Claims

1. A composition comprising a liposome in a medium, said liposome having an interior space separated from the medium by a membrane comprising one or more lipids, wherein said interior space comprises ~~a cationic anti-neoplastic therapeutic entity and a polyol or a sugar, polyanionized with at least two strongly anionic functional groups, which sugar is a monosaccharide or a disaccharide; wherein the cationic entity and the~~an anion selected from the group consisting of a polyanionized polyol or ~~the~~ polyanionized sugar ~~are comprised in a form of an acid or a salt that is entrapped within the liposome, and wherein the composition is a pharmaceutical formulation for parenteral administration~~.

2. The composition of Claim 1 wherein said liposome comprises a transmembrane gradient effective for retention of an entity within said liposome, wherein said transmembrane gradient is an ion gradient, an ammonium ion gradient, a pH gradient, an electrochemical potential gradient, a solubility gradient, or a gradient of a substituted ammonium ion comprising at least one C-N bond.

3. The composition of Claim 1 or Claim 2 wherein said anion comprises

(i) a polyol or sugar moiety selected from the group consisting of a monosaccharide, a disaccharide, a linear polyhydroxylated compound, a cyclic polyhydroxylated compound, an aliphatic alcohol having more than one hydroxyl group, an alicyclic alcohol having more than one hydroxyl group, or a heterocyclic alcohol having more than one hydroxyl group, and

(ii) linked to said polyol moiety, at least two anionic functional groups.

~~2~~4. The composition of Claim ~~1~~3 wherein at least one of said ~~strongly~~ anionic functional groups is a sulfuric acid ester, a phosphoric acid ester, a boric acid ester, a sulfonic acid group, a phosphonic acid group, a thiocarbonic acid group, or a dithiocarbonic acid group.

~~3~~5. The composition of Claim ~~1 or 2~~3 wherein said ~~monosaccharide~~polyol or sugar moiety is selected from the group consisting of arabinose, ribose, xylose, glucose, galactose, sorbose, ~~and~~ fructose,~~; the disaccharide is selected from the group consisting of~~ maltose, sucrose, lactose, ~~and~~ trehalose,~~; and the polyol is selected from the group consisting of~~ ethylene glycol, propylene glycol, glycerol, treitol, erythritol, pentaerythritol, ribitol, arabitol, sorbitol, mannitol, lactitol, maltitol, fructitol, glucitol, xylitol, ~~and~~or inositol.

~~4~~6. The composition of Claim~~s 1~~ 3 wherein ~~the polyanionized sugar~~said polyanion is polysulfated sucrose having from 3 to 8 sulfate groups per molecule~~; and the polyanionized polyol is an inositol polyphosphate~~.

~~5~~7. The composition of Claim~~s 1~~-~~4~~3 wherein said polysulfated sucrose is sucrose octasulfate~~; and the inositol polyphosphate is inositol hexaphosphate~~.

8. The composition of Claim 3 wherein said polyanion is inositol hexaphosphate.

9. The composition of Claim 3 wherein the concentration of said anion in said liposome interior is at least about 0.05, 0.1, 0.2, 0.5, 0.6, 0.7, or 1.0 gram-equivalent/L.

10. The composition of Claim 3 wherein the concentration of said anion in said liposome interior is about 0.65 gram-equivalent/L or about 1.0 gram-equivalent/L.

11. The composition of any one of Claims 1 to 10 wherein the medium is an aqueous medium, said composition further comprising a cationic entity that is a globally cationic entity, a therapeutic entity, or a detectable marker.

~~6~~12. The composition of Claim~~s 1~~-~~5~~11 wherein said ~~therapeutic~~ entity is present in said interior space at a concentration which exceeds the concentration of said ~~therapeutic~~ entity in said medium.

~~7~~13. The composition of Claim~~s 1~~-~~6~~11 wherein said medium is essentially free from said ~~therapeutic~~ entity.

~~8. The composition of Claims 1-7 wherein at least 90% of said therapeutic entity remains encapsulated in the liposome after 6 months at 2 - 8 ºC.~~

~~9. The composition of Claims 1-8 wherein at least 80% of said therapeutic entity remains encapsulated in the liposome after 2 years at 2 - 8 ºC.~~

~~10. The composition of Claims 1-9 wherein said therapeutic entity is contained in the liposomes of said composition at a first entity-to-lipid ratio, and wherein 24 hours following administration of said composition into the bloodstream of a mammal, said therapeutic entity remains contained in said liposomes at a second entity-to-lipid ratio wherein the second entity-to-lipid ratio is over 50% of the first substance-to-lipid ratio.~~

~~11. The composition of Claim 10 wherein said mammal is a rat.~~

~~12~~14. The composition of Claim~~s 1~~-11 wherein the ~~composition has an antineoplastic therapeutic entity-to-lipid~~ molar ratio of said entity to the totality of said lipids is at least about 0.05, at least about 0.1~~0~~, at least about 0.2, at least about 0.3, at least about 0.5, at least about 0.7, or at least about 1.0 ~~wherein said liposome composition has in vivo anti-neoplastic activity at least four-fold higher than the anti-neoplastic activity of the entity in a free non-liposomal form, and wherein the toxicity of said liposome composition administered to a mammal is equal or less than the toxicity of said entity administered to the mammal in a free non-liposomal form~~.

15. The composition of Claim 11 wherein said therapeutic entity is an antimicrobial therapeutic, antiviral therapeutic, or an anti-neoplastic therapeutic.

~~13. The composition of Claims 1-12 wherein the toxicity of said liposome composition administered to a mammal is at least two times less than the toxicity of said anti-neoplastic therapeutic entity administered to said mammal in a free non-liposomal form.~~

~~14. The composition of Claims 1-13 wherein the toxicity of said liposome composition administered to a mammal is at least four times less than the toxicity of said anti-neoplastic therapeutic entity administered to said mammal in a free non-liposomal form.~~

~~15. The composition of Claims 1-14 wherein said anti-neoplastic therapeutic entity is a taxane or a camptothecin topoisomerase I inhibitor.~~

~~16. The composition of Claim 15 wherein said camptothecin topoisomerase I inhibitor is irinotecan.~~

~~17. The composition of Claim 15 or Claim 16 wherein when said composition is administered into the bloodstream of a mammal, the antineoplastic therapeutic entity has a half-release time from said liposomes of at least 10 hours.~~

~~18. The composition of Claim 15 or Claim 16 wherein when said composition is administered into the bloodstream of a mammal, the antineoplastic therapeutic entity has a half-release time from said liposomes of at least 24 hours.~~

~~19. The composition of any one of Claims 15-18 wherein said sugar is the disaccharide polysulfated sucrose and the polyanionized polyol is inositol polyphosphate.~~

~~20. The composition of Claim 19 wherein said polysulfated sucrose is sucrose octasulfate; and said inositol polyphosphate is inositol hexaphosphate.~~

~~21. The composition of Claims 15-20 wherein said topoisomerase inhibitor is entrapped at a concentration of at least about 0.1 to about 2.0 mole drug per mole lipid.~~

~~22. The composition of Claim 17 or Claim 18 wherein said topoisomerase inhibitor is entrapped at a concentration of at least 0.15 mole drug per mole lipid to about 1.5 mole drug per mole lipid.~~

~~23. The composition of Claim 17 or Claim 18 wherein the mammal is a mouse.~~

~~24. The composition of Claims 12-14 wherein the anti-neoplastic activity is determined in vivo in an HT-29 tumor model or a BT-474 tumor model.~~

~~25. The composition of Claim 17 or 18 wherein the mammal is a rat.~~

~~26. The composition of Claims 1-24 wherein said lipids comprise a lipid derivatized with a hydrophilic polymer.~~

~~27. The composition of Claim 26 wherein said hydrophilic polymer-derivatized lipid comprises up to 20 mole % of the totality of said lipids.~~

~~28. The composition of Claim 27 wherein said hydrophilic polymer-derivatized lipid comprises less than 1 mole % of the totality of said lipids.~~

~~29. The composition of Claims 26-28 wherein said liposome has blood circulation longevity in a mammal of less than two times higher than the circulation longevity of an identically composed liposome except for the absence of said hydrophilic polymer-derivatized lipid.~~

~~30. The composition of Claim 29 wherein the mammal is a rat.~~

~~31. The composition of Claim 28 wherein said hydrophilic polymer-derivatized lipid comprises from about 0.1 mole % to about 0.9 mole % of the totality of said lipids.~~

~~32. The composition of Claims 26-31 wherein said hydrophilic polymer is poly(ethylene glycol).~~

~~33. The composition of Claims 26-32 wherein said hydrophilic polymer-derivatized lipid is a poly(ethylene glycol)-derivatized phospholipid, a poly(ethylene glycol)-derivatized diacylglycerol, a poly(ethylene glycol)-derivatized dialkylglycerol, a poly(ethylene glycol)-derivatized ceramide, a poly(ethylene glycol)-derivatized fatty acid, a poly(ethylene glycol)-derivatized fatty alcohol, or a poly(ethylene glycol)-derivatized sterol.~~

~~34. The composition of Claims 26-33 wherein said hydrophilic polymer is poly(ethylene glycol) having molecular weight from about 200 to about 10,000.~~

~~35. The composition of Claims 26-34 wherein said hydrophilic polymer is poly(ethylene glycol) having molecular weight from about 500 to about 5,000.~~

~~36. The composition of Claims 1-35 wherein said liposome comprises a targeting moiety.~~

~~37. The composition of Claim 36 wherein said targeting moiety is a protein, a peptide, a polysaccharide, a polynucleotide, natural small molecule, a synthetic small molecule, or a combination thereof.~~

~~38. The composition of Claim 36 or Claim 37 wherein the targeting moiety is a naturally, synthetically, or recombinantly produced protein comprising an antigen binding sequence of an antibody.~~

~~39. The composition of Claim 36 wherein said targeting moiety is an antibody, an antigen-binding fragment thereof, a single-chain protein comprising the antigen-binding polypeptide sequences of an antibody, or a single-domain antibody.~~

~~40. The composition of Claims 36-39 wherein said targeting moiety is linked to said liposome membrane and exposed to said medium.~~

~~41. The composition of Claim 40 wherein said linked targeting moiety comprises a hydrophilic polymer that links said liposome membrane to said moiety.~~

~~42. The composition of Claim 41 wherein said hydrophilic polymer is poly(ethylene glycol).~~

~~43. The composition of Claim 42 wherein said poly(ethylene glycol) has molecular weight from about 250 to about 30,000.~~

~~44. The composition of Claims 36-43 wherein said targeting moiety effects internalization of said liposome in a cell.~~

45. The composition of Claims 36-44 wherein said targeting moiety selectively binds to a receptor tyrosine kinase, a growth factor receptor, an angiogenic factor receptor, a transferrin receptor, a cell adhesion molecule, or a vitamin receptor.

46. The composition of Claim 45 wherein said receptor tyrosine kinase is a growth factor receptor.

47. The composition of Claim 46 wherein said receptor tyrosine kinase growth factor receptor is an EGFR, ErbB-2 (HER-2), ErbB-3 (HER3), or ErbB-4 (HER4).

48. The composition of Claims 45-47 wherein angiogenic factor receptor is bFGF receptor, or VEGF receptor.

49. The composition of Claims 45-48 wherein the cell adhesion molecule is an integrin.

50. The composition of Claims 43-49 wherein said cell is a malignant cell.

51. A liposomal irinotecan composition comprising liposomes in a an aqueous medium, the liposomes having an interior aqueous space separated from the aqueous medium by a membrane, said membrane comprising lipids, said lipids comprising an uncharged lipid component and a neutral phospholipid, with, entrapped inside the liposomes: 1) irinotecan and sucrose octasulfate, or 2) irinotecan and sucrose octasulfate and a substituted ammonium compound, wherein, when administered into the bloodstream of a mammal, said irinotecan has a half-release time from said liposomes of at least 24 hours and the irinotecan entrapped inside the liposomes is at a concentration that exceeds the irinotecan concentration in the aqueous medium.

52. The liposomal irinotecan composition of claim 51, wherein when administered into the bloodstream of a rat, said irinotecan has a half-release time from said liposomes in excess of 48 hours.

53. The liposomal irinotecan composition of claim 51, wherein said composition is at least 4-fold more active at reducing human colon carcinoma xenograft tumor doubling time in nude mice than free irinotecan given at the same dose and schedule.

54. The liposomal irinotecan composition of claim 53, wherein activity is determined by measuring xenograft tumor size for 56 days.

55. The liposomal irinotecan composition of claim 51, wherein said composition is at least 10-fold more active at reducing human colon carcinoma xenograft tumor doubling time in nude mice than free irinotecan given at the same dose and schedule.

56. The liposomal irinotecan composition of claim 55, wherein activity is determined by measuring xenograft tumor size for 56 days.

57. The liposomal irinotecan composition of claim 51, wherein at least 90% of said irinotecan remains encapsulated in the liposomes after 6 months at 2-8.degree. C.

58. The liposomal irinotecan composition of claim 51 wherein, 48 hours after intravenous bolus administration into a rat there is no detectable conversion of the entrapped irinotecan from lactone form of irinotecan to carboxylate form of irinotecan, when assayed by HPLC in which the eluted products are detected by fluorescence with an excitation at 375 nm and emission at 500 nm.

59. The liposomal irinotecan composition of claim 51, wherein said substituted ammonium compound has a formula: R.sub.1--(R.sub.2--)N.sup.+(--R.sub.3)--R.sub.4, wherein N is a an ammonium nitrogen atom of a first ammonium group, each of R.sub.1, R.sub.2, R.sub.3, R.sub.4 is independently a hydrogen atom or an organic group having each independently not more than 8 carbon atoms, and in totality not more than 18 carbon atoms inclusive, wherein at least one of R.sub.1, R.sub.2, R.sub.3, R.sub.4 is an organic group; wherein the organic group is independently alkyl, alkylidene, heterocyclic alkyl, cycloalkyl, aryl, alkenyl, cycloalkenyl, or a hydroxy-substituted derivative thereof, optionally including S, O, or N atoms forming an ether, ester, thioether, amine, or amide

bond; and wherein at least three of R.sub.1, R.sub.2, R.sub.3, R.sub.4 are the organic groups; or at least one of the organic groups has a secondary or tertiary carbon atom directly linked to the ammonium nitrogen atom.

60. The liposomal irinotecan composition of claim 51, wherein said substituted ammonium compound is selected from the group consisting of isopropylethylammonium, isopropylmethylammonium, diisopropylammonium, tert-butylethylammonium, dicyclohexylammonium, morpholinium, pyridinium, piperidinium, pyrrolidinium, piperazinium, tert-butylammonium, 2-ammonio-2-methyl-propanol-1,2-ammonio-2-methyl-propandiol-1,3, tris-(hydroxyethyl)-ammoniomethane, N,N'-diethyl-ethanolammonium, N,N',N''-tris-(2-hydroxyethyl)ammonium, N,N'-bis-(2-hydroxyethyl)ethylammonium, trimethyl-ammonium, triethylammonium, diethylmethyl-ammonium, diisopropylethylammonium, triisopropylammonium, N-methyl-morpholinium, 1-(2-hydroxyethyl)piperidinium, 1-methylpyrrolidinium, 1,4-dimethyl-piperazinium, tetramethylammonium, tetraethyl-ammonium, and tetrabutylammonium.

61. The liposomal irinotecan composition of claim 60, wherein said substituted ammonium compound is triethylammonium.

62. The liposomal irinotecan composition of claim 51, wherein said membrane further comprises a polymer-conjugated lipid.

63. The liposomal irinotecan composition of claim 51, wherein said composition is a fluid pharmaceutical formulation for parenteral administration.

64. The liposomal irinotecan composition of claim 51, wherein molar ratio of irinotecan to the totality of said lipids is at least 1.0.

65. The liposomal irinotecan composition of claim 51, wherein said irinotecan is present at a ratio of about 1.76 mol irinotecan per mol of said neutral phospholipid.

66. The liposomal irinotecan composition of claim 51, wherein said irinotecan is present at a ratio of about 1.67-1.70 mol irinotecan/g of lipids comprised by the membrane.

67. The liposomal irinotecan composition of claim 51, wherein the relative amounts of said irinotecan and said sucrose octasulfate are at the point of stoichiometric equivalency.

68. The liposomal irinotecan composition of claim 51, wherein said mammal is a mouse.

69. The liposomal irinotecan composition of claim 51, wherein said irinotecan and said sucrose octasulfate are comprised in the form of an acid or a salt.

70. The liposomal irinotecan composition of claim 51, wherein said neutral phospholipid comprises a diacylphosphatidylcholine.

71. The liposomal irinotecan composition of claim 70, wherein said diacylphosphatidylcholine is 1,2-distearoyl-sn-phosphatidylcholine (DSPC).

72. The liposomal irinotecan composition of claim 51, wherein said aqueous medium comprises HEPES and NaCl.

73. The liposomal irinotecan composition of claim 51, wherein said substituted ammonium compound is diethylammonium.

74. The liposomal irinotecan composition of claim 51, wherein said irinotecan is present at a ratio of about 550 mg irinotecan hydrochloride per mmol of said neutral phospholipid.

75. The liposomal irinotecan composition of claim 62, wherein said polymer is a polyethylene glycol-lipid derivative.

76. The liposomal irinotecan composition of claim 75, wherein said polymer-conjugated lipid is N-(methoxy-poly(ethylene glycol)-oxycarbonyl)-distearoylphosphatidylethanolamine (PEG-DSPE).

77. The liposomal irinotecan composition of claim 51, wherein said uncharged lipid component comprises cholesterol.

78. The liposomal irinotecan composition of claim 77, wherein said neutral phospholipid is a lecithin.

79. The liposomal irinotecan composition of claim 78 wherein said lecithin and said cholesterol are at a ratio of about 3:2 by mole.

80. The liposomal irinotecan composition of claim 79 wherein said lecithin is 1,2-distearoyl-sn-phosphatidylcholine (DSPC).

81. The liposomal irinotecan composition of claim 80, comprising 1,2-distearoyl-sn-phosphatidylcholine (DSPC) 200 mol. parts, Cholesterol 133 mol. parts, and N-(methoxy-poly(ethylene glycol)-oxycarbonyl)-distearoylphosphatidylethanolamine (PEG-DSPE) 1 mol. part.

82. The liposomal irinotecan composition of claim 51, wherein leakage of irinotecan from said liposomes during storage is less than 5% over 6 months at 4-8.degree. C.

83. The liposomal irinotecan composition of claim 51, wherein 48 hours after intravenous bolus administration into a rat there is no detectable conversion of entrapped irinotecan to SN-38, when assayed by HPLC in which the eluted products are detected by fluorescence with an excitation at 375 nm and emission at 500 nm.

84. The liposomal irinotecan composition of claim 51, wherein said irinotecan comprises irinotecan hydrochloride.

85. The liposomal irinotecan composition of claim 51, wherein the interior space of the liposomes with entrapped irinotecan and sucrose octasulfate, or the interior space of the liposomes with entrapped irinotecan and sucrose octasulfate and a substituted ammonium compound, has an intraliposomal volume of approximately 1.7 l/mol phospholipid.

16. The composition of Claim 11 wherein said therapeutic entity is an aminoglycoside antibiotic or a fluoroquinolone derivative.

17. The composition of Claim 15 wherein said therapeutic entity is selected from a group consisting of: a topoisomerase inhibitor, a farnesyltransferase inhibitor, a tyrosine kinase inhibitor, a cyclin-dependent kinase inhibitor, a phosphatase inhibitor, an aurora kinase inhibitor, a microtubule depolymerizing agent, a microtubule stabilizing agent, an alkylating agent, an enzyme, an enzyme inhibitor, a histone deacetylase inhibitor, an antimetabolite, a receptor-binding agent, a hormone, a hormone antagonist, a nucleotide, and a polynucleotide.

18. The composition of Claim **Error! Reference source not found.** wherein said anti-neoplastic therapeutic is selected from a group consisting of an anthracycline compound, a camptothecin compound, a vinca alkaloid, an ellipticine compound, a taxane compound, a wortmannin compound, and a pyrazolopyrimidine compound.

19. The composition of Claim 11 wherein said therapeutic entity is selected from a group consisting of: doxorubicin, daunorubicin, mitomycin C, epirubicin, pirarubicin, rubidomycin, carcinomycin, N-acetyladriamycin, rubidazone, 5-imidodaunomycin, N-acetyldaunomycin, daunoryline, mitoxanthrone, camptothecin, 9-aminocamptothecin, 7-ethylcamptothecin, 10-hydroxycamptothecin, 9-nitrocamptothecin, 10,11-methylenedioxycamptothecin, 9-amino-10,11-methylenedioxycamptothecin, 9-chloro-10,11-methylenedioxycamptothecin, irinotecan, topotecan, lurtotecan, silatecan, (7-(4-methylpiperazinomethylene)-10,11-ethylenedioxy-20(S)-camptothecin, 7-(4-methylpiperazinomethylene)-10,11-methylenedioxy-20(S)-camptothecin, 7-(2-N-isopropylamino)ethyl)-(20S)-camptothecin, vincristine, vinblastine, vinorelbine, vinflunine, vinpocetine, vindesine, ellipticine, 6-3-aminopropyl-ellipticine, 2-diethylaminoethyl-ellipticinium and salts thereof.

20. The composition of Claim 11 wherein said therapeutic entity is selected from a group consisting of: an antihistamine ethylenediamine derivative, an anti-protozoal drug, an

amidine compound, an antihelmintic compound, an anti-schistosomal drug, an antifungal triazole, an antimicrobial cephalosporin, an antimicrobial beta-lactam derivative, an antimicrobial of erythromycine group, a penicillin compound, a tetracycline compound, an antimycobacterial drug, an antiviral adamantane compound, a quinidine compound, an antimicrobial quinolone, a sulfonamide; a urinary tract antimicrobial, a nitroimidazole, a cholinergic quaternary ammonium compound, an anti-Alzheimer aminoacridine, an anti-Parkinsonal drug, an anti-muscarinic agent, an adrenergic compound, a serotonin reuptake inhibitor, an ergotamine derivative, a myorelaxant of curare series, a central action myorelaxant, a nicotine receptor antagonist, a beta-adrenoblocker, a benzodiazepine compound, an antiarrhythmic drug, a local anesthetic compound, an ACE inhibitor, an opiate derivative, an antilipidemic, an HMG-coA inhibitor, a hypotensive drug, a non-coronary vasodilator, an acetylcholine esterase inhibitor, and an alkaloid.

8621. A method of encapsulating ~~a cationic anti-neoplastic therapeutic~~an entity into a liposome comprising ~~the step of~~ contacting ~~a~~the composition ~~comprising the liposome in a medium, the liposome having an interior space separated from the medium by a membrane comprising one or more lipids, wherein the interior space comprises a polyol or a sugar, polyanionized with at least two strongly anionic functional groups, which sugar is a monosaccharide or a disaccharide, and wherein a transmembrane gradient of an ammonium ion exists between the liposome and the medium effective for retention of the entity within the liposome,~~of any one of Claims 1 to 10 with the entity ~~for a time sufficient for said therapeutic entity and the polyanionized polyol or polyanionized sugar to become comprised in a form of an acid or a salt that is entrapped in said liposome~~.

~~87. The method of Claim 86 wherein at least a portion of said entity enters the liposome interior space.~~

~~88. The method of Claim 86 wherein at least 90% of said entity enters the liposome interior space.~~

~~89. The method of Claim 86 wherein the proportion of said entity that becomes encapsulated into the liposomes is at least 80%, at least 90%, or at least 95%.~~

~~90. The method of Claim 86 wherein the entity is a camptothecin topoisomerase 1 inhibitor or a taxane.~~

22. The method of Claim 21 wherein the entity is a globally cationic entity, a therapeutic entity, or a detectable marker.

~~91~~23. The method of Claim ~~86~~21 wherein molar ratio of said entity to the totality of said lipids is at least about 0.05, about 0.1, about 0.2, or about 0.3.

24. The method of Claim 21 wherein said therapeutic entity is an antimicrobial therapeutic, antiviral therapeutic, or an anti-neoplastic therapeutic.

25. The method of Claim 21 wherein said therapeutic entity is an aminoglycoside antibiotic or a fluoroquinolone.

26. The method of Claim 22 wherein said therapeutic entity is selected from a group consisting of: a topoisomerase inhibitor, a farnesyltransferase inhibitor, a tyrosine kinase inhibitor, a cyclin-dependent kinase inhibitor, a phosphatase inhibitor, an aurora kinase inhibitor, a microtubule depolymerizing agent, a microtubule stabilizing agent, an alkylating agent, an enzyme, an enzyme inhibitor, a histone deacetylase inhibitor, an antimetabolite, a receptor-binding agent, a hormone, a hormone antagonist, a nucleotide, and a polynucleotide.

27. The method of Claim 22 wherein said therapeutic entity is selected from a group consisting of an anthracycline compound, a camptothecin compound, a vinca alkaloid, an ellipticine compound, a taxane compound, a wortmannin compound, and a pyrazolopyrimidine compound.

28. The method of Claim 22 wherein said therapeutic entity is selected from a group consisting of: doxorubicin, daunorubicin, mitomycin C, epirubicin, pirarubicin, rubidomycin, carcinomycin, N-acetyladriamycin, rubidazone, 5-imidodaunomycin, N-acetyldaunomycin, daunoryline, mitoxanthrone, camptothecin, 9-aminocamptothecin, 7-ethylcamptothecin, 10-hydroxycamptothecin, 9-nitrocamptothecin, 10,11-methylenedioxycamptothecin, 9-amino-10,11-methylenedioxycamptothecin, 9-chloro-10,11-methylenedioxycamptothecin, irinotecan, topotecan, lurtotecan, silatecan, (7-(4-methylpiperazinomethylene)-10,11-ethylenedioxy-20(S)-camptothecin, 7-(4-methylpiperazinomethylene)-10,11-methylenedioxy-20(S)-camptothecin, 7-(2-N-isopropylamino)ethyl)-(20S)-camptothecin, vincristine, vinblastine, vinorelbine, vinflunine, vinpocetine, vindesine, ellipticine, 6-3-aminopropyl-ellipticine, 2-diethylaminoethyl-ellipticinium and salts thereof, datelliptium, retelliptine, paclitaxel, and docetaxel.

29. The method of Claim 22 wherein said therapeutic entity is selected from a group consisting of: an antihistamine ethylenediamine derivative, an anti-protozoal drug, an amidine compound, an antihelmintic compound, an anti-schistosomal drug, an antifungal triazole, an antimicrobial cephalosporin, an antimicrobial beta-lactam, an antimicrobial of erythromycine group, a penicillin compound, a tetracycline compound, an antimycobacterial drug, an antiviral adamantane compound, a quinidine compound, an antimicrobial quinolone, a sulfonamide; a urinary tract antimicrobial, a nitroimidazole, a cholinergic quaternary ammonium compound, an anti-Alzheimer aminoacridine, an anti-Parkinsonal drug, an anti-muscarinic agent, an adrenergic compound, a serotonin reuptake inhibitor, an ergotamine derivative, a myorelaxant of curare series, a central action myorelaxant, a nicotine receptor antagonist, a beta-adrenoblocker, a benzodiazepine compound, an antiarrhythmic drug, a local anesthetic compound, an ACE inhibitor, an opiate derivative, an antilipidemic, an HMG-coA inhibitor, a hypotensive drug, a non-coronary vasodilator, an acetylcholine esterase inhibitor, and an alkaloid.

~~92~~30. The method of any one of Claims ~~86~~21 to 29 wherein said contacting is in an aqueous solution.

~~93~~31. The method of Claim ~~92~~30 wherein said aqueous solution has pH in the range of about 4 to about 7.

~~94~~32. The method of Claim ~~92~~30 wherein said aqueous solution has ionic strength equivalent or less than that of 50 mM sodium chloride.

~~95~~33. The method of Claim ~~92~~31 wherein ~~the~~said aqueous solution has ionic strength equivalent or less than that of 20 mM sodium chloride.

~~96~~34. The method of Claim ~~95~~30, wherein the ~~pH of the~~ aqueous solution ~~is~~has pH between about ~~5~~6.0 and about 7.0, and the entity is a vinca alkaloid ~~selected from the group consisting of camptothecin, 9-amino-camptothecin, 7-ethylcamptothecin, 10-hydroxycamptothecin, 9-nitrocamptothecin, 10,11-methylenedioxycamptothecin, 9-amino-10,11-methylenedioxycamptothecin, 9-chloro-10,11-methylenedioxy-camptothecin, irinotecan, topotecan, lurtotecan, silatecan, TAS-103, (7-(4-methyl-piperazino-methylene)-10,11-ethylenedioxy-20(S)-camptothecin, 7-(4-methylpiperazino-methylene)-10,11-methylenedioxy-20(S)-camptothecin, and 7-(2-N-isopropylamino)-ethyl)-(20S)-camptothecin~~.

~~97~~35. The method of Claim ~~96~~34 wherein the pH of the aqueous solution is ~~between about 5.0 and~~ about 6.5, and the entity is ~~Topotecan or Irinotecan~~vinorelbine.

36. The method of Claim 33 wherein the pH of the aqueous solution is between about 5 and about 7, and the entity is a camptothecin.

37. The method of Claim 36 wherein the pH of the aqueous solution is between about 5.0 and about 6.5, and the entity is Topotecan or Irinotecan.

~~98~~38. The method of Claim ~~94~~32 or 33, wherein following said contacting, the ionic strength of said aqueous solution is increased to more than that of 50 mM sodium chloride.

~~99~~39. The method of Claim ~~98~~38 wherein said ionic strength is increased to at least that of 100 mM sodium chloride.

~~100~~40. The method of Claim ~~99~~39 wherein said ionic strength is increased to at least that of 150 mM sodium chloride.

41. A kit for providing a liposomally encapsulated entity, comprising the composition of any one of Claims 1 to 10, an instruction for using the composition to encapsulate an entity, and the entity for encapsulation, wherein the entity for encapsulation is optionally provided in a separate container.

42. A kit of Claim 41 wherein the entity is a globally cationic substance, a therapeutic entity, or a detectable marker.

43. A composition of any one of Claims 1 to 20 wherein the liposome further comprises a substituted ammonium compound having in a aqueous solution at ambient temperature a pKa value of at least 8.0, at least 8.5, at least 9.0, at least 9.5, or at least 10.0.

44. A method of Claim 21 or 22 wherein said liposome further comprises a substituted ammonium compound having in a aqueous solution at ambient temperature a pKa value of at least 8.0, at least 8.5, at least 9.0, at least 9.5, or at least 10.0.

45. A composition of any one of Claims 1 to 7, 9 to 15 and 17 to 19 wherein the anion is sucrose octasulfate and the cation is an antineoplastic therapeutic.

46. The composition of Claim 45 wherein the antineoplastic therapeutic is a topoisomerase 1 inhibitor.

47. The composition of Claim 46 wherein the topoisomerase 1 inhibitor is a camptothecin.

48. The composition of Claim 47 wherein the camptothecin is irinotecan.

49. The composition of Claim 48 wherein the irinotecan and the sucrose octasulfate are at stoichiometric equivalency.

50. A liposome containing an entity encapsulated according to the method of any one of Claims 21 to 24, 26 to 28, and 30 to 40.

51. The liposome of Claim 50 wherein the anion is sucrose octasulfate and the cation is an antineoplastic therapeutic.

52. The liposome of Claim 51 wherein the antineoplastic therapeutic is a topoisomerase 1 inhibitor.

53. The liposome of Claim 52 wherein the topoisomerase 1 inhibitor is a camptothecin.

54. The liposome of Claim 53 wherein the camptothecin is irinotecan.

55. The composition of Claim 54 wherein the irinotecan and the sucrose octasulfate are at stoichiometric equivalency.