effective for a certain period of time, if at all, for a patient or a particular cancer type before the drug losses its effectiveness.

[0006] Doxorubicin is an exemplary small molecule chemotherapeutic drug that exerts its therapeutic effect by intercalating the DNA of replicating cells, and preventing their division. However, doxorubicin has several adverse events, the most prominent being of cardiac nature and hand-foot syndrome, which limit its use and/or the upper dose for administration to humans. Several attempts have been made to make doxorubicin more patient-friendly. One of the most successful formulations of doxorubicin is a liposomal formulation, commercialized as DOXIL® or generic liposomal doxorubicin as "LipoDox". However, this formulation suffers from shortcomings that limit the use of doxorubicin in the treatment of diseases that should respond to its administration.

[0007] Trastuzumab, marketed as Herceptin®, is an antibody chemotherapeutic agent that binds to HER2, present on the surface of many (but not all) breast cancer cell types. However, trastuzumab-resistant cancers can also arise after the start of treatment, limiting the efficacy of the therapeutic.

[0008] The disclosures of all publications, patents, and patent applications referred to herein are hereby incorporated herein by reference in their entireties.

SUMMARY

[0009] In one aspect, there is provided a composition comprising nanoparticles comprising a carrier polypeptide and a double-stranded oligonucleotide, wherein the carrier polypeptide comprises a cell-targeting segment, a cell-penetrating segment, and an oligonucleotide-binding segment; and wherein the molar ratio of the carrier polypeptide to the double-stranded oligonucleotide in the nanoparticle composition is less than about 6:1. In some embodiments, the molar ratio of the carrier polypeptide to the double-stranded oligonucleotide in the nanoparticle composition is about 4:1 to less than about 6:1. In some embodiments, the molar ratio of the carrier polypeptide to the double-stranded oligonucleotide in the nanoparticle composition is about 4:1.

[0010] In some embodiments, the average size of the nanoparticles in the composition is no greater than about 50 nm.

[0011] In some embodiments, the molar ratio of the carrier polypeptide to the double-stranded oligonucleotide in the nanoparticles is less than about 6:1. In some embodiments,

[0018] In some embodiments, there is provided an article of manufacture comprising any one of the described compositions in a vial. In some embodiments, the vial is sealed.
[0019] In some embodiments, there is provided a kit comprising any one of the described compositions and an instruction for use.
[0020] In some embodiments, there is provided a method of treating cancer in a subject comprising administering a composition described herein to the subject. In some embodiments, the cancer is a HER3+ cancer. In some embodiments, the cancer is a drug-resistant cancer. In some embodiments, the cancer is breast cancer, glial cancer, ovarian cancer, or prostate cancer. In some embodiments, the cancer is triple-negative breast cancer. In some embodiments, the cancer is metastatic. In some embodiments, the cancer is resistant to a HER2+ antibody chemotherapeutic agent, lapatinib, or an anthracycline. In some embodiments, the cancer is resistant to doxorubicin or liposomal doxorubicin. In some embodiments, the cancer is resistant to trastuzumab or pertuzumab. In some embodiments, the cancer is resistant to lapatinib.
[0020a] In another aspect, there is provided use of the composition as described herein in the manufacture of a medicament for treating cancer in a subject.
[0021] Also provided herein there is a method of killing a chemotherapeutic drug-resistant cancer cell comprising contacting the chemotherapeutic drug-resistant cancer cell with a plurality of nanoparticles, the nanoparticles comprising a carrier polypeptide comprising a cell-targeting segment, a cell-penetrating segment, and an oligonucleotide-binding segment; a double-stranded oligonucleotide bound to the oligonucleotide-binding segment; and a chemotherapeutic drug bound to the double-stranded oligonucleotide.
[0021a] In another aspect, there is provided use of a composition comprising a plurality of nanoparticles in the manufacture of a medicament for killing a chemotherapeutic drug-resistant cancer cell, the nanoparticles comprising: a carrier polypeptide comprising a cell-targeting segment, a cell-penetrating segment, and an oligonucleotide-binding segment;
a double-stranded oligonucleotide bound to the oligonucleotide-binding segment; and
a chemotherapeutic drug bound to the double-stranded oligonucleotide;
wherein the chemotherapeutic drug-resistant cancer is an anthracycline resistant cancer or a taxane resistant cancer.
[0022] In another embodiment provided herein, there is a method of treating a subject with a chemotherapeutic drug-resistant cancer, comprising administering to the subject a composition comprising nanoparticles, the nanoparticles comprising a carrier polypeptide comprising a cell-targeting segment, a cell-penetrating segment, and an oligonucleotide-binding segment; a double-stranded oligonucleotide bound to the oligonucleotide-binding segment; and a chemotherapeutic drug bound to the double-stranded oligonucleotide.
[0022a] In another aspect, there is provided use of a composition comprising a plurality of nanoparticles in the manufacture of a medicament for treating a subject with a chemotherapeutic drug-resistant cancer, the nanoparticles comprising: a carrier polypeptide comprising a cell-targeting segment, a cell-penetrating segment, and an oligonucleotide-binding segment; a double-stranded oligonucleotide bound to the oligonucleotide-binding segment; and a chemotherapeutic drug bound to the double-stranded oligonucleotide;
wherein the chemotherapeutic drug-resistant cancer is an anthracycline resistant cancer or a taxane resistant cancer.
[0023] In some embodiments, the chemotherapeutic drug is intercalated into the double-stranded oligonucleotide.
[0024] In some embodiments, the chemotherapeutic drug-resistant cancer is a HER3+ cancer. In some embodiments, the chemotherapeutic drug-resistant cancer is breast cancer, glial cancer, ovarian cancer, or prostate cancer. In some embodiments, the chemotherapeutic drug-resistant cancer is triple-negative breast cancer. In some embodiments, the

20. The composition of claim 18 or 19, wherein the penton base segment comprises a truncated penton base polypeptide.

21. The composition of any one of claims 1-20, wherein the oligonucleotide-binding segment is positively charged.

22. The composition of any one of claims 1-21, wherein the oligonucleotide-binding segment comprises polylysine.

23. The composition of any one of claims 1-22, wherein the oligonucleotide-binding segment comprises decalysine.

24. Use of the composition of any one of claims 1-23 in the manufacture of a medicament for treating cancer in a subject.

25. Use of a composition comprising a plurality of nanoparticles in the manufacture of a medicament for killing a chemotherapeutic drug-resistant cancer cell, the nanoparticles comprising:

a carrier polypeptide comprising a cell-targeting segment, a cell-penetrating segment, and an oligonucleotide-binding segment;

a double-stranded oligonucleotide bound to the oligonucleotide-binding segment; and

a chemotherapeutic drug bound to the double-stranded oligonucleotide;

wherein the chemotherapeutic drug-resistant cancer is an anthracycline resistant cancer or a taxane resistant cancer.

26. Use of a composition comprising a plurality of nanoparticles in the manufacture of a medicament for treating a subject with a chemotherapeutic drug-resistant cancer, the nanoparticles comprising:

a carrier polypeptide comprising a cell-targeting segment, a cell-penetrating segment, and an oligonucleotide-binding segment;

a double-stranded oligonucleotide bound to the oligonucleotide-binding segment; and

a chemotherapeutic drug bound to the double-stranded oligonucleotide;

wherein the chemotherapeutic drug-resistant cancer is an anthracycline resistant cancer or a taxane resistant cancer.

27. The use of claim 25 or 26 wherein the chemotherapeutic drug is intercalated into the double-stranded oligonucleotide.

28. The use of any one of claims 25-27, wherein the chemotherapeutic drug-resistant cancer is a HER3+ cancer.

29. The use of any one of claims25-28, wherein the chemotherapeutic drug-resistant cancer is breast cancer, glial cancer, ovarian cancer, or prostate cancer.

30. The use of any one of claims 25-29, wherein the chemotherapeutic drug-resistant cancer is triple-negative breast cancer.

31. The use of any one of claims 25-30, wherein the chemotherapeutic drug-resistant cancer is metastatic.

32. The use of any one of claims 25-31, wherein the chemotherapeutic drug-resistant cancer is resistant to doxorubicin or liposomal doxorubicin.

33. The use of any one of claims 25-32, wherein the average size of the nanoparticles is no greater than about 50 nm.

34. The use of any one of claims 25-33, wherein the double stranded oligonucleotide is DNA.

35. The use of any one of claims 25-33, wherein the double stranded oligonucleotide is RNA.

36. A method of making a nanoparticle composition comprising:

combining a carrier polypeptide and a double-stranded oligonucleotide at a molar ratio of less than about 6:1, thereby forming a plurality of nanoparticles;

wherein the carrier polypeptide comprises a cell-targeting segment, a cell-penetrating segment, and an oligonucleotide-binding segment.

37. The method of claim 36, wherein the molar ratio of the carrier polypeptide to the double-stranded oligonucleotide is about 4:1 to less than about 6:1.

38. The method of claim 36 or 37, wherein the molar ratio of the carrier polypeptide to the double-stranded oligonucleotide is about 4:1.

39. The method of any one of claims 36-38, further comprising combining the double-stranded oligonucleotide and a small-molecule drug prior to combining the double-stranded oligonucleotide and the carrier polypeptide.

40. The method of claim 39, wherein the double-stranded oligonucleotide and the small-molecule drug are combined at a molar ratio of about 1:1 to about 1:60.

41. The method of claim 39 or 40 further comprising separating unbound small-molecule drug from the double-stranded oligonucleotide prior to combining the double-stranded oligonucleotide and the carrier polypeptide.

42. The method according to any one of claims 36-41, further comprising separating unbound carrier polypeptide or unbound double-stranded oligonucleotide from the plurality of nanoparticles.

43. The method according to any one of claims 36-42, wherein the double-stranded oligonucleotide is DNA.

44. The method according to any one of claims 36-42, wherein the double-stranded oligonucleotide is RNA.

45. The method according to any one of claims 36-44, wherein the small-molecule drug is a chemotherapeutic agent.

46. The method according to any one of claims 36-45, wherein the small-molecule drug is an anthracycline or a taxane.

47. The method according to any one of claims 36-46, wherein the small-molecule drug is doxorubicin.

48. The method according to any one of claims 36-47, wherein the cell-targeting segment comprises a heregulin sequence or a variant thereof.

49. The method according to any one of claims 36-48, wherein the cell-penetrating segment comprises a penton base polypeptide or a variant thereof.

50. The method according to any one of claims 36-49, wherein the oligonucleotide-binding segment is positively charged.

51. The method according to any one of claims 36-50, wherein the oligonucleotide-binding segment comprises polylysine.

52. The method according to any one of claims 36-51, wherein the oligonucleotide-binding segment comprises decalysine.