bypasses the BBB. Therapeutic agents can be delivered into the brain with a minimum of the toxicity, therefore, as well as to normal tissue and to organs commonly accessed by systemic delivery.

SUMMARY

[0009a] In one aspect, there is provided use of a composition for manufacture of a medicament for the treatment of a brain tumor, wherein the composition comprises a plurality of intact, bacterially derived minicells and wherein: (a) each minicell comprises an antibody that specifically recognizes a tumor cell antigen, and (b) the brain tumor has blood vessels with fenestrations in the vessel walls through which the minicells can extravasate passively.

[0010] In view of the drawbacks affecting conventional approaches in this area, a method is provided for administering systemically a therapeutically effective amount of a composition comprised of a plurality of intact, bacterially derived minicells, where each minicell of the plurality encompasses an anti-neoplastic agent. By the same token, the present description contemplates the use of such composition for manufacture of a medicament for the treatment of a brain tumor. The plurality can include at least about 10^8 minicells, including but not limited to at least about 10^{10} minicells. Also, a composition as described here can contain less than about 10 EU free endotoxin and/or at most 1 parent bacterial cell per 10^8 minicells, *e.g.*, per 10^{10} minicells..

[0011] The anti-neoplastic agent encompassed by the minicells can be a radionuclide, for example, such as yttrium-90, technetium-99m, iodine-123, iodine-131, rubidium-82, thallium-201, gallium-67, fluorine-18, xenon-133, or indium-111, which can be attached to a protein or a carbohydrate on the surface of the minicells, or it can be attached on the surface of the tumor targeting ligand attached on the surface of the minicells. In this context, the composition can contain, for instance, between about 30 Gy to about 100 Gy radioactivity. The anti-neoplastic agent also can be a chemotherapy drug, where, for example, the composition contains at most about 1 mg thereof. Moreover, the anti-neoplastic agent can be a functional nucleic acid or a polynucleotide encoding a functional nucleic acid. Thus, the functional nucleic acid can inhibit a gene that promotes tumor cell proliferation, angiogenesis or resistance to chemotherapy and/or that inhibits apoptosis or cell cycle arrest. Illustrative of

the class of functional nucleic acids are ribonucleic acid molecules selected from the group consisting of siRNA, miRNA, shRNA, lincRNA, antisense RNA, and ribozyme.

[0012] Pursuant to certain embodiments in accordance with any of the foregoing, each minicell of the above-mentioned plurality can comprise a ligand having a specificity to a non-phagocytic mammalian cell surface receptor, *e.g.*, a tumor cell antigen. Accordingly, the

WHAT IS CLAIMED IS:

1. A method for treating a brain tumor in a subject, comprising administering systemically a therapeutically effective amount of a composition comprised of a plurality of intact, bacterially derived minicells, wherein each minicell of said plurality encompasses an anti-neoplastic agent.

2. The method of claim 1, wherein said anti-neoplastic agent is a radionuclide.

3. The method of claim 2, wherein the radionuclide is selected from yttrium-90, technetium-99m, iodine-123, iodine-131, rubidium-82, thallium-201, gallium-67, fluorine-18, xenon-133, and indium-111.

4. The method of claim 2, wherein the radionuclide is attached to a protein or a carbohydrate on the surface of said minicells.

5. The method of claim 4, wherein the radionuclide is attached to a bispecific antibody that is associated with the surface of the minicells.

6. The method of any one of claims 2-5, wherein said composition contains about 30 Gy to about 100 Gy radioactivity.

7. The method of claim 1, wherein said anti-neoplastic agent is a chemotherapy drug.

8. The method of claim 7, wherein said chemotherapy drug has a molecular weight of more than about 400 Daltons.

9. The method of claim 7 or 8, wherein said chemotherapy drug has a LD_{50} that is lower than the ED_{50} of said chemotherapy drug for a targeted cancer.

10. The method of any one of claims 7-9, wherein said composition contains at most about 1 mg of said chemotherapy drug.

11. The method of claim 1, wherein said anti-neoplastic agent is a functional nucleic acid or a polynucleotide encoding a functional nucleic acid.

12. The method of claim 11, wherein said functional nucleic acid inhibits a gene that promotes tumor cell proliferation, angiogenesis or resistance to chemotherapy and/or that inhibits apoptosis or cell cycle arrest.

13. The method of claim 11, wherein said functional nucleic acid is selected from siRNA, miRNA, shRNA, lincRNA, antisense RNA, or ribozyme.

14. The method of claim 1, wherein said anti-neoplastic agent is a polynucleotide encoding a gene that promotes apoptosis.

15. The method of any one of claim 1-14, wherein each minicell of said plurality comprises a ligand having a specificity to a non-phagocytic mammalian cell surface receptor.

16. The method of claim 15, wherein said receptor is a tumor cell antigen.

17. The method of claim 16, wherein said ligand comprises an antibody that specifically recognizes said tumor cell antigen.

18. The method of any one of claims 1-17, wherein said plurality includes at least about 10^8 minicells.

19. The method of claim 18, wherein said plurality includes at least about 10^{10} minicells.

20. The method of any one of claims 1-19, wherein said composition contains less than about 10 EU free endotoxin.

21. The method of any one of claims 1-20, wherein said composition contains at most 1 parent bacterial cell per 10^8 minicells.

22. The method of anyone of claims 1-21, wherein said brain tumor is selected from the group consisting of glioblastoma, astrocytic tumor, oligodendroglial tumor, ependymoma, craniopharyngioma, pituitary tumor, primary lymphoma of the brain, pineal gland tumor, primary germ cell tumor of the brain, and combinations thereof.

23. The method of claim 22, wherein said brain tumor is metastatic brain tumor.

24. Use of a composition for manufacture of a medicament for the treatment of a brain tumor, wherein the composition comprises a plurality of intact, bacterially derived minicells, each minicell of said plurality encompassing an anti-neoplastic agent.

25. The use of claim 24, wherein said composition contains at most about 1 mg of a chemotherapy drug as said anti-neoplastic agent.

26. The use of claim 24, wherein said anti-neoplastic agent is a functional nucleic acid or a polynucleotide encoding a functional nucleic acid.

27. The use of claim 26, wherein said functional nucleic acid inhibits a gene that promotes tumor cell proliferation, angiogenesis or resistance to chemotherapy and/or that inhibits apoptosis or cell cycle arrest.

28. The use of claim 24, wherein said anti-neoplastic agent is a polynucleotide encoding a gene that promotes apoptosis.

29. The use of claim 24, wherein said anti-neoplastic agent is a radionuclide.

30. The use of claim 24, wherein said plurality includes at least about 10^{10} minicells.

31. The use of claim 24, wherein said composition contains less than about 10 EU free endotoxin.

32. The use of claim 24, wherein each minicell of said plurality comprises a ligand having a specificity to a non-phagocytic mammalian cell surface receptor.

33. The use of claim 24, wherein said brain tumor is selected from the group consisting of glioblastoma, astrocytic tumor, oligodendroglial tumor, ependymoma, craniopharyngioma, pituitary tumor, primary lymphoma of the brain, pineal gland tumor, primary germ cell tumor of the brain, and combinations thereof.

34. The use of claim 33, wherein said brain tumor is metastatic brain tumor.

35. The use of claim 24, wherein said anti-neoplastic agent is a chemotherapy drug that has a molecular weight of more than about 400 Daltons.

36. The use of claim 35, wherein said chemotherapy drug has a LD_{50} that is lower than the ED_{50} of said chemotherapy drug for a targeted cancer.

Claims

1. Use of a composition for manufacture of a medicament for the treatment of a brain tumor, wherein the composition comprises a plurality of intact, bacterially derived minicells and wherein:

(a) each minicell comprises an antibody that specifically recognizes a tumor cell antigen, and

(b) the brain tumor has blood vessels with fenestrations in the vessel walls through which the minicells can extravasate passively.

2. The use of claim 1, wherein the minicells further comprise an anti-neoplastic agent.

3. The use of claim 2, wherein the anti-neoplastic agent is a functional nucleic acid or a polynucleotide encoding a functional nucleic acid.

4. The use of claim 2, wherein the functional nucleic acid is siRNA, miRNA, shRNA, lincRNA, antisense RNA, or ribozyme.

5. The use of claim 2, wherein the anti-neoplastic agent is a polynucleotide encoding a gene that promotes apoptosis.

6. The use of claim 2, wherein the anti-neoplastic agent is a radionuclide.

7. The use of any one of claims 1- 6, wherein the plurality includes at least about 10^8 minicells.

8. The use of claim 7, wherein the plurality includes at least about 10^{10} minicells.

9. The use of claim 1-8, wherein the composition comprises less than about 10 EU free endotoxin.

10. The use of any one of claims 1-9, wherein the composition comprises at most 1 parent bacterial cell per 10^8 minicells.

11. The use of claim 1-10, wherein each minicell of the plurality comprises a ligand having a specificity to a non-phagocytic mammalian cell surface receptor.

12. The use of claim 11, wherein the receptor is a tumor cell antigen.

13. The use of any one of claims 1-12, wherein the brain tumor is selected from the group consisting of glioblastoma, astrocytic tumor, oligodendroglial tumor, ependymoma, craniopharyngioma, pituitary tumor, primary lymphoma of the brain, pineal gland tumor, primary germ cell tumor of the brain, and combinations thereof.

14. The use of claim 13, wherein the brain tumor is a metastatic brain tumor.

15. The use of claim 1, wherein the brain tumor is glioblastoma.

16. The use of claim 1 or 15, wherein the tumor is a stage II, III, or IV tumor.

17. The use of claim 1 or 15, wherein the tumor is a stage III or IV tumor.

18. The use of claim 1 or 15, wherein angiogenesis has initiated in the tumor.

19. The use of claim 1 or 15, wherein vascularization has initiated in the tumor.