim 9, 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 proteinaceous molecule, such as an amine group of a lysine or an N-terminus of the first proteinaceous molecule.

11. The therapeutic combination for use of any one of the claims 1-10, wherein the epitope is an epitope on a tumor-cell receptor, preferably a tumor-cell specific epitope, and wherein the receptor is preferably a tumor-cell specific receptor, more preferably a receptor 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, most preferably selected from CD71, HER2 and EGFR.

12. The therapeutic combination for use of claim 11, wherein the tumor-cell receptor, preferably the tumor-cell specific receptor, is internalized by the tumor cell after binding to the first proteinaceous molecule of any one of the claims 1-11 and/or after binding to the second proteinaceous molecule of any one of the claims 1-11, and wherein preferably binding of the first proteinaceous molecule and/or the second proteinaceous molecule to the tumor-cell receptor, such as the tumor-cell specific receptor, is followed by tumor-cell receptor-mediated internalization, e.g. via endocytosis, of a complex of the first proteinaceous molecule and the tumor-cell receptor and of a complex of the second proteinaceous molecule and the tumor-cell receptor.

13. The therapeutic combination for use of any one of the claims 1-12, wherein the binding site of the first proteinaceous molecule and the second proteinaceous molecule comprise or consist of any one of 3B7, ADCT-502, Affilutin, AGS-16M18, AGS-67E, alemtuzumab, AMG-172, AMG-595, ASG-15ME, ASG-5ME, ASP-6183, AVE-9633, Avicidin, BAY-794620, B-B4, Bismab-A, bivatuzumab, BIWI-1, brentuximab, cantuzumab ravtansine, CDX-014, cetuximab, Cixutumumab, clivatuzumab tetraxetan, CNTO 95, coltuximab ravtansine, daratumumab, DCDS-0780A, denintuzumab mafodotin, depatuxizumab mafodotin, DS6, edrecolomab, epratuzumab, etaracizumab, gemtuzumab, glembatumumab vedotin, Herceptin, HTI-1511, huB4, huC242, HuMax-CD74-ADC, huMy9-6, huN901, ibritumomab, ibritumomab tiuxetan, IMGN-289, IMGN-388, IMGN-779, ImmuRAIT-LL2, indusatumab vedotin, Inotuzumab, inotuzumab ozogamicin, labetuzumab, lifastuzumab vedotin, lorvotuzumab mertansine, MLN-2704, MM-302, MM-310, Moxetumomab, Neuradiab, nimotuzumab, Obinutuzumab, ofatumumab, OKT-10 anti-CD38 monoclonal antibody, OKT-9 anti-CD71 monoclonal antibody of the IgG type, Oncolysin B, Oncolysin S, oregovomab, panitumumab, pertuzumab, PF-06263507, PF-06647263, PF-06650808, Pinatuzumab, pinatuzumab vedotin, Polatuzumab, RG-7598, RG-7600, RG-7636, RG-7841, RG-7882, rituximab, rovalpituzumab tesirine, sacituzumab govitecan, SAR-428926, SAR-566658, SC-004, SC-006, SGN-15, SGNCD-123A, SGNCD-19B, SGNCD-352A, SGN-CD70A, sibrotuzumab, sofituzumab vedotin, tositumomab, Trastuzumab, trastuzumab emtansine, vadastuximab talirine, vandortuzumab vedotin, vorsetuzumab mafodotin, XMT-1522 or ZW-33,, preferably cetuximab or trastuzumab or OKT-9, or at least one cell-surface molecule binding fragment and/or -domain thereof, with the proviso that the first binding site is the same as the second binding site.

14. The therapeutic combination for use of any one of the claims 1-13, wherein the effector moiety comprised by the second proteinaceous molecule_comprises or consists of any one or more of an oligonucleotide, a nucleic acid and a xeno nucleic acid, 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), , more preferably a BNA, for example a BNA for silencing HSP27 protein expression.

15. The therapeutic combination for use of any one of the claims 1-14, wherein the effector moiety comprised by the second proteinaceous molecule comprises or consists of at least one proteinaceous molecule, selected from any one or more of apoptin, Shiga toxin, Shiga-like toxin, Pseudomonas aeruginosa exotoxin (PE) or exotoxin A of PE, full-length or truncated diphtheria toxin (DT), cholera toxin, 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, frog RNase, granzyme B or angiogenin from humans; preferably the protein toxin is dianthin and/or saporin.

16. The therapeutic combination for use according to any one of claims 1-15, wherein the effector moiety comprised by the second proteinaceous molecule is a BNA for silencing HSP27 protein expression, dianthin or saporin.

17. The therapeutic combination for use of any one of the claims 1-16, wherein the second proteinaceous molecule comprises or consists of any one of ADCT-502, Affilutin, AGS-16M18, AGS-67E, AMG-172, AMG-595, ASG-15ME, ASG-5ME, ASP-6183, AVE-9633, Avicidin, BAY-794620, Bismab-A, BIWI-1, Brentuximab vedotin, cantuzumab ravtansine, CDX-014, clivatuzumab tetraxetan, coltuximab ravtansine, DCDS-0780A, denintuzumab mafodotin, depatuxizumab mafodotin, Gemtuzumab ozogamicin, glembatumumab vedotin, HTI-1511, HuMax-CD74-ADC, ibritumomab tiuxetan, IMGN-289, IMGN-388, IMGN-779, ImmuRAIT-LL2, indusatumab vedotin, inotuzumab ozogamicin, lifastuzumab vedotin, lorvotuzumab mertansine, MLN-2704, MM-302, MM-310, Moxetumomab pasudotox, Neuradiab, Oncolysin B, Oncolysin S, PF-06263507, PF-06647263, PF-06650808, pinatuzumab vedotin, Polatuzumab vedotin, RG-7598, RG-7600, RG-7636, RG-7841, RG-7882, rovalpituzumab tesirine, sacituzumab govitecan, SAR-428926, SAR-566658, SC-004, SC-006, SGN-15, SGNCD-123A, SGNCD-19B, SGNCD-352A, SGN-CD70A, sofituzumab vedotin, trastuzumab emtansine, vadastuximab talirine, vandortuzumab vedotin, vorsetuzumab mafodotin, XMT-1522 and ZW-33, or at least one tumor-cell receptor binding-domain thereof and/or at least one tumor-cell receptor binding-fragment thereof, wherein said domain(s) or fragment(s) comprise(s) the effector moiety and

are preferably (a) tumor-cell specific receptor binding-domain(s) and/or (a) tumor-cell specific receptor binding-fragment(s).

18. The therapeutic combination for use of any one of the claims 1-17, wherein the first proteinaceous molecule comprises 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.

19. The therapeutic combination for use of any one of the claims 1-18, wherein the at least one saponin is covalently bound directly to an amino-acid residue of the first proteinaceous molecule, preferably to a cysteine and/or to a lysine, and/or is covalently bound via at least one linker and/or via at least one cleavable linker and/or via at least one oligomeric or polymeric scaffold, preferably 1-8 of such scaffolds or 2-4 of such scaffolds, wherein the at least one scaffold is optionally based on a dendron, wherein 1-32 saponins, such as 2, 3, 4, 5, 6, 8, 10, 16, 32 saponins, or any number of saponins therein between, such as 7, 9, 12 saponins, are covalently bound to the at least one scaffold.

20. The therapeutic combination for use of any one of the claims 1-19, wherein the cleavable linker is subject to cleavage under acidic conditions, reductive conditions, enzymatic conditions 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 disulphide bond.

21. The therapeutic combination for use of any one of the claims 7-20, wherein the cleavable linker 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 $\leq$ 5.5.

22. The therapeutic combination for use of any one of the claims 19-21, wherein the oligomeric or polymeric scaffold comprises a polymeric or oligomeric structure and comprises at least one chemical group, the at least one chemical group for covalently coupling of the scaffold to the amino-acid residue of said first proteinaceous molecule.

23. The therapeutic combination for use of any one of the claims 19-22, wherein the at least one saponin is covalently bound to the polymeric or oligomeric structure of the scaffold via a cleavable linker according to any one of the claims 20-22.

24. The therapeutic combination for use of any one of the claims 19-23, wherein the at least one saponin is covalently bound to the polymeric or oligomeric structure of the scaffold via any one or more of an imine bond, a hydrazone bond, a hydrazide bond, an oxime bond, a 1,3-dioxolane bond, a disulphide bond, a thio-ether bond, an amide bond, a peptide bond or an ester bond, preferably via at least one linker.

25. The therapeutic combination for use of any one of the claims 19-24, wherein the at least one saponin comprises an aldehyde function in position C-23 and optionally a glucuronic acid function in the carbohydrate substituent at the C-3beta-OH group of the at least one saponin, which aldehyde function is involved in the covalent bonding to the polymeric or oligomeric structure of the scaffold, and/or, if present, the glucuronic acid function is involved in the covalent bonding to the polymeric or oligomeric structure of the scaffold, either via direct binding or via at least one linker.

26. The therapeutic combination for use of claim 25, 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 polymeric or oligomeric structure of the scaffold, such as a sulfhydryl group of a cysteine.

27. The therapeutic combination for use of claim 25 or 26, 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 polymeric or oligomeric structure of the scaffold, such as an amine group of a lysine or an N-terminus of a proteinaceous molecule.

28. The therapeutic combination for use of any one of the claims 19-27, wherein the at least one chemical group of the scaffold, for covalently coupling of the oligomeric or polymeric scaffold to the amino-acid residue of said first proteinaceous molecule, is a click chemistry group, preferably selected from a tetrazine, an azide, an alkene or an alkyne, or a cyclic derivative of these groups, more preferably the click chemistry group is an azide.

29. The therapeutic combination for use of any one of the claims 19-28, wherein the polymeric or oligomeric structure of the scaffold comprises a linear, branched and/or cyclic polymer, oligomer, dendrimer, dendron, dendronized polymer, dendronized oligomer, poly-lysine, a poly-ethylene glycol, or an assembly of these polymeric or oligomeric structures which assembly is preferably built up by covalent cross-linking.