ii) building units (BU), each building unit being a lysine residue or an analogue thereof;

wherein the core unit is covalently attached to at least two building units *via* amide linkages, each amide linkage being formed between a nitrogen atom present in the core unit and a carbon atom of an acyl group present in a building unit;

b) a HER2 targeting agent which is a peptidic moiety having a molecular weight of up to about 80 kDa and comprising an antigen-binding site, which is covalently linked to the dendrimer by a spacer group;

c) a therapeutic agent which is covalently linked to a surface building unit of the dendrimer; and

d) a hydrophilic polymeric group that is covalently linked to surface building units of the dendrimer.

In some ~~embodiment~~examples, the peptidic moiety is selected from: a heavy chain antibody, Fab, Fv, scFv or a single domain antibody. In some ~~embodiment~~examples, the peptidic moiety comprises or consists of a heavy chain variable (V_H) domain. In some ~~embodiment~~examples, the peptidic moiety comprises or consists of a light chain variable (V_L) domain.

In some ~~embodiment~~examples, the targeting agent has a molecular weight of about 5 kDa to about 30 kDa. In some ~~embodiment~~examples, the targeting agent has a molecular weight of about 5 kDa to about 18 kDa. In some ~~embodiment~~examples, the targeting agent has a molecular weight of about 5 kDa to about 15 kDa. In some ~~embodiment~~examples, the targeting agent has a molecular weight of about 10 kDa to about 16 kDa. In some ~~embodiment~~examples, the targeting agent has a molecular weight of about 14 kDa to about 18 kDa.

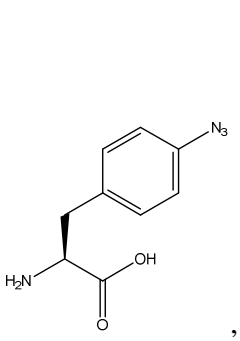
In some ~~embodiment~~examples, the targeting agent comprises less than 120 amino acid residues.

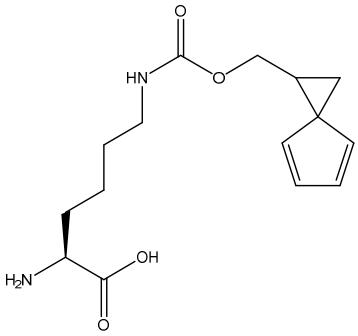
In some ~~embodiment~~examples, the targeting agent comprises or consists of any of the amino acid sequences as defined herein.

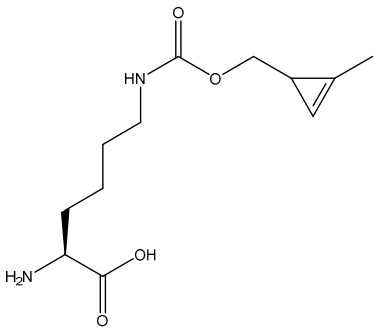
In some ~~embodiment~~examples, one targeting agent is covalently linked to the dendrimer. In some ~~embodiment~~examples, more than one targeting agent is covalently linked to the dendrimer.

In some ~~embodiment~~examples, the targeting agent precursor comprises an unnatural amino acid residue, the unnatural amino acid residue having a side-chain including a reactive functional

group. In some ~~embodiment~~examples, the unnatural amino acid residue is a residue of,



,


, or


.

In some ~~embodiment~~examples, the targeting agent is covalently linked to the spacer group *via* the C-terminus of the targeting moiety.

In some ~~embodiment~~examples, the spacer group precursor comprises a reactive functional group which is an alkyne group. In some ~~embodiment~~examples, the alkyne group is a dibenzocyclooctyne group.

In some ~~embodiment~~examples, the spacer group is covalently attached to a surface building unit of the dendrimer. In some ~~embodiment~~examples, the spacer group is covalently attached to the core unit.

In some ~~embodiment~~examples, the covalent linkage between the targeting agent and the spacer group has been formed by reaction between complementary reactive functional groups present on a targeting agent precursor and a spacer group precursor. In some ~~embodiment~~examples, the spacer group comprises an alkene group.

In some ~~embodiment~~examples, the therapeutic agent is a chemotherapeutic agent. In some ~~embodiment~~examples, the therapeutic agent is a cytotoxic agent. In some ~~embodiment~~examples, the therapeutic agent is an ultracytotoxic agent. In some ~~embodiment~~examples, the therapeutic agent is an auristatin or a maytansinoid. In some ~~embodiment~~examples, the therapeutic agent is monomethyl auristatin E. In some ~~embodiment~~examples, the therapeutic agent is monomethyl auristatin F. In some ~~embodiment~~examples, the therapeutic agent is SN-38. In some ~~embodiment~~examples, the therapeutic agent is cabazitaxel.

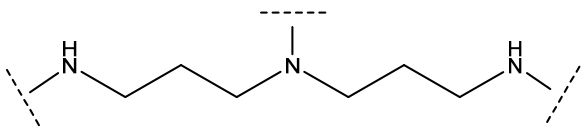
In some ~~embodiment~~examples, the therapeutic agent is covalently linked to a surface building unit of the dendrimer *via* a linker. In some ~~embodiment~~examples, the therapeutic agent is covalently linked to a surface building unit of the dendrimer *via* a cleavable linker. In some ~~embodiment~~examples, the cleavable linker comprises a Val-Cit-PAB group.

In some ~~embodiment~~examples, the conjugate comprises a hydrophilic polymeric group covalently linked to surface building units of the dendrimer. In some ~~embodiment~~examples, the hydrophilic polymeric group is a PEG group, which is covalently linked to surface building

units of the dendrimer. In some ~~embodiment~~examples, the PEG groups have an average molecular weight in the range of from about 500 to about 2500 g/mole.

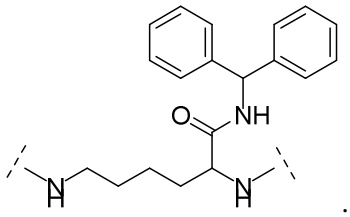
In some ~~embodiment~~examples, the spacer group comprises a PEG group.

In some ~~embodiment~~examples, the core unit comprises the structure:



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In some ~~embodiment~~examples, the core unit comprises the structure:

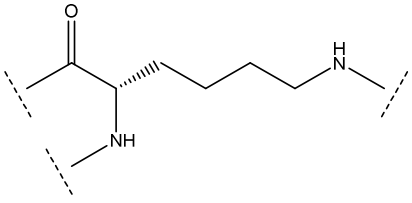


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In some ~~embodiment~~examples, the core unit is BHALys.

In some ~~embodiment~~examples, the dendrimer has from one to five generations of building units. In some ~~embodiment~~examples, the dendrimer has three to five generations of building units. In some ~~embodiment~~examples, the dendrimer has three generations of building units. In some ~~embodiment~~examples, the dendrimer has four generations of building units. In some ~~embodiment~~examples, the dendrimer has five generations of building units.

In some ~~embodiment~~examples, the building units are each:



.

In some ~~embodiment~~examples, the conjugate is for administration in combination with a further active agent.

In some ~~embodiment~~examples, the conjugate is internalised within a HER2-expressing cell.

In some ~~embodiment~~examples, administration of the conjugate results in reduced side effects in comparison to administration of an equivalent dose of free therapeutic agent.

In some ~~embodiment~~examples, administration of the conjugate provides for at least a 50% reduction in the maximum plasma concentration of released therapeutic agent in comparison to administration of an equivalent dose of free therapeutic agent.

In ~~a second aspect~~another example, there is provided a composition comprising a plurality of conjugates as defined herein.

In another ~~third~~ aspect, there is provided a pharmaceutical composition, comprising:

i) a conjugate as described herein; and

ii) a pharmaceutically acceptable excipient.

In some ~~embodiment~~examples, the composition is formulated for parenteral delivery.

In some ~~embodiment~~examples, the conjugate or composition is for use in the treatment of cancer.

In another example~~fourth aspect~~, there is provided a method of treating cancer comprising administering to a subject in need thereof a therapeutically effective amount of the conjugate or composition as described herein.

In ~~a fifth~~another aspect, there is provide the use of the conjugate or composition as described herein, in the manufacture of a medicament for the treatment of cancer.

In some ~~embodiment~~examples, the cancer is ovarian cancer, breast cancer, stomach cancer, uterine cancer, or another cancer characterised by abnormal expression of the ERBB2 gene.

In ~~a sixth aspect~~another example, there is provided, a method of killing a HER2-expressing cell, comprising:

contacting a conjugate as defined herein with a HER2-expressing cell such that the conjugate is internalised within the cell, whereby the therapeutic agent kills the HER2-expressing cell.

It will be appreciated that further aspects, ~~embodiment~~examples, and examples, are described herein, which may include one or more of the ~~embodiment~~examples or features as described above.

Brief Description of the Drawings

Figure 1 shows SDS Page analysis of compounds 74, 75 and 76 stained with Coomassie blue.

Figure 2 shows SDS Page and fluorescent imaging analysis of compound 77 and 78.

Figure 3 shows SDS Page and fluorescent imaging analysis of compound 41 (Lane A: Crude mixture; Lane B: Purified conjugate), 42(Lane C:Crude mixture; Lane D: Purified conjugate), 43 (Lane E:Crude mixture; Lane F: Purified conjugate) , 44 (Lane G: Crude mixture; Lane H: Purified conjugate) and 45 (Purified conjugate).

Claims

1. A dendrimer-targeting agent conjugate, comprising:

a) a dendrimer comprising

i) a core unit (C); and

ii) building units (BU), each building unit being a lysine residue or an analogue thereof;

wherein the core unit is covalently attached to at least two building units *via* amide linkages, each amide linkage being formed between a nitrogen atom present in the core unit and a carbon atom of an acyl group present in a building unit;

b) a HER2 targeting agent which is a peptidic moiety having a molecular weight of up to about 80 kDa and comprising an antigen-binding site, which is covalently linked to the dendrimer by a spacer group;

c) a therapeutic agent which is covalently linked to a surface building unit of the dendrimer; and

d) a hydrophilic polymeric group that is covalently linked to surface building units of the dendrimer.

2. A conjugate as claimed in claim 1, wherein the peptidic moiety is selected from: a heavy chain antibody, Fab, Fv, scFv or a single domain antibody.

3. A conjugate as claimed in claim 1 or claim 2, wherein the peptidic moiety comprises or consists of a heavy chain variable (V_H) domain.

4. A conjugate as claimed in any of claims 1 to 3, wherein the peptidic moiety comprises or consists of a light chain variable (V_L) domain.

5. A conjugate as claimed in any of claims 1 to 4, wherein the targeting agent has a molecular weight of ~~about~~ 5 kDa to ~~about~~ 30 kDa, or ~~.~~

~~6. A conjugate as claimed in claim 5, wherein the targeting agent has a molecular weight of about 5 kDa to about 15 kDa, or.~~

~~7. A conjugate as claimed in claim 6, wherein the targeting agent has a molecular weight of about~~ 10 kDa to ~~about~~ 16 kDa.

6~~8~~. A conjugate as claimed in any of claims 1 to 5~~7~~, wherein the targeting agent comprises less than 120 amino acid residues.

7~~9~~. A conjugate as claimed in any of claims 1 to 6~~8~~, wherein the targeting agent comprises or consists of any of the amino acid sequences as defined herein.

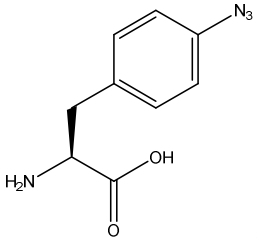
8~~10~~. A conjugate as claimed in any of claims 1 to 7~~9~~, wherein one targeting agent is covalently linked to the dendrimer.

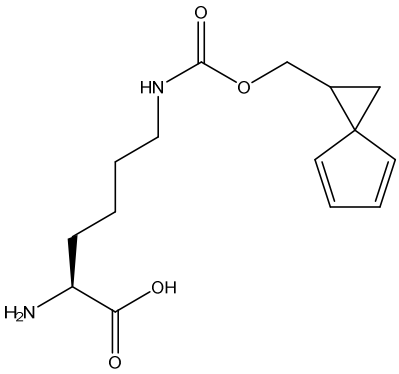
9~~11~~. A conjugate as claimed in any of claims 1 to 8~~9~~, wherein more than one targeting agent is covalently linked to the dendrimer.

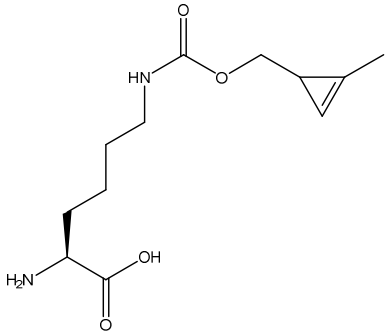
10~~12~~. A conjugate as claimed in any of claims 1 to 9~~11~~, wherein the covalent linkage between the targeting agent and the spacer group has been formed by reaction between complementary reactive functional groups present on a targeting agent precursor and a spacer group precursor.

11~~13~~. A conjugate as claimed in claim 10~~12~~, wherein the targeting agent precursor comprises an unnatural amino acid residue, the unnatural amino acid residue having a side-chain including a reactive functional group~~.~~, optionally

~~14. A conjugate as claimed in claim 13,~~ wherein the unnatural amino acid residue is a residue of



,


or


.

12~~15~~. A conjugate as claimed in any of claims 1 to 11~~14~~, wherein the targeting agent is covalently linked to the spacer group *via* the C-terminus of the targeting agent.

13~~16~~. A conjugate as claimed in any of claims 10~~12~~ to 12~~15~~, wherein the spacer group precursor comprises a reactive functional group which is an alkyne group, optionally ~~.~~

~~17. A conjugate as claimed in claim 16,~~ wherein the alkyne group is a dibenzocyclooctyne group.

14~~18~~. A conjugate as claimed in any one of claims 1 to 13~~15~~, wherein the therapeutic agent is selected from the group consisting of a chemotherapeutic agent~~.~~

~~19. A conjugate as claimed in any one of claims 1 to 18, wherein the therapeutic agent is,~~ a cytotoxic agent and ~~.~~

~~20. A conjugate as claimed in any one of claims 1 to 19, wherein the therapeutic agent is~~ an ultracytotoxic agent.

15~~21~~. A conjugate as claimed in claim 14~~20~~, wherein the therapeutic agent is an auristatin or a maytansinoid, optionally~~.~~

~~22. A conjugate as claimed in claim 21,~~ wherein the therapeutic agent is monomethyl auristatin E or ~~.~~

~~23. A conjugate as claimed in claim 21, wherein the therapeutic agent is~~ monomethyl auristatin F.

16~~24~~. A conjugate as claimed in any of claims 1 to 15~~23~~, wherein the therapeutic agent is covalently linked to a surface building unit of the dendrimer *via* a linker.

17~~25~~. A conjugate as claimed in any of claims 1 to 16~~24~~, wherein the therapeutic agent is covalently linked to a surface building unit of the dendrimer *via* a cleavable linker, optionally~~.~~

~~26. A conjugate as claimed in claim 25,~~ wherein the cleavable linker comprises either a Val-Cit-PAB group or a Val-Arg-PAB-P-Trigger group.

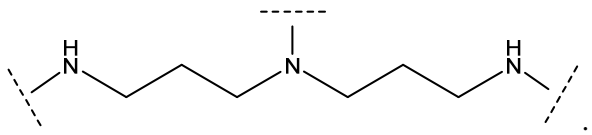
18~~27~~. A conjugate as claimed in any of claims 1 to 17~~26~~, wherein the hydrophilic polymeric group is selected from the group consisting of polyethylene glycol (PEG), polyethyloxazoline (PEOX), or polysarcosine.

19~~28~~. A conjugate as claimed in any of claims 1 to 18~~27~~, wherein the conjugate comprises PEG groups that are covalently linked to surface building units of the dendrimer.

20~~29~~. A conjugate as claimed in claim 19~~28~~, wherein the PEG groups have an average molecular weight in the range of from ~~about~~ 500 to ~~about~~ 2500 g/mole.

21~~30~~. A conjugate as claimed in any of claims 1 to 20~~29~~, wherein the spacer group comprises a PEG group.

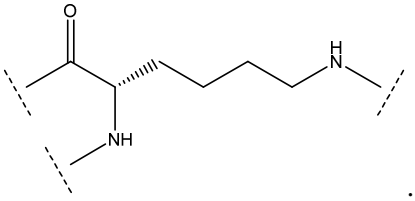
22~~31~~. A conjugate as claimed in any of claims 1 to 21~~30~~, wherein the core unit comprises the structure:



23~~32~~. A conjugate as claimed in any of claims 1 to 22~~31~~, wherein the dendrimer has from one to five generations of building units, optionally~~.~~

~~33. A conjugate as claimed in claim 32,~~ wherein the dendrimer has three generations of building units.

24~~34~~. A conjugate as claimed in any of claims 1 to 23~~33~~, wherein the building units are each:



2535. A conjugate as claimed in any of claims 1 to 2434, for administration in combination with a further active agent.

~~36. A conjugate as claimed in any of claims 1 to 35, wherein the conjugate is internalised within a HER2 expressing cell.~~

~~37. A conjugate as claimed in any one of claims 1 to 36, wherein administration of the conjugate results in reduced side effects in comparison to administration of an equivalent dose of free therapeutic agent.~~

~~38. A conjugate as claimed in any of claims 1 to 37, wherein administration of the conjugate results in at least a 50% reduction in the maximum plasma concentration of released therapeutic agent in comparison to administration of an equivalent dose of free therapeutic agent.~~

~~39. A composition comprising a plurality of conjugates as defined in any of claims 1 to 38.~~

~~40~~26. A pharmaceutical composition, comprising:

i) a conjugate as claimed in any of claims 1 to 25~~39~~; and

ii) a pharmaceutically acceptable excipient.

2741. A composition as claimed in claim 26~~39 or 40~~, wherein the composition is formulated for parenteral delivery.

2842. A conjugate as claimed in any of claims 1 to 25~~38~~, or a composition as claimed in ~~any of~~ claim~~s~~ 26 or 27~~39 to 41~~, for use in the treatment of cancer.

~~43. A method of treating cancer comprising administering to a subject in need thereof a therapeutically effective amount of a conjugate as claimed in any of claims 1 to 38 or a composition as claimed in any of claims 39 to 42.~~

2944. Use of a conjugate as claimed in any of claims 1 to 2538, or of a composition as claimed in ~~any of~~ claim~~s~~ 26 or 27~~39 to 43~~, in the manufacture of a medicament for the treatment of cancer.

4530.~~-~~ A ~~method, use, or~~ conjugate or composition for use~~,~~ as claimed in ~~any of~~ claim~~s~~ ~~42 to 44~~28, or a use as claimed in claim 29, wherein the cancer is ovarian cancer, breast cancer, stomach cancer, uterine cancer, or another cancer characterised by abnormal expression of the ERBB2 gene.

~~46. A method of killing a HER2-expressing cell, comprising:~~

~~contacting a conjugate as claimed in any of claims 1 to 38 with a HER2-expressing cell such that the conjugate is internalised within the cell, whereby the therapeutic agent kills the HER2-expressing cell.~~