WHAT IS CLAIMED IS:

1. A lipid nanoparticle composition comprising:

(i) at least one zwitterionic polymer-containing lipid in which a lipid moiety is covalently attached to a zwitterionic polymer;

(ii) at least one non-cationic lipid selected from charged and uncharged lipids, wherein the non-cationic lipid is not attached to a polymer;

(iii) at least one cationic or ionizable lipid containing a secondary, tertiary, or quaternary amino group and

(iv) at least one therapeutic substance.

2. The composition of claim 1, wherein said lipid moiety in component (i) is a diacylglyceride.

3. The composition of claim 1, wherein component (i) excludes a polyalkylene oxide segment.

4. The composition of claim 1, wherein the zwitterionic polymer in component (i) is selected from the group consisting of a poly(carboxybetaine) (PCB), a poly(sulfobetaine), a poly(phosphobetaine), poly(phosphatidylcholine), glutamic acid-lysine (EK)-containing polypeptide, a poly(trimethylamine N-oxide) polymer and a poly(zwitterionic phosphatidyl serine).

5. The composition of claim 1, wherein the zwitterionic polymer in component (i) is a betaine polymer.

6. The composition of claim 5, wherein the betaine polymer is a poly(carboxybetaine), poly(sulfobetaine), or poly(phosphobetaine) polymer.

7. The composition of claim 1, wherein the non-cationic lipid in component (ii) contains a zwitterionic moiety.

8. The composition of claim 7, wherein the zwitterionic moiety is selected from the group consisting of a phosphobetaine, phosphatidylcholine, carboxybetaine, sulfobetaine,

trimethylamine N-oxide, glutamic acid-lysine (EK)-containing peptide, or zwitterionic phosphatidyl serine moiety.

9. The composition of claim 1, wherein the non-cationic lipid is selected from the group consisting of a dioleoylphosphatidylglycerol (DOPG), dipalmitoylphosphatidylglycerol (DPPG), dioleoylphosphatidylethanolamine (DOPE), palmitoyloleoyl-phosphatidylethanolamine (POPE), dipalmitoylphosphatidylethanolamine (DPPE), dimyristoylphosphoethanolamine (DMPE), distearoylphosphatidylethanolamine (DSPE), 16-O-monomethyl-phospho ethanolamine, 16-O-dimethyl-phosphoethanolamine, 18-1-trans-phosphoethanolamine, 1-stearoyl-2-oleoyl phosphatidyethanolamine (SOPE), and 1,2-dioleoyl-sn glycero-3-phophoethanolamine (transDOPE).

10. The composition of claim 1, wherein component (ii) excludes a polyalkylene oxide segment.

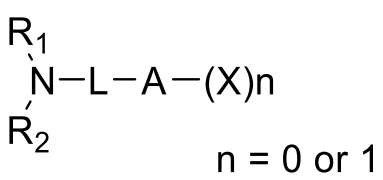
11. The composition of claim 1, wherein the non-cationic lipid in component (ii) is a phospholipid.

12. The composition of claim 11, wherein the phospholipid is a phosphatidyl serine lipid.

13. The composition of claim 1, wherein the cationic or ionizable lipid in component (iii) possesses a secondary, tertiary, or quaternary amino group.

14. The composition of claim 1, wherein the cationic or ionizable lipid in component (iii) possesses a secondary, tertiary, or quaternary group along with a functional group which is negatively charged under physiological conditions.

15. The composition of Claim 14, where the cationic or ionizable lipid comprises:



wherein:

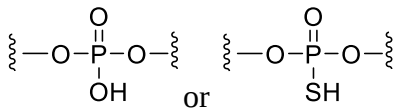
R_1/R_2 = H or an alkyl group and wherein the alkyl group can be saturated, unsaturated, branched, and/or unbranched, and can further comprise one or more heteroatoms including but not limited to N, O, F, Si, P, S, Cl, Br, and F;

L comprises a covalent linker group between N and A, wherein the covalent linker group can comprise one or more of $-CH_2-$, $-CH_2CH(OH)-$, $-CH_2CHClCH_2-$, $-CH_2OCH_2-$, $-CH_2SCH_2-$, $-CH_2SSCH_2-$, $-CH_2COOCH_2-$, C, H, and can further comprise one or more heteroatoms including but not limited to N, O, F, Si, P, S, Cl, Br, and F; and

A-(X)n is a functional group that is negatively charged under certain pH conditions and can comprise:

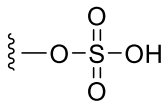
(i) A(X)n is a carboxylic acid group (A = -COOH and n=0) or

(ii) A(X)n is a phosphate, where A =



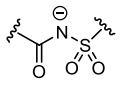
and n = 1. X = H or an alkyl group that is saturated or unsaturated, branched or not branched, all-carbon or containing heteroatoms such as but not limited to N, O, F, Si, P, S, Cl, Br, and F or

(iii) A(X)n is a sulfonic acid group, where A =



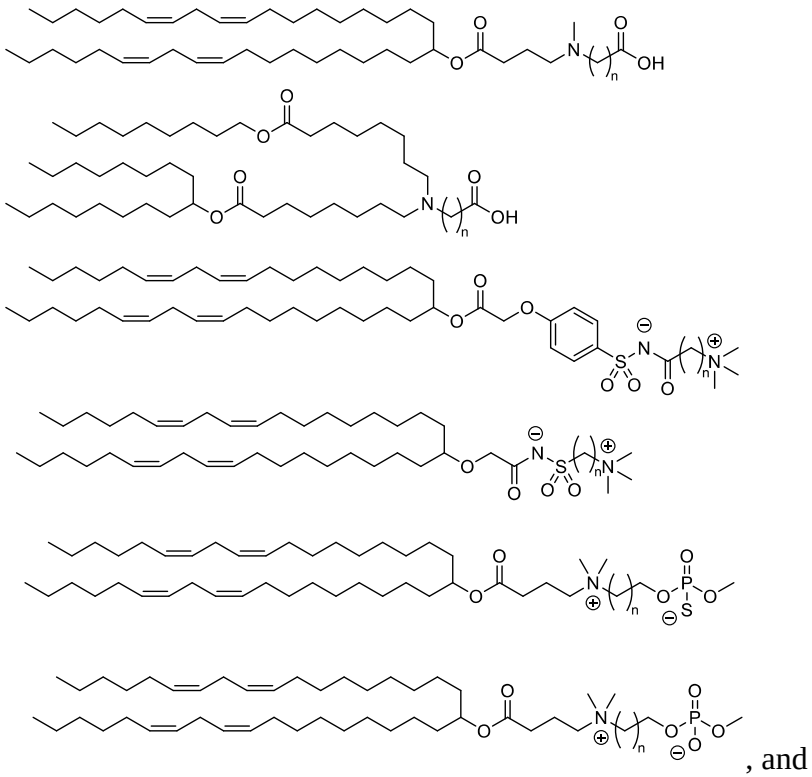
and n = 0

(iv) A(X)n is a sulfonamide group, where A =



and n = 1, X = H or an alkyl group that is saturated or unsaturated, branched or not branched, all carbon and hydrogen or containing heteroatoms such as but not limited to N, O, F, Si, P, S, Cl, Br, and F.

16. The composition of Claim 14, where the functional group is selected from the group consisting of:



, and

wherein n=1 to 10.

17. The composition of claim 1, wherein the cationic or ionizable lipid in component (iii) excludes a polyalkylene oxide segment.

18. The composition of claim 1, wherein the lipid nanoparticle composition further comprises: (v) cholesterol or derivative thereof.

19. The composition of claim 1, wherein the therapeutic substance in component (iv) is a nucleic acid molecule.

20. The composition of claim 19, wherein the nucleic acid molecule is an RNA.

21. The composition of claim 20, wherein the RNA is mRNA.

22. The composition of claim 20, wherein the RNA is viral mRNA.

23. The composition of claim 20, wherein the RNA is selected from the group consisting of message RNA (mRNA), small interfering RNA (siRNA), microRNA (miRNA), circularRNA (circRNA), long-noncoding RNA (lncRNA), antisense oligonucleotide (ASO), a CRISPR-related RNA, a Cas nuclease mRNA, a guide RNA, a single-guide RNA, and combinations thereof.

24. The composition of claim 20, wherein the therapeutic substance is a spike protein of a virus.

25. Use of ~~A method of delivering a therapeutic substance to a subject, the method comprising administering to said subject~~ a lipid nanoparticle composition comprising:

(i) at least one zwitterionic polymer-containing lipid in which a lipid moiety is covalently attached to a zwitterionic polymer;

(ii) at least one non-cationic lipid selected from charged and uncharged lipids, wherein the non-cationic lipid is not attached to a polymer;

(iii) at least one cationic or ionizable lipid containing a secondary, tertiary, or quaternary amino group; and

(iv) at least one therapeutic substance,

for the manufacture of a therapeutic substance for use in a method of delivering the therapeutic substance to a subject, where the lipid nanoparticle composition is to be administered to said subject.

26. The ~~method~~ use of claim 25, wherein the lipid nanoparticle composition is to be delivered to cells of the subject.

27. The ~~method~~ use of claim 25, wherein the therapeutic substance is a nucleic acid molecule, and administration thereof results in gene therapy of the subject.

28. The ~~method~~ use of claim 25, wherein the therapeutic substance is a nucleic acid molecule, and administration thereof results in vaccination of the subject.

29. The ~~method~~ use of claim 25, wherein said lipid moiety in component (i) is a diacylglyceride.

30. The ~~method~~ use of claim 25, wherein component (i) excludes a polyalkylene oxide segment.

31. The ~~method~~ use of claim 25, wherein the zwitterionic polymer in component (i) is selected from the group consisting of a poly(carboxybetaine) (PCB), a poly(sulfobetaine), a poly(zwitterionic phosphobetaine), glutamic acid-lysine (EK)-containing polypeptide, poly(phosphatidylcholine), and a poly(trimethylamine N-oxide) polymer.

32. The ~~method~~ use of claim 25, wherein the zwitterionic polymer in component (i) is a betaine polymer.

33. The ~~method~~ use of claim 32, wherein the betaine polymer is a carboxy betaine polymer.

34. The ~~method~~ use of claim 25, wherein the non-cationic lipid in component (ii) contains a zwitterionic moiety.

35. The ~~method~~ use of claim 34, wherein the zwitterionic moiety is selected from the group consisting of a phosphobetaine, phosphatidylcholine, carboxybetaine, sulfobetaine, trimethylamine N-oxide, glutamic acid-lysine (EK)-containing peptide, or zwitterionic phosphatidyl serine moiety.

36. The ~~method~~ use of claim 25, wherein the non-cationic lipid is selected from the group consisting of a dioleoylphosphatidylglycerol (DOPG), dipalmitoylphosphatidylglycerol (DPPG), dioleoylphosphatidylethanolamine (DOPE), palmitoyloleoyl-phosphatidylethanolamine (POPE), dipalmitoylphosphatidylethanolamine (DPPE), dimyristoylphosphoethanolamine (DMPE), distearoylphosphatidylethanolamine (DSPE), 16-O-monomethyl-phospho ethanolamine, 16-O-dimethyl-phosphoethanolamine, 18-1-trans-phosphoethanolamine, 1-stearoyl-2-oleoyl phosphatidyethanolamine (SOPE), and 1,2-dioleoyl-sn glycero-3-phophoethanolamine (transDOPE).

37. The ~~method~~ use of claim 25, wherein component (ii) excludes a polyalkylene oxide segment.

38. The ~~method~~ use of claim 25, wherein the non-cationic lipid in component (ii) is a phospholipid.

39. The ~~method~~ use of claim 38, wherein the phospholipid is a phosphatidyl serine lipid.

40. The ~~method~~ use of claim 25, wherein the cationic or ionizable lipid possesses a secondary, tertiary, or quaternary amino group.

41. The ~~method~~ use of claim 25, wherein the cationic or ionizable lipid excludes a polyalkylene oxide segment.

42. The ~~method~~ use of claim 25, wherein the lipid nanoparticle composition further comprises: (v) cholesterol or derivative thereof.

43. The ~~method~~ use of claim 25, wherein the therapeutic substance is a nucleic acid molecule.

44. The ~~method~~ use of claim 43, wherein the nucleic acid molecule is an RNA.

45. The ~~method~~ use of claim 44, wherein the RNA is mRNA.

46. The ~~method~~ use of claim 44, wherein the RNA is selected from the group consisting of message RNA (mRNA), small interfering RNA (siRNA), microRNA (miRNA), circularRNA (circRNA), long-noncoding RNA (lncRNA), antisense oligonucleotide (ASO), viral mRNA, CRISPR RNA, Cas nuclease mRNA, guide RNA, single-guide RNA, and combinations thereof.

47. The ~~method~~ use of claim 25, wherein the therapeutic substance is a spike protein of a virus.

48. A lipid composition containing a lipid moiety attached to a secondary, tertiary, or quaternary amine group along with a functional group, wherein the functional group is negatively charged under physiological conditions.

49. A lipid composition comprising the lipid moiety of claim 15.

50. A lipid composition comprising the lipid moiety of claim 16.

51. Use of ~~a~~the lipid nanoparticle composition of any one of claims 1-24 for the manufacture of a therapeutic agent for use in a~~A~~ method for targeted delivery of ~~a~~ the

therapeutic agent to a secondary lymphoid organ (SLO) in a subject, the method comprising:

obtaining ~~a~~ the lipid nanoparticle composition ~~of any one of claims 1-24~~, the lipid nanoparticle composition further comprising a phosphoserine-containing lipid (PS)~~; and~~,

wherein ~~administering~~ an effective amount of the lipid nanoparticle composition is to be administered to the subject, and

wherein the therapeutic agent is to be targeted to a secondary lymphoid organ (SLO) of the subject.

52. The ~~method~~ use of claim 51, wherein the therapeutic agent comprises a nucleic acid molecule.

53. The ~~method~~ use of claim 51, wherein the phosphoserine-containing lipid is selected from the group consisting of 1,2-dioleoyl-sn-glycero-3-phospho-L-serine (DOPS), naturally occurring PS-lipid, L-α-phosphatidylserine, and/or zwitterionic PS-lipid.

54. The ~~method~~ use of claim 51, wherein the SLO is selected from spleen and lymph nodes.

55. The ~~method~~ use of claim 51, wherein the targeted delivery of the therapeutic agent carries out cancer immunotherapy, autoimmune disease immunotherapy, vaccination and/or gene editing.

56. Use of ~~a~~the lipid nanoparticle composition of any one of claims 1-24 for the manufacture of a therapeutic agent for use in a~~A~~ method for targeted delivery of ~~a~~the therapeutic agent to macrophages in a subject, the method comprising:

obtaining ~~a~~ the lipid nanoparticle composition ~~of any one of claims 1-24~~, the lipid nanoparticle composition further comprising a phosphoserine-containing lipid (PS)~~; and~~ ,

wherein ~~administering~~ an effective amount of the lipid nanoparticle composition is to be administered to the subject, and

wherein the therapeutic agent is to be targeted to macrophages of the subject.

57. The ~~method~~ use of claim 56, wherein the therapeutic agent comprises a nucleic acid molecule.

58. The ~~method~~ use of claim 56, wherein the phosphoserine-containing lipid is selected from the group consisting of 1,2-dioleoyl-sn-glycero-3-phospho-L-serine (DOPS), naturally occurring PS-lipid, L-α-phosphatidylserine, and/or zwitterionic PS-lipid.

59. The ~~method~~ use of claim 56, wherein the therapeutic agent is to be targeted to macrophages of the subject thereby further targeting the therapeutic agent to the spleen and/or lymph nodes.

60. The ~~method~~ use of claim 56, wherein the targeted delivery of the therapeutic agent carries out cancer immunotherapy, autoimmune disease immunotherapy, vaccination, and/or gene editing.

61. Use of a lipid nanoparticle composition for the manufacture of a therapeutic agent for use in a~~A~~ method for targeted delivery of ~~a~~ the therapeutic agent to a secondary lymphoid organ (SLO) in a subject, the method comprising:

obtaining a lipid nanoparticle composition, the lipid nanoparticle composition further comprising a phosphoserine-containing lipid (PS)~~; and~~ ,

wherein ~~administering~~ an effective amount of the lipid nanoparticle composition is to be administered to the subject, and

wherein the therapeutic agent is to be targeted to a secondary lymphoid organ (SLO) of the subject.

62. Use of ~~a~~the lipid composition of any one of claims 48-50 for the manufacture of a therapeutic agent for use in a~~A~~ method for targeted delivery of the~~a~~ therapeutic agent to a secondary lymphoid organ (SLO) in a subject, the method comprising:

obtaining ~~a~~ the lipid ~~nanoparticle~~ composition ~~of any one of claims 48-50~~, the lipid ~~nanoparticle~~ composition further comprising a phosphoserine-containing lipid (PS)~~; and~~ ,

wherein ~~administering~~ an effective amount of the lipid ~~nanoparticle~~ composition is to be administered to the subject, and

wherein the therapeutic agent is to be targeted to a secondary lymphoid organ (SLO) of the subject.

63. Use of a lipid nanoparticle composition for the manufacture of a therapeutic agent for use in a~~A~~ method for targeted delivery of ~~a~~ the therapeutic agent to macrophages in a subject, the method comprising:

obtaining a lipid nanoparticle composition, the lipid nanoparticle composition further comprising a phosphoserine-containing lipid (PS)~~; and~~,

wherein ~~administering~~ an effective amount of the lipid nanoparticle composition is to be administered to the subject, and

wherein the therapeutic agent is to be targeted to macrophages of the subject.

64. Use of ~~a~~the lipid composition of any one of claims 48-50 for the manufacture of a therapeutic agent for use in a~~A~~ method for targeted delivery of the~~a~~ therapeutic agent to macrophages in a subject, the method comprising:

obtaining ~~a~~ the lipid ~~nanoparticle~~ composition ~~of any one of claims 48-50~~, the lipid ~~nanoparticle~~ composition further comprising a phosphoserine-containing lipid (PS)~~; and~~ ,

wherein ~~administering~~ an effective amount of the lipid ~~nanoparticle~~ composition is to be administered to the subject,

wherein the therapeutic agent is to be targeted to macrophages of the subject.

65. The lipid nanoparticle composition of any one of claims 1-24 or the lipid composition of any one of claims 48-50 for use in therapy.