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

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

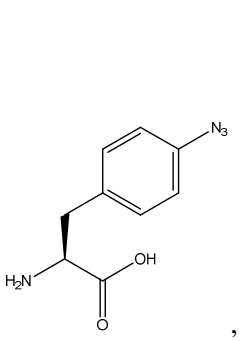
In some examples, the targeting agent comprises less than 120 amino acid residues.

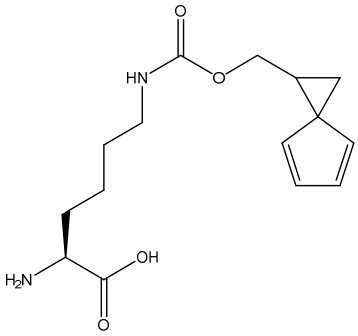
In some examples, the targeting agent comprises or consists of any of the amino acid sequences as defined herein.

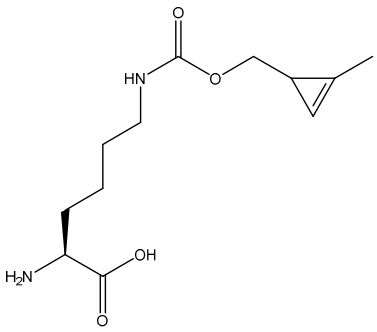
In some examples, one targeting agent is covalently linked to the dendrimer. In some examples, more than one targeting agent is covalently linked to the dendrimer.

In some 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 examples, the unnatural amino acid residue is a residue of,



,


, or


.

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

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

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

In some 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 examples, the spacer group comprises an alkene group.

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

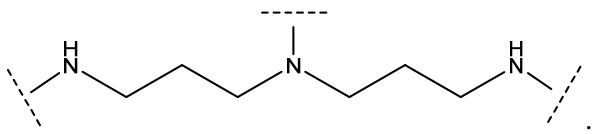
In some examples, the therapeutic agent is covalently linked to a surface building unit of the dendrimer *via* a linker. In some examples, the therapeutic agent is covalently linked to a surface building unit of the dendrimer *via* a cleavable linker. In some examples, the cleavable linker comprises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

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

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

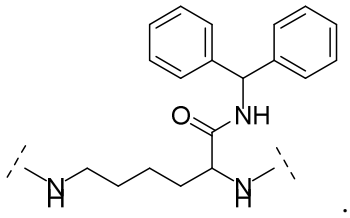
In some examples, the spacer group comprises a PEG group.

In some examples, the core unit comprises the structure:



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In some examples, the core unit comprises the structure:

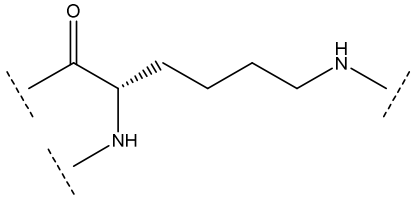


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In some examples, the core unit is BHALys.

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

In some examples, the building units are each:



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

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

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

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

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

i) a conjugate as described herein; and

ii) a pharmaceutically acceptable excipient.

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

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

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

In 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, examples, and examples, are described herein, which may include one or more of the 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 5 kDa to 30 kDa, or 5 kDa to 15 kDa, or 10 kDa to 16 kDa.

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

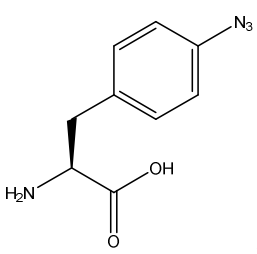
7. A conjugate as claimed in any of claims 1 to 6, wherein the targeting agent comprises or consists of any of the amino acid sequences as defined herein.

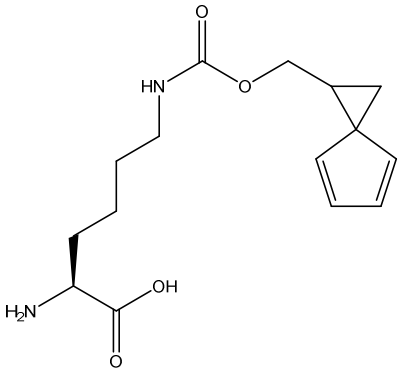
8. A conjugate as claimed in any of claims 1 to 7, wherein one targeting agent is covalently linked to the dendrimer.

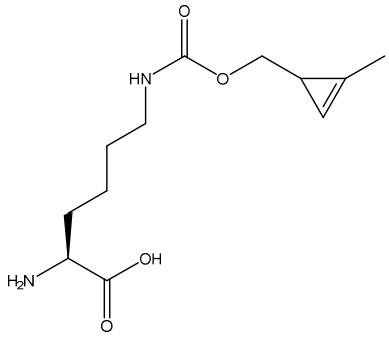
9. A conjugate as claimed in any of claims 1 to 8, wherein more than one targeting agent is covalently linked to the dendrimer.

10. A conjugate as claimed in any of claims 1 to 9, 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. A conjugate as claimed in claim 10, 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 wherein the unnatural amino acid residue is a residue of



,


or


.

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

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

14. A conjugate as claimed in any one of claims 1 to 13, wherein the therapeutic agent is selected from the group consisting of a chemotherapeutic agent, a cytotoxic agent and an ultracytotoxic agent.

15. A conjugate as claimed in claim 14, wherein the therapeutic agent is an auristatin or a maytansinoid, optionally wherein the therapeutic agent is monomethyl auristatin E or monomethyl auristatin F.

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

17. A conjugate as claimed in any of claims 1 to 16, wherein the therapeutic agent is covalently linked to a surface building unit of the dendrimer *via* a cleavable linker, optionally wherein the cleavable linker comprises either a Val-Cit-PAB group or a Val-Arg-PAB-P-Trigger group.

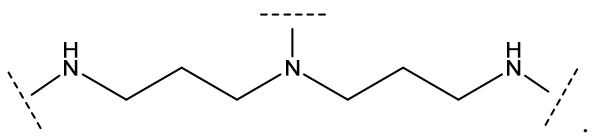
18. A conjugate as claimed in any of claims 1 to 17, wherein the hydrophilic polymeric group is selected from the group consisting of polyethylene glycol (PEG), polyethyloxazoline (PEOX), or polysarcosine.

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

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

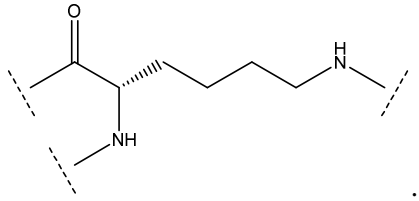
21. A conjugate as claimed in any of claims 1 to 20, wherein the spacer group comprises a PEG group.

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



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

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



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25. A conjugate as claimed in any of claims 1 to 24, for administration in combination with a further active agent.

26. A pharmaceutical composition, comprising:
i) a conjugate as claimed in any of claims 1 to 25; and
ii) a pharmaceutically acceptable excipient.

27. A composition as claimed in claim 26, wherein the composition is formulated for parenteral delivery.

28. A conjugate as claimed in any of claims 1 to 25, or a composition as claimed in claim 26 or 27, for use in the treatment of cancer.

29. Use of a conjugate as claimed in any of claims 1 to 25, or of a composition as claimed in claim 26 or 27, in the manufacture of a medicament for the treatment of cancer.

30. A conjugate or composition for use as claimed in claim 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.