CLAIMS

WHAT IS CLAIMED IS:

1. A composition comprising

a carrier capable of entering a polarized epithelial cell or transcytosing across a polarized epithelial cell; and

a heterologous payload, wherein a molar ratio of the heterologous payload to the carrier is greater than 1:1.

2. The composition of claim 1, wherein the composition comprises a transition metal cation.

3. The composition of claim 2, wherein the transition metal cation is selected from the group consisting of Fe^{2+}, Mn^{2+}, Zn^{2+}, Co^{2+}, Ni^{2+}, and Cu^{2+}.

4. The composition of claim 3, wherein the transition metal cation is Zn^{2+}.

5. The composition of claim 1, wherein the composition comprises a polycation.

6. The composition of claim 5, wherein the polycation is protamine.

7. The composition of any one of claims 1-6, wherein the carrier comprises a portion of a Cholix polypeptide.

8. The composition of claim 7, wherein the carrier consists of a portion of a Pseudomonas exotoxin A.

9. The composition of claim 7, wherein the carrier consists of a portion of a Cholix polypeptide.

10. The composition of claim 8, wherein the Cholix polypeptide consists of an amino acid sequence with a C-terminus at any one of amino acid positions 206 to 425 of SEQ ID NO: 7

11. The composition of claim 8, wherein the Cholix polypeptide consists of an amino acid sequence with a C-terminus at any one of amino acid positions 150 to 205 of SEQ ID NO: 7.

12. The composition of claim 8, wherein the Cholix polypeptide consists of an amino acid sequence with a C-terminus at any one of amino acids 150 to 195 of SEQ ID NO: 7.

13. The composition of claim 8, wherein the Cholix polypeptide consists of an amino acid sequence with an N-terminus at any one of amino acid positions 1 to 41 of SEQ ID NO: 7.

14. The composition of claim 8, wherein the Cholix polypeptide consists of an amino acid sequence with an N-terminus at any one of amino acid positions 35 to 40 of SEQ ID NO: 7.

15. The composition of claim 8, wherein the Cholix polypeptide consists of an amino acid sequence from amino acid position 40 of the sequence set forth in SEQ ID NO: 7 to any one of amino acid positions 150 to 205 of the sequence set forth in SEQ ID NO: 7.

16. The composition of claim 8, wherein the Cholix polypeptide has a C-terminus at any one of amino acid positions 150 to 187 of the sequence set forth in SEQ ID NO: 7.

17. The composition of claim 8, wherein the Cholix polypeptide consists of the amino acid sequence set forth in SEQ ID NO: 8.

18. The composition of claim 8, wherein the Cholix polypeptide consists of the amino acid sequence set forth in SEQ ID NO: 9 or SEQ ID: NO: 10.

19. The composition of any one of claims 10-14, wherein amino acids positions are numbered based on alignment of the Cholix polypeptide to the sequence set forth in SEQ ID NO: 7, wherein amino acid positions are numbered from N-terminus to C-terminus and starting with position 1 at the N-terminus.

20. The composition of claim 1, wherein the heterologous payload is selected from the group consisting of a macromolecule, small molecule, peptide, polypeptide, nucleic acid, mRNA, miRNA, shRNA, siRNA, antisense molecule, antibody, DNA, plasmid, vaccine, polymer nanoparticle, and a catalytically-active material.

21. The composition of claim 20, wherein the heterologous payload is a therapeutic payload.

22. The composition of claim 1, wherein the heterologous payload is selected from the group consisting of a dye and radiopharmaceutical, hormone, cytokine, anti-TNF agent, glucose lowering agent, tumor associated antigen, peptide, and polypeptide.

23. The composition of claim 1, wherein the heterologous payload is a polypeptide that is a modulator of inflammation in a gastrointestinal tract.

24. The composition of claim 1, wherein the heterologous payload is a glucagon-like peptide-2 (GLP-2) analog.

25. The composition of claim 24, wherein the GLP-2 analog is Teduglutide.

26. The composition of claim 1, wherein the heterologous payload is a cytokine.

27. The composition of claim 26, wherein the cytokine is selected from the group consisting of IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16, IL-17, IL-18, IL-19, IL-20, IL-21, IL-22, IL-23, IL-24, IL-25, IL-26, IL-27, IL-28, IL-29, and IL-30.

28. The composition of claim 27, wherein the cytokine is IL-10.

29. The composition of claim 28, wherein the cytokine is IL-22.

30. The composition of claim 26, wherein the cytokine lacks a native secretion signal.

31. The composition of claim 21, wherein the therapeutic payload is a hormone.

32. The composition of claim 31, wherein the hormone is a human growth hormone (hGH).

33. The composition of claim 1, wherein the heterologous payload is a glucose-lowering agent.

34. The composition of claim 1, wherein the heterologous payload is an incretin, glucagon proprotein, glucagon peptide, glucagon-like peptide 1, glucagon-like peptide 2, glicentin, glicentin-related polypeptide, gastric inhibitory polypeptide preprotein, gastric inhibitory polypeptide, dipeptidyl peptidase 4, glucose transporter member 4, preproglucagon, insulin receptor substrate 1, insulin, insulin analog, apolipoprotein A-II, solute carrier family 2, facilitated glucose transporter member 1, glycogen synthase 1, glycogen synthase 2, tyrosine-protein phosphatase non-receptor type 1, RAC-alpha serine threonine-protein kinase, peroxisome proliferator-activated receptor gamma, hexokinase 3, phosphatidylinositol-3,4,5-triphosphate 3-phosphatase and dual-specificity protein, pyruvate dehydrogenase kinase 1, calcium-binding and coiled-coil domain-containing protein 1, Max-like protein X, fructose-bisphosphate aldolase A, glucagon-like peptide 1 receptor, glucagon-like peptide 2 receptor, gastric inhibitory polypeptide receptor, insulin-like growth factor 1 receptor, insulin-like growth factor 2 receptor, insulin receptor, GLP-1 agonist-exenatide, GLP-1 agonist-Liraglutide, exenatide, exendin-4, exendin-3, GIPR agonist (Des-Ala2-GIP1-30), GIPR agonist-Truncated GIP1-30, GLP-1R agonist (aa 1-37 of GIP), GLP-1R agonist (aa 7-36 of GIP), lixisenatide (tradenames Adlyxin®, and Lyxumia®, Sanofi), liraglutide (tradename Victoza®, Novo Nordisk A/S), semaglutide (tradename Ozempic®, Novo Nordisk A/S), albiglutide (tradename Tanzeum®, GlaxoSmithKline; GLP-1 dimer fused to albumin), dulaglutide (tradename Trulicity®, Eli Lilly), glucose-dependent insulinotropic polypeptide, multi-specific peptide agonist, Tirzepatide (Eli Lilly), SAR425899 (Sanofi), dual amylin calcitonin receptor agonist DACRA-089, glargine/Lantus®, glulisin/Apidra®, glarine/Toujeo®, insuman®, detemir/Levemir®, lispro/Humalog®/Liprolog®, Degludec/DegludecPlus, insulin aspart, insulin and analogues (e.g. LY-2605541, LY2963016, NN1436), PEGylated insulin Lispro, Humulin®, Linjeta, SuliXen®, NN1045, Insulin plus SymlinTM, PE0139, fast-acting and short-acting insulins (e.g. Linjeta, PH20, NN1218, HinsBet), (APC-002) hydrogel, oral, inhalable, transdermal and sublingual insulins (e.g. Exubera®, Nasulin®, Afrezza®, Tregopil®, TPM 02, Capsulin, Oral-lyn®, Cobalamin®, oral insulin, ORMD-0801, NN1953, NN1954, NN1956, VIAtab, and Oshadi oral insulin), or an exendin-4 analog, wherein the exendin-4 analog is desPro36-exendin-4(1-39)-Lys6NH2; H-des(Pro36, 37)-exendin-4-Lys4-NH2; H-des(Pro36, 37)-exendin-4-Lys5-NH2; desPro36[Asp28]exendin-4 (1-39); desPro36[IsoAsp28]exendin-4 (1-39); desPro36[Met(O)14, Asp28]exendin-4 (1-39); desPro36[Met(O)14, IsoAsp28]exendin-4 (1-39); desPro36[Trp(O2) 26, Asp28]exendin-4 (1-39); or desPro36[Trp(O2) 25,

IsoAsp28]exendin-4 (1-39); desPro36[Met(O)14 Trp(O2)25, Asp28]exendin-4 (1-39); or desPro36[Met(O)14 Trp(O2)25, IsoAsp28]exendin-4 (1-39).

35. The composition of claim 1, wherein the heterologous paylaod is insulin or an insulin analog.

36. The composition of claim 1, wherein the heterologous payload is exenatide.

37. The composition of claim 1, wherein the heterologous payload comprises a fluorescent label.

38. The composition of claim 37, wherein the fluorescent label is a fluorescein.

39. The composition of claim 38, wherein the heterologous payload is an exenatide-fluorescein complex.

40. The composition of claim 1, wherein the composition is resistant to cleavage by a pancreatic enzyme.

41. The composition of claim 40, wherein at least 50% of the carrier is intact at 2 hours in a pancreatin assay, wherein the pancreatin assay comprises incubating the composition comprising 100 µg of the carrier with 10 µg of pancreatin in 100 µL phosphate buffered saline (PBS) at 37 °C..

42. The composition of claim 2, wherein a molar ratio of the transition metal cation to the carrier is from about 100:1 to about 300,000:1.

43. The composition of claim 2, wherein a molar ratio of the transition metal cation to the carrier is from about 1000:1 to about 30,000:1.

44. The composition of claim 2, wherein a molar ratio of the transition metal cation to the carrier is from about 1000:1 to about 10,000: 1.

45. The composition of claim 6, wherein a molar ratio of the protamine to the carrier is from about 10:1 to about 0.01:1.

46. The composition of claim 1, wherein the molar ratio of the heterologous payload to the carrier is from about 2:1 to about 6000:1.

47. The composition of claim 6, wherein a molar ratio of the protamine to the carrier is about 1:1

48. The composition of claim 1, wherein the molar ratio of the heterologous payload to the carrier is from about 2:1 to about 10:1.

49. The composition of claim 1, wherein the molar ratio of the heterologous payload to the carrier is about 7:1.

50. The composition of claim 1, wherein the molar ratio of the heterologous payload to the carrier is about 7.16:1.

51. The composition of claim 1, wherein the heterologous payload is a polypeptide comprising the sequence of SEQ ID NO: 11 or SEQ ID NO: 14.

52. The composition of claim1, wherein the heterologous payload is a polypeptide comprising the sequence of SEQ ID NO: 18 or SEQ ID NO: 19.

53. The composition of claim 1, wherein the heterologous payload is a polypeptide comprising the sequence of SEQ ID NO: 20.

54. The composition of claim 1, wherein the heterologous payload is a polypeptide comprising the sequence of SEQ ID NO: 21.

55. The composition of claim 1, wherein the heterologous payload is a polypeptide comprising the sequence of SEQ ID NO: 22.

56. The composition of claim 1, wherein the composition is encapsulated.

57. The composition of claim 56, wherein the encapsulated composition is configured to release the heterologous payload under a first condition but not under a second condition.

58. The composition of claim 56, wherein the encapsulated composition is configured to release the heterologous payload at a high pH but not at a low pH.

59. The composition of claim 56, wherein the encapsulated composition comprises an enteric coating.

60. The composition of claim 1, wherein the composition is a particle.

61. The composition of claim 1, wherein the composition comprises a polycation.

62. The composition of claim 1, whereinwherein the carrier is capable of transporting the heterologous payload in the polarized epithelial cell or transcytosing the heterologous payload across a polarized epithelial cell.

63. The composition of claim 61, wherein the carrier is coupled to the polycation.

64. The composition of claim 61, wherein the polycation is protamine, poly-lysine, poly-ornithine, poly-ethylene-imine (PEI), prolamin, protamine, polyvinyl pyrrolidone (PVP), polyarginine, polyvinylamine, or a combination thereof.

65. The composition of claim 61, wherein the polycation is a protamine salt.

66. The composition of claim 65, wherein the protamine salt is protamine sulfate, protamine acetate, protamine bromide, protamine chloride, protamine caproate, protamine trifluoroacetate, protamine HCO_3, protamine propionate, protamine lactate, protamine formate, protamine nitrate, protamine citrate, protamine monohydrogenphosphate, protamine dihydrogenphosphate, protamine tartrate, or protamine perchlorate.

67. The composition of claim 66, wherein the protamine salt is protamine sulfate.

68. A composition comprising a carrier, wherein the carrier is capable of entering a polarized epithelial cell or transcytosing across a polarized epithelial cell, wherein at least 60%

of the carrier is intact at 0.5 hours in a pancreatin assay, wherein the pancreatin assay comprises incubating the composition comprising 100 µg of the carrier with 10 µg of pancreatin in 100 µL phosphate buffered saline (PBS) at 37 °C.

69. The composition of claim 68, wherein at least 90% of the carrier is intact at 2 hours in the pancreatin assay.

70. The composition of claim 68, further comprising a cation.

71. The composition of claim 70, wherein the cation is a metal cation or a polycation.

72. The composition of claim 71, wherein the cation is a metal cation.

73. The composition of claim 72, wherein the metal cation is a transition metal cation.

74. The composition of claim 68, wherein the carrier consists of a portion of a Pseudomonas exotoxin A.

75. The composition of claim 68, wherein the carrier consists of a portion of a Cholix polypeptide.

76. The composition of claim 74, wherein the Cholix polypeptide consists of an aminoacid sequence with a C-terminus at any one of amino acid positions 206 to 425 of SEQ ID NO: 7.

77. The composition of claim 74, wherein the Cholix polypeptide consists of an amino acid sequence with a C-terminus at any one of amino acid positions 150 to 205 of SEQ ID NO: 7.

78. The composition of claim 74, wherein the Cholix polypeptide consists of an amino acid sequence with a C-terminus at any one of amino acids 150 to 195 of SEQ ID NO: 7.

79. The composition of claim 74, wherein the Cholix polypeptide consists of an amino acid sequence with an N-terminus at any one of amino acid positions 1 to 41 of SEQ ID NO: 7.

80. The composition of claim 74, wherein the Cholix polypeptide consists of an amino acid sequence with an N-terminus at any one of amino acid positions 35 to 40 of SEQ ID NO: 7.

81. The composition of claim 74, wherein the Cholix polypeptide consists of an amino acid sequence from amino acid position 40 of the sequence set forth in SEQ ID NO: 7 to any one of amino acid positions 150 to 205 of the sequence set forth in SEQ ID NO: 7.

82. The composition of claim 74, wherein the Cholix polypeptide has an C-terminus at any one of amino acid positions 150 to 187 of the sequence set forth in SEQ ID NO: 7.

83. The composition of claim 74, wherein the Cholix polypeptide consists of the amino acid sequence set forth in SEQ ID NO: 8.

84. The composition of claim 74, wherein the Cholix polypeptide consists of the amino acid sequence set forth in SEQ ID NO: 9 or SEQ ID: NO: 10.

85. The composition of any one of claims 76-84, wherein amino acids positions are numbered based on alignment of the Cholix polypeptide to the sequence set forth in SEQ ID NO: 7, wherein amino acid positions are numbered from N-terminus to C-terminus and starting with position 1 at the N-terminus.

86. A composition comprising a Cholix variant ending at position 195-347 and a heterologous payload, wherein the heterologous payload is a glucose regulating agent.

87. The composition of claim 86, wherein the ending position of the Cholix variant is determined relative to SEQ ID NO: 7.

88. The composition of claim 86, wherein the carrier is capable of transcytosing the heterologous payload across a polarized epithelial cell.

89. The composition of claim 86, wherein the glucose regulating agent is a glucose-lowering agent.

90. The composition of claim 89, wherein the glucose-lowering agent is an incretin, glucagon proprotein, glucagon peptide, glucagon-like peptide 1, glucagon-like peptide 2, glicentin, glicentin-related polypeptide, gastric inhibitory polypeptide preprotein, gastric inhibitory polypeptide, dipeptidyl peptidase 4, glucose transporter member 4, preproglucagon, insulin receptor substrate 1, insulin, insulin analog, apolipoprotein A-II, solute carrier family 2, facilitated glucose transporter member 1, glycogen synthase 1, glycogen synthase 2, tyrosine-protein phosphatase non-receptor type 1, RAC-alpha serine threonine-protein kinase, peroxisome proliferator-activated receptor gamma, hexokinase 3, phosphatidylinositol-3,4,5-triphosphate 3-phosphatase and dual-specificity protein, pyruvate dehydrogenase kinase 1, calcium-binding and coiled-coil domain-containing protein 1, Max-like protein X, fructose-bisphosphate aldolase A, glucagon-like peptide 1 receptor, glucagon-like peptide 2 receptor, gastric inhibitory polypeptide receptor, insulin-like growth factor 1 receptor, insulin-like growth factor 2 receptor, insulin receptor, GLP-1 agonist-exenatide, GLP-1 agonist-Liraglutide, exenatide, exendin-4, exendin-3, GIPR agonist (Des-Ala2-GIP1-30), GIPR agonist-Truncated GIP1-30, GLP-1R agonist (aa 1-37 of GIP), GLP-1R agonist (aa 7-36 of GIP), lixisenatide (tradenames Adlyxin®, and Lyxumia®, Sanofi), liraglutide (tradename Victoza®, Novo Nordisk A/S), semaglutide (tradename Ozempic®, Novo Nordisk A/S), albiglutide (tradename Tanzeum®, GlaxoSmithKline; GLP-1 dimer fused to albumin), dulaglutide (tradename Trulicity®, Eli Lilly), glucose-dependent insulinotropic polypeptide, multi-specific peptide agonist, Tirzepatide (Eli Lilly), SAR425899 (Sanofi), dual amylin calcitonin receptor agonist DACRA-089, glargine/Lantus®, glulisin/Apidra®, glarine/Toujeo®, insuman®,

detemir/Levemir®, lispro/Humalog®/Liprolog®, Degludec/DegludecPlus, insulin aspart, insulin and analogues (e.g. LY-2605541, LY2963016, NN1436), PEGylated insulin Lispro, Humulin®, Linjeta, SuliXen®, NN1045, Insulin plus SymlinTM, PE0139, fast-acting and short-acting insulins (e.g. Linjeta, PH20, NN1218, HinsBet), (APC-002) hydrogel, oral, inhalable, transdermal and sublingual insulins (e.g. Exubera®, Nasulin®, Afrezza®, Tregopil®, TPM 02, Capsulin, Oral-lyn®, Cobalamin®, oral insulin, ORMD-0801, NN1953, NN1954, NN1956, VIAtab, and Oshadi oral insulin), or an exendin-4 analog, wherein the exendin-4 analog is desPro36-exendin-4(1-39)-Lys6NH2; H-des(Pro36, 37)-exendin-4-Lys4-NH2; H-des(Pro36, 37)-exendin-4-Lys5-NH2; desPro36[Asp28]exendin-4 (1-39); desPro36[IsoAsp28]exendin-4 (1-39); desPro36[Met(O)14, Asp28]exendin-4 (1-39); desPro36[Met(O)14, IsoAsp28]exendin-4 (1-39); desPro36[Trp(O2) 26, Asp28]exendin-4 (1-39); or desPro36[Trp(O2) 25, IsoAsp28]exendin-4 (1-39); desPro36[Met(O)14 Trp(O2)25, Asp28]exendin-4 (1-39); or desPro36[Met(O)14 Trp(O2)25, IsoAsp28]exendin-4 (1-39).

91. The composition of claim 86, wherein the heterologous payload comprises an incretin.

92. The composition of claim 86, wherein the heterologous payload comprises exenatide or insulin.

93. The composition of claim 86, wherein the composition comprises a particle.

94. The composition of claim 86, wherein the heterologous payload is exendin-3, efpeglenatide, semaglutide, GLP-1R agonist (aa 1-37 of GIP), GLP-1R agonist (aa 7-36 of GIP), tirzepatide, oxyntomodulin, GIPR agonist-truncated GIP1-30, dual amylin calcitonin receptor agonist, preproinsulin, insulin aspart, insulin glargine, or insulin lispro.

95. A composition comprising

a carrier derived from a bacterial toxin capable of entering a polarized epithelial cell or transcytosing across a polarized epithelial cell; and

a transition metal cation or a polycation, wherein the polycation is molecule or chemical complex having more than 2 positive charges.

96. The composition of claim 95, wherein the composition comprises a transition metal cation.

97. The composition of 96, wherein the transition metal cation is selected from the group consisting of Fe^{2+}, Mn^{2+}, Zn^{2+}, Co^{2+}, Ni^{2+}, and Cu^{2+}.

98. The composition of claim 95, wherein the transition metal cation is Zn^{2+}.

99. The composition of claim 95 , wherein the composition comprises the polycation.

100. The composition of claim 99, wherein the polycation is protamine, poly-lysine, poly-ornithine, poly-ethylene-imine (PEI), prolamin, protamine, polyvinyl pyrrolidone (PVP), polyarginine, polyvinylamine, or a combination thereof.

101. The composition of claim 99, wherein the polycation is a protamine salt.

102. The composition of claim 99, wherein the protamine salt is protamine sulfate, protamine acetate, protamine bromide, protamine chloride, protamine caproate, protamine trifluoroacetate, protamine HCO_3, protamine propionate, protamine lactate, protamine formate, protamine nitrate, protamine citrate, protamine monohydrogenphosphate, protamine dihydrogenphosphate, protamine tartrate, or protamine perchlorate.

103. The composition of claim 99, wherein the protamine salt is protamine sulfate.

104. The composition of claim 95, further comprising a heterologous payload.

105. The composition of claim 103, wherein the heterologous payload comprises exenatide, insulin, or human growth hormone.

106. The composition of claim 95, wherein the carrier consists of Pseudomonas exotoxin A or a portion of a Pseudomonas exotoxin A.

107. The composition of claim 104, wherein the carrier consists of a polypeptide of SEQ ID NO: 69 or a portion of a SEQ ID NO: 69.

108. The composition of claim 95, wherein the carrier consists of a portion of a Cholix polypeptide.

109. The composition of claim 95, wherein the Cholix polypeptide consists of an amino acid sequence with a C-terminus at any one of amino acid positions 206 to 425 of SEQ ID NO: 1.

110. The composition of claim 95, wherein the Cholix polypeptide consists of an amino acid sequence with a C-terminus at any one of amino acid positions 150 to 205 of SEQ ID NO: 1.

111. The composition of claim 95, wherein the Cholix polypeptide consists of an amino acid sequence with a C-terminus at any one of amino acids 150 to 195 of SEQ ID NO: 1.

112. The composition of claim 95, wherein the Cholix polypeptide consists of an amino acid sequence with an N-terminus at any one of amino acid positions 1 to 41 of SEQ ID NO: 1.

113. The composition of claim 95, wherein the Cholix polypeptide consists of an amino acid sequence with an N-terminus at any one of amino acid positions 35 to 40 of SEQ ID NO: 1.

114. The composition of claim 95, wherein the Cholix polypeptide consists of an amino acid sequence from amino acid position 40 of the sequence set forth in SEQ ID NO: 7 to any one of amino acid positions 150 to 205 of the sequence set forth in SEQ ID NO: 7.

115. The composition of claim 95, wherein the Cholix polypeptide has a C-terminus at any one of amino acid positions 150 to 187 of the sequence set forth in SEQ ID NO: 7.

116. The composition of claim 95, wherein the Cholix polypeptide consists of the amino acid sequence set forth in SEQ ID NO: 8.

117. The composition of claim 95, wherein the Cholix polypeptide consists of the amino acid sequence set forth in SEQ ID NO: 9 or SEQ ID: NO: 10.

118. The composition of any one of claims 107-115, wherein amino acids positions are numbered based on alignment of the Cholix polypeptide to the sequence set forth in SEQ ID NO: 7, wherein amino acid positions are numbered from N-terminus to C-terminus and starting with position 1 at the N-terminus.

119. The composition of claim 95, wherein the composition comprises a particle.

120. A composition comprising insulin, wherein at least 20% of the insulin is intact at 1 hour in a pancreatin assay comprising incubating the composition comprising insulin with pancreatin in PBS at 37 °C.

121. The composition of claim 118, further comprising a carrier derived from a bacterial toxin, wherein the carrier is capable of transporting into the polarized epithelial cell or transcytosing across a polarized epithelial cell.

122. The composition of claim 119, wherein the carrier consists of a portion of a Cholix polypeptide.

123. The composition of claim 118, wherein the composition comprises a transition metal cation.

124. The composition of claim 121, wherein the transition metal cation is selected from the group consisting of Fe^{2+}, Mn^{2+}, Zn^{2+}, Co^{2+}, Ni^{2+}, and Cu^{2+}.

125. The composition of claim 121, wherein the transition metal cation is Zn^{2+}.

126. The composition of claim 118, wherein the composition comprises a polycation.

127. The composition of claim 125, wherein the polycation is protamine.

128. The composition of any one of claims 1-125, wherein the composition comprises a particle.

129. The composition of claim 126, wherein the particle comprises a microparticle.

130. The composition of claim 127, wherein the microparticle is formed by spray drying.

131. The composition of claim 126, wherein the particle has a diameter of about 50 nm to about 20 μm.

132. A pharmaceutical composition comprising the composition of any of claims 1-129.

133. A pharmaceutical composition comprising the composition of any of claims 1-129 and a preservative.

134. A pharmaceutical composition comprising the composition of any of claims 1-130 and a pharmaceutically acceptable excipient.

135. A method comprising administering to a subject the pharmaceutical composition of any one of claims 130-132.

136. The method of claim 133, wherein the subject has an inflammatory disease, an autoimmune disease, a cancer, or a metabolic disorder.

137. The method of claim 134, wherein the subject has a metabolic disorder.

138. The method of claim 135, the metabolic disorder is diabetes, diabetes as a consequence of obesity, hyperglycemia, dyslipidemia, hypertriglyceridemia, syndrome X, insulin resistance, impaired glucose tolerance (IGT), diabetic dyslipidemia, hyperlipidemia, fatty liver disease, nonalcoholic steatohepatitis (NASH), hepatitis, obesity, vascular disease, heart disease, stroke, impaired glucose tolerance, raised fasting glucose, insulin resistance, urinary albumin secretion, central obesity, hypertension, elevated triglycerides, elevated LDL cholesterol and reduced HDL cholesterol, hyperglycemia, hyperinsulinemia, dyslipidemia, ketosis, hypertriglyceridemia, syndrome X, insulin resistance, impaired fasting glucose, impaired glucose tolerance (IGT), diabetic dyslipidemia, gluconeogenesis, excess glycogenolysis, diabetic ketoacidosis, hypertriglyceridemia, hypertension, diabetic nephropathy, renal insufficiency, renal failure, hyperphagia, muscle wasting, diabetic neuropathy, diabetic retinopathy, diabetic coma, arteriosclerosis, coronary heart disease, peripheral artery disease, or hyperlipidemia.

139. A method comprising combining a bacterial derived carrier with a heterologous payload and a cation to produce a particle.

140. The method of claim 137, wherein the heterologous payload is selected from the group consisting of a dye, radiopharmaceutical, hormone, cytokine, anti-TNF agent, glucose lowering agent, tumor associated antigen, peptide, and polypeptide.

141. The method of claim 137, further comprising spray drying the bacterial derived carrier, the heterologous payload and the cation.

142. The method of claim 137, wherein the method comprises (a) preparing a mixture comprising the isolated carrier and payload; (b) preparing a mixture comprising protamine

sulfate and $NaPO_4$; and (c) combining the mixture of (a) to the mixture of (b) and allowing the combined mixture to set overnight at room temperature.

143. The method of claim 140, wherein the method further comprises step (d) disrupting the particles from step (c) into smaller particles by increasing the ionic strength of the combined mixture from step (c).

144. The method of claim 140, wherein the preparation of step (a) does not comprise $ZnCl_2$.

145. The method of claim 140, wherein the preparation of step (a) comprises $ZnCl_2$.

CLAIMS

WHAT IS CLAIMED IS:

1. A composition comprising

a carrier derived from a bacterial toxin capable of entering a polarized epithelial cell or transcytosing across a polarized epithelial cell; and

a transition metal cation or a polycation, wherein the polycation is a molecule or chemical complex having more than 2 positive charges.

2. The composition of claim 1, wherein the composition comprises the transition metal cation.

3. The composition of claim 2, wherein the transition metal cation is selected from the group consisting of Fe^{2+}, Mn^{2+}, Zn^{2+}, Co^{2+}, Ni^{2+}, and Cu^{2+}.

4. The composition of claim 3, wherein the transition metal cation comprises Zn^{2+}.

5. The composition of claim 1, wherein the composition comprises the polycation.

6. The composition of claim 5, wherein the polycation comprises protamine, poly-lysine, poly-ornithine, poly-ethylene-imine (PEI), prolamin, protamine, polyvinyl pyrrolidone (PVP), polyarginine, polyvinylamine, or a combination thereof.

7. The composition of claim 5, wherein the polycation comprises a protamine salt.

8. The composition of claim 7, wherein the protamine salt comprises protamine sulfate, protamine acetate, protamine bromide, protamine chloride, protamine caproate, protamine trifluoroacetate, protamine HCO_3, protamine propionate, protamine lactate, protamine formate, protamine nitrate, protamine citrate, protamine monohydrogenphosphate, protamine dihydrogenphosphate, protamine tartrate, or protamine perchlorate.

9. The composition of claim 7, wherein the protamine salt comprises protamine sulfate.

10. The composition of claim 1, further comprising a heterologous payload.

11. The composition of claim 10, wherein the heterologous payload comprises insulin or human growth hormone.

12. The composition of claim 1, wherein the carrier comprises Pseudomonas exotoxin A or a portion of the Pseudomonas exotoxin A.

13. The composition of claim 12, wherein the carrier comprises the sequence set forth in SEQ ID NO: 69 or a portion of the sequence set forth in SEQ ID NO: 69.

14. The composition of claim 1, wherein the carrier comprises a Cholix polypeptide.

15. The composition of claim 14, wherein the Cholix polypeptide consists of an amino acid sequence with a C-terminus at any one of amino acid positions 206 to 425, wherein the amino acid positions are based on alignment of the Cholix polypeptide to the sequence set forth in SEQ ID NO: 7, starting with position 1 at the N-terminus.

16. The composition of claim 14, wherein the Cholix polypeptide consists of an amino acid sequence with a C-terminus at any one of amino acid positions 150 to 205, wherein the amino acid positions are based on alignment of the Cholix polypeptide to the sequence set forth in SEQ ID NO: 7, starting with position 1 at the N-terminus.

17. The composition of claim 14, wherein the Cholix polypeptide consists of an amino acid sequence with a C-terminus at any one of amino acids 150 to 195, wherein the amino acid positions are based on alignment of the Cholix polypeptide to the sequence set forth in SEQ ID NO: 7, starting with position 1 at the N-terminus.

18. The composition of claim 14, wherein the Cholix polypeptide consists of an amino acid sequence with an N-terminus at any one of amino acid positions 1 to 41, wherein the amino acid positions are based on alignment of the Cholix polypeptide to the sequence set forth in SEQ ID NO: 7, starting with position 1 at the N-terminus.

19. The composition of claim 14, wherein the Cholix polypeptide consists of an amino acid sequence with an N-terminus at any one of amino acid positions 35 to 40, wherein the amino acid positions are based on alignment of the Cholix polypeptide to the sequence set forth in SEQ ID NO: 7, starting with position 1 at the N-terminus.

20. The composition of claim 14, wherein the Cholix polypeptide consists of an amino acid sequence from amino acid position 40 to any one of amino acid positions 150 to 205, wherein the amino acid positions are based on alignment of the Cholix polypeptide to the sequence set forth in SEQ ID NO: 7, starting with position 1 at the N-terminus.

21. The composition of claim 14, wherein the Cholix polypeptide has a C-terminus at any one of amino acid positions 150 to 187, wherein the amino acid positions are based on alignment of the Cholix polypeptide to the sequence set forth in SEQ ID NO: 7, starting with position 1 at the N-terminus.

22. The composition of claim 14, wherein the Cholix polypeptide consists of the amino acid sequence set forth in SEQ ID NO: 66, and the carrier further comprises a methionine N-terminal to the sequence set forth in SEQ ID NO: 66.

23. The composition of claim 14, wherein the Cholix polypeptide consists of the amino acid sequence set forth in SEQ ID NO: 2, and the carrier further comprises a methionine N-terminal to the sequence set forth in SEQ ID NO: 2.

24. The composition of claim 10, wherein the heterologous payload comprises an incretin.

25. The composition of claim 24, wherein the incretin comprises glucagon-like peptide-1 (GLP-1) or gastric inhibitory peptide (GIP).

26. The composition of claim 10, wherein the heterologous payload comprises an incretin mimetic peptide.

27. The composition of claim 26, wherein the incretin mimetic peptide comprises liraglutide, dulaglutide, semaglutide, exenatide, albiglutide, or lixisenatide.

28. The composition of claim 10, wherein the heterologous payload comprises tirzepatide.

29. The composition of claim 10, wherein the heterologous payload comprises glucagon-like peptide 2 (GLP-2) or a GLP-2 analog.

30. The composition of claim 29, wherein the heterologous payload comprises the GLP-2 analog, wherein the GLP-2 analog is teduglutide.