WE CLAIM

1. A composition comprising (a) a plurality of intact, bacterially-derived minicells, wherein each minicell of said plurality encompasses regulatory RNA that is packaged in said minicell, and (b) a pharmaceutically acceptable carrier therefor, wherein there is an absence from said minicells of a construct for in situ expression of said regulatory RNA, wherein said regulatory RNA is selected from the group consisting of siRNA, miRNA and shRNA, and wherein said plurality contains a therapeutically effective amount of said regulatory RNA.

2. The composition of claim 1, wherein said regulatory RNA targets the RNA transcript encoding a protein that contributes to drug resistance, apoptosis resistance or neoplasticity.

3. The composition of claim 1, wherein said regulatory RNA targets the transcript of P-glycoprotein, MDR-2, or MDR-3.

4. The composition of claim 1, wherein said regulatory RNA targets the transcript of MRP2, BCR-ABL, STI-571 resistance-associated protein, lung resistance-related protein, cyclooxygenase-2, nuclear factor kappa, XRCC1, ERCC1, GSTP1, mutant β-tubulin, or a growth factor.

5. The composition of claim 1, wherein said regulatory RNA targets a transcript of Bcl-2, Bcl-XL, A1/Bfl 1, focal adhesion kinase or p53 protein.

6. The composition of claim 1, wherein said regulatory RNA targets a transcript of β-Catenin, PKC-α, C-RAF, K-Ras, DP97 Dead box RNA helicase, cdk1, DNMT1, FLIP, C-Sfc, 53BPI, Polycomb group protein EZH2, ErbB1, HPV-16 E5 and E7, Fortilin & MCI1P, KSP, DIP13α, MBD2, p21, KLF4, tpt/TCTP, SPK1 & SPK2, P300, PLK1, Trp53, Ras, ErbB1, VEGF, or BAG-1.

7. The composition of claim 1, further comprising a drug.

8. The composition of claim 7, wherein said regulatory RNA targets the transcript encoding a protein that contributes to resistance to said drug.

9. The composition of claim 8, wherein said drug is packaged in an intact, bacterially-derived minicell.

10. The composition of claim 9, wherein said regulatory RNA and said drug are packaged within the same minicell.

11. The composition of claim 1, further comprising a bispecific ligand.

12. The composition of claim 11, wherein said bispecific ligand comprises a first arm that carries specificity for a minicell surface structure and a second arm that carries specificity for a non-phagocytic mammalian cell surface receptor.

13. The composition of claim 1 or claim 12, wherein said regulatory RNA is siRNA.

14. The composition of claim 12, wherein said mammalian cell surface receptor is capable of activating receptor-mediated endocytosis of said minicell.

15. The composition of claim 11, wherein said bispecific ligand comprises an antibody or antibody fragment.

16. The composition of claim 1, wherein said composition contains fewer than about 1 contaminating parent bacterial cell per 10^9 minicells.

17. The composition of claim 1, wherein said composition contains fewer than about 1 contaminating parent bacterial cell per 10^{10} minicells.

18. The composition of claim 1, wherein said composition contains fewer than about 1 contaminating parent bacterial cell per 10^{11} minicells.

19. The composition according of claim 1 for use as a medicament.

20. The composition of claim 19, wherein said regulatory RNA is shRNA.

21. The composition of claim 19, wherein said regulatory RNA is siRNA.

22. The composition of claim 19 for use in the treatment of drug-resistance or apoptosis resistance.

23. The composition of claim 19 for use in the treatment of cancer or neoplasticity, further comprising a bispecific ligand, said bispecific ligand comprising a first arm that carries specificity for a minicell surface structure and a second arm that carries specificity for a non-phagocytic mammalian cell surface receptor.

24. The composition of claim 23, wherein said cancer is selected from the group consisting of stomach cancer, urinary tract cancer, bladder cancer, ovarian cancer, breast cancer, colon cancer and colonic epithelial cancer.

25. The composition of claim 19, wherein said medicament is for use in combination with a drug wherein said regulatory RNA targets the transcript of a protein that contributes to resistance to said drug.

26. The composition of claim 25, wherein said drug is packaged in an intact, bacterially derived minicell.

27. The composition of claim 26, wherein said regulatory RNA and said drug are packaged within the same minicell.

28. A method for formulating minicells of the composition of claim 1, comprising co-incubating in a buffer (A) a plurality of intact, bacterially-derived minicells with (B) plasmid-free, regulatory RNA, thereby obtaining minicells that contain said regulatory RNA, wherein said regulatory RNA is selected from the group consisting of siRNA, miRNA and shRNA.

29. The method of claim 28, wherein said regulatory RNA is shRNA.

30. The method of claim 28, wherein said regulatory RNA is siRNA.

31. The method of claim 29, wherein the amount of siRNA present in said minicells that contain said siRNA is such that 10^{10} minicells package at least about 1.3 µg of siRNA.

32. The method of any one of claims 28 to 31, wherein said incubation is carried out in buffered saline.

WE CLAIM:

1. A composition comprising (a) a plurality of intact minicells, each minicell of said plurality encompassing plasmid-free functional nucleic acid, and (b) a pharmaceutically acceptable carrier therefor.

2. The composition of claim 1, wherein said plurality contains a therapeutically effective amount of said functional nucleic acid.

3. The composition of claim 1, wherein said functional nucleic acid is a regulatory RNA.

4. The composition of claim 3, wherein said regulatory RNA is selected from the group consisting of siRNA, miRNA and shRNA.

5. The composition of claim 1, wherein said functional nucleic acid is not chemically modified.

6. The composition of claim 1, wherein said functional nucleic acid is DNA.

7. The composition of claim 1, wherein said functional nucleic acid targets the RNA transcript encoding a protein that contributes to drug resistance.

8. The composition of claim 1, wherein said functional nucleic acid targets the transcript of P-glycoprotein, MDR-2, or MDR-3.

9. The composition of claim 1, wherein said functional nucleic acid targets the transcript of MRP2, BCR-ABL, STI-571 resistance-associated protein, lung resistance-related protein, cyclooxygenase-2, nuclear factor kappa, XRCC1, ERCC1, GSTP1, mutant β-tubulin, or a growth factor.

10. The composition of claim 1, wherein said functional nucleic acid targets the RNA transcript encoding a protein that contributes to apoptosis resistance.

11. The composition of claim 10, wherein said functional nucleic acid targets a transcript of Bcl-2, Bcl-X_L, A1/Bfl 1, focal adhesion kinase or p53 protein.

12. The composition of claim 1, wherein said functional nucleic acid targets a RNA transcript of encoding a protein that contributes to neoplasticity.

13. The composition of claim 12, wherein said functional nucleic acid targets a transcript of β-Catenin, PKC-α, C-RAF, K-Ras, DP97 Dead box RNA helicase, cdk1, DNMT1, FLIP, C-Sfc, 53BPI, Polycomb group protein EZH2, ErbB1, HPV-16 E5 and E7, Fortilin & MCI1P, KSP, DIP13α, MBD2, p21, KLF4, tpt/TCTP, SPK1 & SPK2, P300, PLK1, Trp53, Ras, ErbB1, VEGF, or BAG-1.

14. The composition of claim 1, further comprising a drug.

15. The composition of claim 14, wherein said functional nucleic acid targets the transcript encoding a protein that contributes to resistance to said drug.

16. The composition of claim 14, wherein said drug is packaged in an intact minicell.

17. The composition of claim 16, wherein said functional nucleic acid and said drug are packaged within the same minicell.

18. The composition of claim 1, further comprising a bispecific ligand.

19. The composition of claim 18, wherein said bispecific ligand comprises a first arm that carries specificity for a minicell surface structure and a second arm that carries specificity for a non-phagocytic mammalian cell surface receptor.

20. The composition of claim 19, wherein said minicell surface structure is an O-polysaccharide component of a lipopolysaccharide on said minicell surface.

21. The composition of claim 19, wherein said mammalian cell surface receptor is capable of activating receptor-mediated endocytosis of said minicell.

22. The composition of claim 18, wherein said bispecific ligand comprises an antibody or antibody fragment.

23. The composition of claim 1, wherein said composition contains fewer than about 1 contaminating parent bacterial cell per 10^7 minicells.

24. The composition of claim 1, wherein said composition contains fewer than about 1 contaminating parent bacterial cell per 10^8 minicells

25. The composition of claim 1, wherein said composition contains fewer than about 1 contaminating parent bacterial cell per 10^9 minicells

26. The composition of claim 1, wherein said composition contains fewer than about 1 contaminating parent bacterial cell per 10^{10} minicells

27. The composition of claim 1, wherein said composition contains fewer than about 1 contaminating parent bacterial cell per 10^{11} minicells.

28. A method of delivering functional nucleic acid, comprising (a) providing a plurality of intact minicells in a pharmaceutically acceptable carrier, each minicell of said plurality encompassing plasmid-free functional nucleic acid, and (b) bringing minicells of said plurality into contact with mammalian cells such that said mammalian cells engulf minicells of said plurality, whereby said functional nucleic acid is released into the cytoplasm of the target cells.

29. The method of claim 28, wherein said functional nucleic acid is a regulatory RNA.

30. The method of claim 29, wherein said regulatory RNA is selected from the group consisting of siRNA, miRNA and shRNA.

31. The method of claim 28, wherein said functional nucleic acid is DNA.

32. The method of claim 28, wherein contact between said minicells and said mammalian cells occurs *in vitro*.

33. The method of claim 28, wherein contact between said minicells and said mammalian cells occurs *in vivo*.

34. The method of claim 33, wherein at least a portion of said plurality comprises a therapeutically effective amount of said functional nucleic acid.

~~35. The method of claim 28, wherein said functional nucleic acid targets the transcript~~ encoding a protein that contributes to drug-resistance.

36. The method of claim 28, wherein said functional nucleic acid targets the transcript of P-glycoprotein, MDR-2 or MDR-3.

37. The method of claim 28, wherein said functional nucleic acid targets the transcript of MRP2, BCR-ABL, STI-571 resistance-associated protein, lung resistance-related protein, cyclooxygenase-2, nuclear factor kappa, XRCC1, ERCC1, GSTP1, mutant β-tubulin, or a growth factor.

38. The method of claim 28, wherein said functional nucleic acid targets the transcript of a protein that contributes to apoptosis resistance.

39. The method of claim 38, wherein said functional nucleic acid targets a transcript of Bcl-2, Bcl-X_L, A1/Bfl 1, focal adhesion kinase or p53 protein.

40. The method of claim 28, wherein said functional nucleic acid targets a transcript of a protein that contributes to neoplasticity.

41. The method of claim 40, wherein said functional nucleic acid targets a transcript of β-Catenin, PKC-α, C-RAF, K-Ras, DP97 Dead box RNA helicase, cdk1, DNMT1, FLIP, C-Sfc, 53BPI, Polycomb group protein EZH2, ErbB1, HPV-16 E5 and E7, Fortilin & MCI1P, DIP13α, KSP, MBD2, p21, KLF4, tpt/TCTP, SPK1 & SPK2, P300, PLK1, Trp53, Ras, ErbB1, VEGF, or BAG-1.

42. The method of claim 28, further comprising a step (c) of delivering a drug to said target mammalian cell.

43. The method of claim 42, wherein said functional nucleic acid targets the transcript of a protein that contributes to resistance to said drug.

44. The method of claim 42, wherein said drug is packaged in an intact minicell.

45. The method of claim 44, wherein said functional nucleic acid and said drug are packaged within the same minicell.

46. The method of claim 42, wherein step (c) occurs subsequent to steps (a) and (b).

47. The method of claim 42, wherein said drug is delivered concurrently with step (b).

48. The method of claim 28, wherein step (b) entails bringing a bispecific ligand into contact with at least some of said intact minicells and said target mammalian cell, such that said bispecific ligand causes minicells to bind to said mammalian cell.

49. The method of claim 48, wherein said target mammalian cell is a non-phagocytic cell.

50. The method of claim 48, wherein said bispecific ligand comprises a first arm that carries specificity for a minicell surface structure and a second arm that carries specificity for a non-phagocytic mammalian cell surface receptor.

51. The method of claim 50, wherein said minicell surface structure is an O-polysaccharide component of a lipopolysaccharide on said minicell surface.

52. The method of claim 50, wherein said mammalian cell surface receptor is capable of activating receptor-mediated endocytosis of said minicell.

53. The method of claim 48, wherein said bispecific ligand comprises an antibody or antibody fragment.

54. The method of claim 28, wherein said mammalian cell is phagocytosis- or endocytosis-competent.

55. A method for formulating a minicell of the composition of claim 1, comprising co-incubating a plurality of intact minicells with functional nucleic acid in a buffer.

56. The method of claim 55, wherein said functional nucleic acid is a regulatory RNA.

57. The method of claim 55, wherein said regulatory RNA is selected from the group consisting of siRNA, miRNA and shRNA.

58. The method of claim 55, wherein said functional nucleic acid is DNA.

59. The method of claim 55, wherein said co-incubation comprises gentle shaking.

60. The method of claim 55, wherein said co-incubation lasts about 0.5 hour.

61. The method of claim 55, wherein said co-incubation lasts about one hour.

62. The method of claim 55, wherein said buffer comprises buffered saline.

63. The method of claim 62, wherein said buffered saline is in gelatin form.

64. The method of claim 55, wherein said buffer comprises a 1X phosphate buffer solution.

65. The method of claim 55, wherein said co-incubation is conducted at a temperature of about 4°C to about 37°C.

66. The method of claim 55, wherein said co-incubation is conducted at a temperature of about 20°C to about 30°C.

67. The method of claim 55, wherein said co-incubation is conducted at a temperature of about 25°C.

68. The method of claim 55, wherein said co-incubation is conducted at a temperature of about 37°C.

69. The method of claim 68, wherein said co-incubation comprises about 10^{10} minicells.

70. The method of claim 55, wherein said co-incubation comprises about 10^{7}, 10^{8}, 10^{9}, 10^{10}, 10^{11},10^{12} or 10^{13} minicells.

71. The method of claim 55, wherein said co-incubation comprises about 10^{10} minicells.