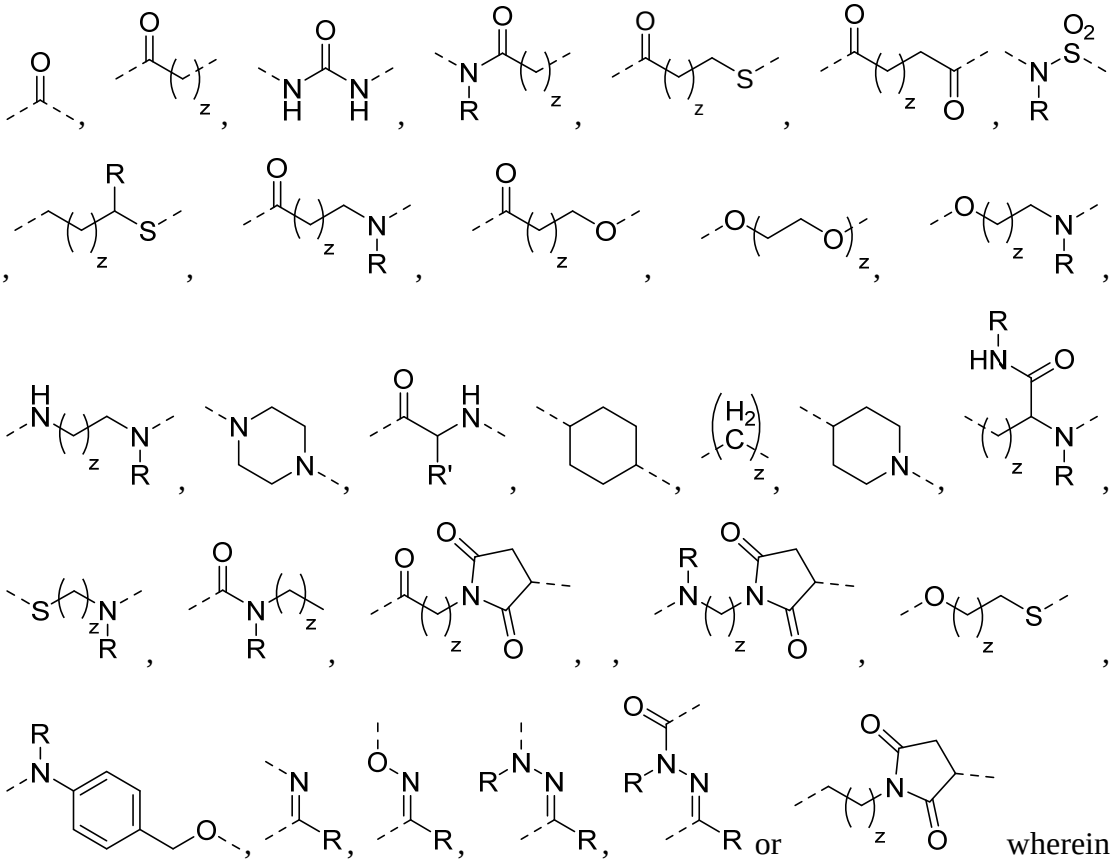
[0005] The development of nanotechnologies for effective delivery of drugs or drug candidates to specific diseased cells and tissues, e.g., to cancer cells, in specific organs or tissues, in a temporospatially regulated manner potentially can overcome or ameliorate therapeutic challenges, such as systemic toxicity. However, while targeting of the delivery system may preferentially deliver drug to a site where therapy is needed, the drug released from the nanoparticle may not for example, remain in the region of the targeted cells in efficacious amounts or may not remain in the circulation in a relatively non-toxic state for a sufficient amount of time to decrease the frequency of treatment or permit a lower amount of drug to be administered while still achieving a therapeutic effect. Accordingly, there is a need in the art for improved drug targeting and delivery, including identification of targeting molecules that can be incorporated into particles and whose presence does not substantially interfere with efficacy of the drug.

SUMMARY

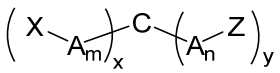
[0006] Applicants have created molecules that are conjugates of a somatostatin receptor binding moiety and an active agent, e.g., a cancer therapeutic agent such as a platinum-containing agent. Furthermore, such conjugates can be encapsulated into particles. The conjugates and particles are useful for delivering active agents such as tumor cytotoxic agents to cells expressing somatostatin receptors (SSTRs).

[0007] Applicants have developed novel conjugates and particles, including polymeric nanoparticles, and pharmaceutical formulations thereof. The conjugates of an active agent such as a therapeutic, prophylactic, or diagnostic agent are attached via a linker to a targeting moiety that can bind a somatostatin receptor. The conjugates and particles can provide improved temporospatial delivery of the active agent and/or improved biodistribution compared to delivery of the active agent alone. In some cases, the targeting moiety can also act as a therapeutic agent. In some embodiments, the targeting agent does not substantially interefere with efficacy of the therapeutic agent *in vivo*. Methods of making conjugates, particles, and formulations comprising such particles are described herein. Such particles are useful for treating or preventing diseases that are susceptible to the active agent, for example, treating or preventing cancer or infectious diseases.



or wherein z = 0-40, R is H or an optionally substituted alkyl group, and R' is any side chain found in either natural or unnatural amino acids.

[0018] In some embodiments, the linker can be a compound according to Formula Ic:

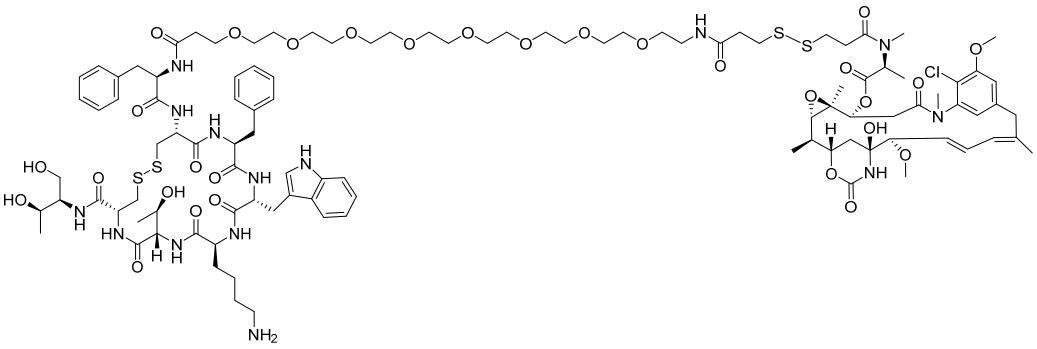


Ic

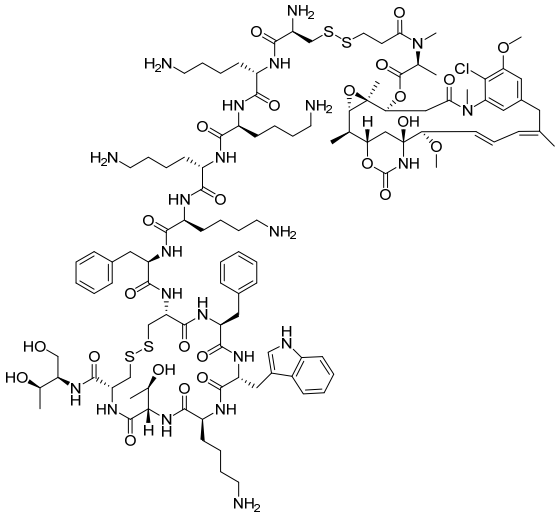
wherein A is defined above, m=0-40, n=0-40, x=1-5, y=1-5, and C is a branching element defined herein.

[0019] C in Formula Ic is a branched unit containing three to six functionalities for covalently attaching spacer units, ligands, or active drugs, selected from amines, carboxylic acids, thiols, or succinimides, including amino acids such as lysine, 2,3-diaminopropanoic acid, 2,4-diaminobutyric acid, glutamic acid, aspartic acid, and cysteine.

[0020] A non-limiting example of a conjugate of the present disclosure is a compound selected from the group consisting of the following compounds:



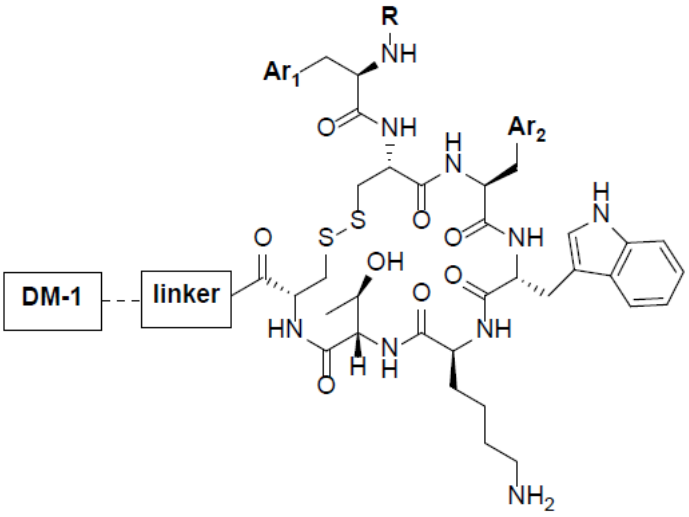
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[0021] In some embodiments, the active agent Z is DM1. In some embodiments, the somatostatin receptor targeting moiety X is selected from somatostatin, seglitide, Tyr^3-octreotate (TATE), cyclo(AA-Tyr-DTrp-Lys-Thr-Phe), or analogs or derivatives thereof. X may covalently bind to linker Y at its C-terminus or N-terminus. In some embodiments, the targeting moiety X comprises at least one D-Phe residue and the phenyl ring of the D-Phe residue of the targeting moiety X has been replaced by a linker-containing moiety.

[0021a] In one aspect of the present disclosure, there is provided a conjugate or its pharmaceutically available salt, wherein the conjugate comprises the formula of



33, wherein

R is selected from the group consisting of H, alkyl, aryl, carbonyl, amide, alcohol, and

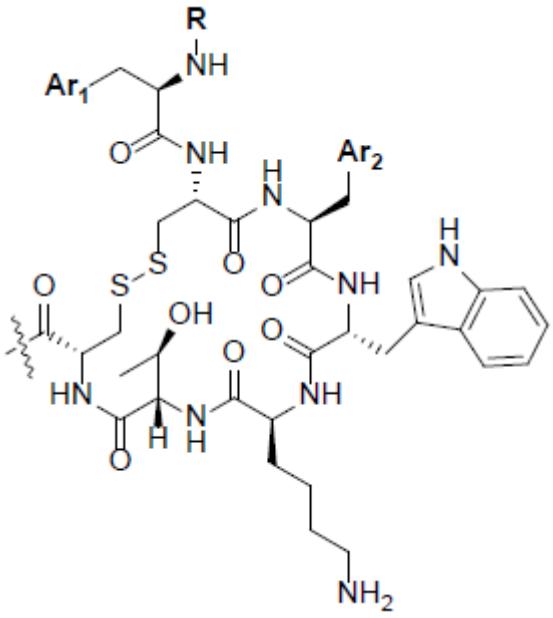
amine groups; and

Ar_1 and Ar_2 are independently selected from the group consisting of heterocyclyl, aryl, and heteroaryl groups.

[0021b] In another aspect of the present disclosure, there is provided a particle comprising a conjugate disclosed herein and at least one polymeric matrix.

[0021c] In a further aspect of the present disclosure, there is provided a pharmaceutical formulation comprising the conjugate disclosed herein or the particle disclosed herein and at least one pharmaceutically acceptable excipient.

[0021d] In another aspect of the present disclosure, there is provided a conjugate comprising an active agent coupled to a somatostatin receptor (SSTR) targeting moiety by a linker, wherein the active agent is mertansine (DM1) and the SSTR targeting moiety is octreotide, octreotate, Tyr3-octreotate (TATE), or a derivative of TATE with the following structure:



, wherein R is selected from the group consisting of H, alkyl, aryl, carbonyl, amide, alcohol, and amine groups, and Ar_1 and Ar_2 are independently selected from heterocyclyl, aryl, and heteroaryl groups.

[0021e] In a further aspect of the present disclosure, there is provided a pharmaceutical formulation comprising the conjugate disclosed herein and at least one pharmaceutically acceptable excipient.

[0021f] In another aspect of the present disclosure, there is provided the formulation disclosed herein for use in therapy.

[0021g] In a further aspect of the present disclosure, there is provided a use of the formulation disclosed herein in the manufacture of a medicament for treating cancer.

[0021h] In another aspect of the present disclosure, there is provided a use of the formulation disclosed herein in the manufacture of a medicament for inhibiting the rate of growth of a tumor, the size of a tumor or the volume of a tumor.

[0021i] In another aspect of the present disclosure, there is provided the formulation disclosed herein for use in delivering DM1 to a tumor in a subject.

[0021j] In another aspect of the present disclosure, there is provided the conjugate disclosed herein, or the particle disclosed herein, for use in therapy.

[0021k] In another aspect of the present disclosure, there is provided a use of the conjugate disclosed herein, or the particle disclosed herein, in the manufacture of a medicament for treating cancer.

[0021l] In another aspect of the present disclosure, there is provided a use of the conjugate disclosed herein, or the particle disclosed herein, in the manufacture of a medicament for inhibiting the rate of growth of a tumor, the size of a tumor or the volume of a tumor.

[0021m] In another aspect of the present disclosure, there is provided a conjugate disclosed herein, or the particle disclosed herein, for use in delivering DM1 to a tumor in a subject.

[0022] The present disclosure also provides hydrophobic ion-pairing complexes containing the conjugate of the present disclosure and counterions. In some embodiments, the counterions are negatively charged. The present disclosure also provides particles containing the conjugate of the present disclosure or the hydrophobic ion-pairing complexes of the conjugate of the present disclosure . The present disclosure further provides pharmaceutical formulations containing the conjugates or particles containing the conjugates described

herein, or pharmaceutically acceptable salts thereof, in a pharmaceutically acceptable vehicle.

[0023] The present disclosure also providesparticles containing the conjugate of the present disclosure . In some embodiments, the particle has a diameter between 10 nm and 5000 nm. In some embodiments, the particle has a diameter between 30 nm and 70 nm, 120 nm and 200 nm, 200 nm and 5000 nm, or 500 nm – 1000 nm.

[0024] Methods of making the conjugates and particles containing the conjugates are provided. Methods are also provided for treating a disease or condition, the method comprising administering a therapeutically effective amount of the particles containing a conjugate to a subject in need thereof. In an embodiment, the conjugates are targeted to a cancer or hyperproliferative disease, for example, lymphoma, renal cell carcinoma, leukemia, prostate cancer, lung cancer (e.g., small cell lung cancer (SCLC) and non-SCLC), pancreatic cancer (e.g., ductal), melanoma, colorectal cancer, ovarian cancer (e.g., epithelial ovarian cancer), breast cancer, glioblastoma (e.g., astrocytoma and glioblastoma multiforme), stomach cancer, liver cancer, sarcoma, bladder cancer, testicular cancer, esophageal cancer, head and neck cancer, endometrial cancer and leptomeningeal carcinomatosis.

BRIEF DESCRIPTION OF THE DRAWINGS

[0025] Figure 1 is a graph of the blood plasma concentration (μM) of the octreotide-cabazitaxel conjugate of Example 1 as a function of time (hours) after tail vein injection in rats. The formulations injected contained either the free octreotide-cabazitaxel conjugate or octreotide-cabazitaxel nanoparticles of Example 11.

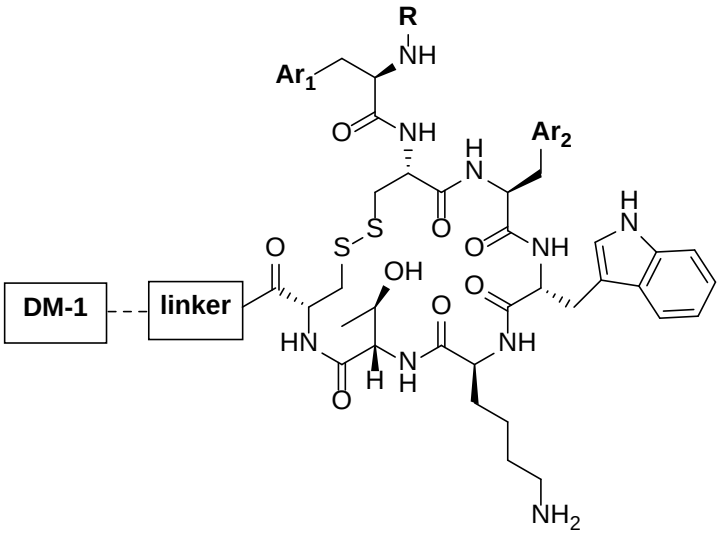
[0026] Figure 2 is a graph of the blood plasma concentration (μM) of the octreotide-doxorubicin conjugate of Example 2 as a function of time (hours) after tail vein injection in rats. The formulations injected contained either the free octreotide-doxorubicin conjugate or octreotide-doxorubicinnanoparticles of Example 12.

[0027] Figure 3 is a graph of various conjugates represented as bars and showing on the Y-axis their activity in an H524 proliferation assay with and without competition by octreotide. The Y-axis shows the ratio of the IC_{50} with octreotide added to the IC_{50} without octretide added. This assay demonstrates the extent to which the activity of the conjugates depends on the somatostain receptors. Only DM1 conjugates show a ratio significantly greater than 1. This illustrates the suprprising finding that only DM1 conjugates show activity that is dependent on the receptor.

CLAIMS

We claim:

1. A conjugate or its pharmaceutically available salt, wherein the conjugate comprises the formula of



33, wherein

R is selected from the group consisting of H, alkyl, aryl, carbonyl, amide, alcohol, and amine groups; and

Ar_1 and Ar_2 are independently selected from the group consisting of heterocyclyl, aryl, and heteroaryl groups.

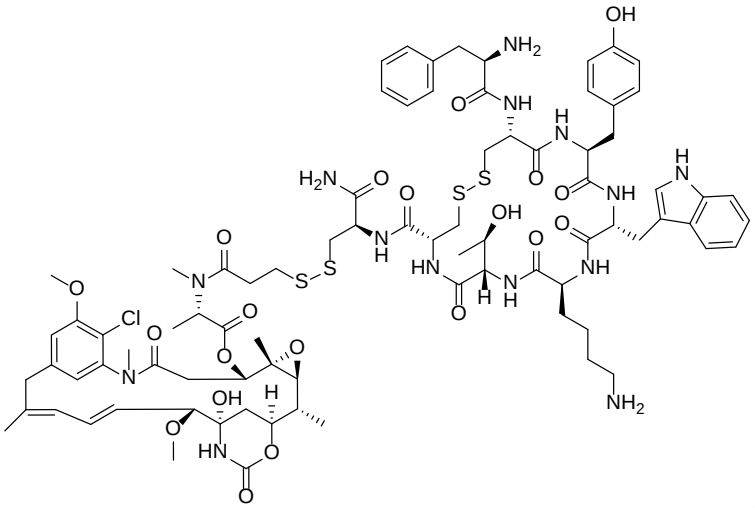
2. The conjugate of claim 1, wherein the linker is not a cleavable linker.

3. The conjugate of claim 1, wherein the linker is a cleavable linker.

4. The conjugate of claim 3, wherein the linker comprises an ester bond, disulfide, amide, acylhydrazone, ether, carbamate, carbonate, or urea.

5. The conjugate of claim 1, wherein the conjugate comprises a formula selected from the group consisting of Compound **35**, Compound **37**, Compound **39**, Compound **41**, Compound **43**, Compound **45**, Compound **47**, Compound **49**, Compound **51**, Compound **53**, Compound **55**, Compound **57**, Compound **59**, Compound **61**, Compound **63**, and Compound **65**.

6. The conjugate of claim 1, wherein the conjugate has the formula of



57.

7. A particle comprising a conjugate of any one of claims 1-6 and at least one polymeric matrix.

8. The particle of claim 7, wherein the polymeric matrix comprises one or more polymers selected from the group consisting of hydrophobic polymers, hydrophilic polymers, and copolymers thereof.

9. The particle of claim 8, wherein the hydrophobic polymers are selected from the group consisting of polyhydroxyacids, polyhydroxyalkanoates, polycaprolactones, poly(orthoesters), polyanhydrides, poly(phosphazenes), poly(lactide-co-caprolactones), polycarbonates, polyesteramides, polyesters, and copolymers thereof.

10. The particle of claim 9, wherein the hydrophilic polymers are selected from the group consisting of polyalkylene glycols, polyalkylene oxides, poly(oxyethylated polyol), poly(olefinic alcohol), polyvinylpyrrolidone), poly(hydroxyalkylmethacrylamide), poly(hydroxyalkylmethacrylate), poly(saccharides), poly(hydroxy acids), poly(vinyl alcohol), polyethylene oxides, polyethylene glycols, poly(propylene glycol), polyoxazolines, and copolymers thereof.

11. The particle of claim 10, wherein the polymeric matrix comprises one or more polymers selected from the group consisting of poly(lactic acid), poly(glycolic acid), poly(lactic-co-glycolic acid), and copolymers thereof.

12. The particle of any one of claims 7-11, wherein the particle has a diameter between 10 nm and 5000 nm.

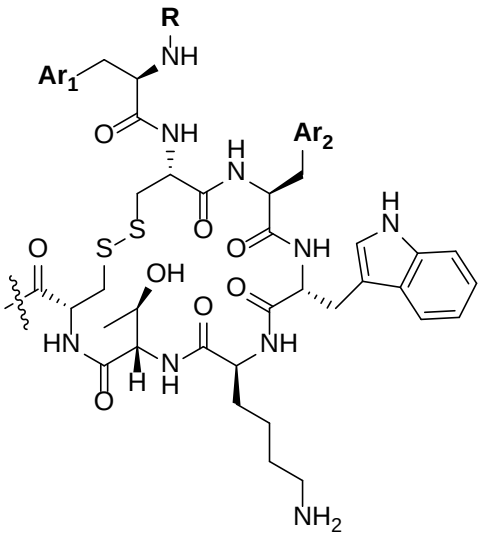
13. The particle of claim 12, wherein the particle has a diameter between about 30 nm and 70 nm, 70 nm and 120 nm, 120 nm and 200 nm, 200 nm and 5000 nm, or 500 nm and 1000 nm.

14. The particle of claim 7, wherein the polymeric matrix comprises two or more different polymers.

15. The particle of any one of claims 7-14, wherein the conjugate is present in an amount between 0.05% and 50 % (w/w) based upon the weight of the particle.

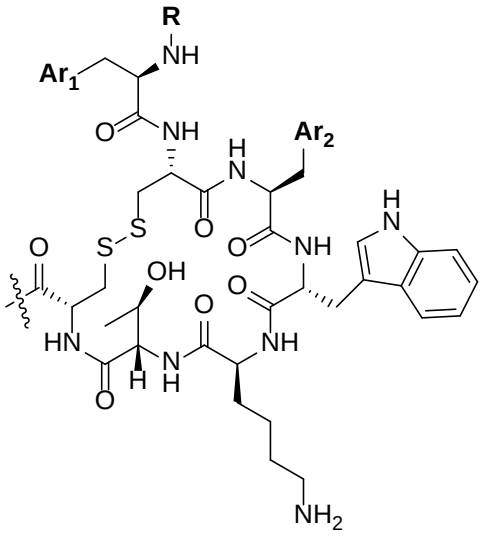
16. A pharmaceutical formulation comprising the conjugate of any one of claims 1-6 or the particle of any one of claims 7-15 and at least one pharmaceutically acceptable excipient.

17. A conjugate comprising an active agent coupled to a somatostatin receptor (SSTR) targeting moiety by a linker, wherein the active agent is mertansine (DM1) and the SSTR targeting moiety is octreotide, octreotate, Tyr3-octreotate (TATE), or a derivative of



TATE with the following structure: , wherein R is selected from the group consisting of H, alkyl, aryl, carbonyl, amide, alcohol, and amine groups, and Ar_1 and Ar_2 are independently selected from heterocyclyl, aryl, and heteroaryl groups.

18. The conjugate of claim 17, wherein the SSTR targeting moiety is Tyr^3-octreotate (TATE) or



a derivative of TATE with the following structure: , wherein R is selected from the group consisting of H, alkyl, aryl, carbonyl, amide, alcohol, and amine groups, and
Ar_1 and Ar_2 are independently selected from heterocyclyl, aryl, and heteroaryl groups.

19. A pharmaceutical formulation comprising the conjugate in any one of claims 17-18 and at least one pharmaceutically acceptable excipient.

20. A formulation of claim 16 or claim 19 for use in therapy.

21. Use of the formulation of claim 16 or claim 19 in the manufacture of a medicament for treating cancer.

22. The use of claim 21, wherein the cancer is selected from the group consisting of lung cancer, breast cancer, colorectal cancer, ovarian cancer, pancreatic cancer, colorectal cancer, bladder cancer, prostate cancer, cervical cancer, renal cancer, leukemia, central nervous system cancers, myeloma, and melanoma.

23. Use of the formulation of claim 16 or claim 19 in the manufacture of a medicament for inhibiting the rate of growth of a tumor, the size of a tumor or the volume of a tumor.

24. A formulation of claim 16 or claim 19 for use in delivering DM1 to a tumor in a subject.

25. A conjugate of any one of claims 1-6 or 17-18, or the particle of any one of claims 7-15, for use in therapy.

26. Use of the conjugate of any one of claims 1-6 or 17-18, or the particle of any one of claims 7-15, in the manufacture of a medicament for treating cancer.

27. The use of claim 26, wherein the cancer is selected from the group consisting of lung cancer, breast cancer, colorectal cancer, ovarian cancer, pancreatic cancer, colorectal cancer, bladder cancer, prostate cancer, cervical cancer, renal cancer, leukemia, central nervous system cancers, myeloma, and melanoma.

28. Use of the conjugate of any one of claims 1-6 or 17-18, or the particle of any one of claims 7-15, in the manufacture of a medicament for inhibiting the rate of growth of a tumor, the size of a tumor or the volume of a tumor.

29. A conjugate of any one of claims 1-6 or 17-18, or the particle of any one of claims 7-15, for use in delivering DM1 to a tumor in a subject.