WHAT IS CLAIMED IS:

1. An extracellular vesicle (EV) comprising a biologically active molecule (BAM) covalently linked to the EV via an anchoring moiety (AM) according to the formula:

$$[AM]\text{-}L_1\text{-}[SP_1]\text{-}L_2\text{-}[SP_2]\text{-}L_3\text{-}[BAM] \quad \text{(Formula 1)}$$

wherein:

[AM] is the anchoring moiety;

L_1 is a cleavable or non-cleavable linkage;

L_2 and L_3 are optional cleavable or non-cleavable linkages;

SP_1 is an optional first spacer; and,

SP_2 is an optional second spacer.

2. The extracellular vesicle of claim 1, wherein the anchoring moiety [AM] comprises a sterol, a lipid, a vitamin, a peptide, or a combination thereof and optionally a spacer.

~~3. The extracellular vesicle of claim 2, wherein the optional spacer is an alkyl spacer.~~

~~4. The extracellular vesicle of claim 3, wherein the alkyl spacer is C1, C2, C3, C4, C5, C6, C7, C8, C9, C10, C11, C12, C13, C14, or C15.~~

~~5. The extracellular vesicle of claim 3, wherein the alkyl spacer is C6 or C8.~~

~~6. The extracellular vesicle of claim 2, wherein the optional spacer is a glycol spacer.~~

~~7. The extracellular vesicle of claim 5, wherein the glycol spacer has 2 (diethylene glycol), 3 (triethylene glycol), 4 (tetraethylene glycol; TEG), 5 (pentaethylene glycol), 6 (hexaethylene glycol; HEG), 7, 8, 9, 10, 11, 12, 13, 14, or 15 glycol units.~~

~~8. The extracellular vesicle of claim 5, wherein the glycol spacer is tetraethylene glycol (TEG).~~

~~9. The extracellular vesicle of claim 2, wherein the sterol is selected from the group consisting of cholesterol, ergosterol, 7-dehydrocholesterol, 24S-hydroxycholesterol, lanosterol, cycloartenol, fucosterol, saringosterol, campesterol, β-sitosterol, sitostanol, coprostanol, avenasterol, and stigmasterol.~~

~~10. The extracellular vesicle of claim 2, wherein the sterol is cholesterol.~~

~~11. The extracellular vesicle of claim 2, wherein the lipid is a fatty acid.~~

~~12. The extracellular vesicle of claim 11, wherein the fatty acid is a straight chain fatty acid.~~

~~13. The extracellular vesicle of claim 11, wherein the fatty acid is a straight chain fatty acid, a branched fatty acid, an unsaturated fatty acid, a monounsaturated fatty acid, a polyunsaturated fatty acid, a hydroxyl fatty acid, a polycarboxylic acid, or any combination thereof.~~

~~14. The extracellular vesicle of claim 12, wherein the straight chain fatty acid is butyric acid, caproic acid, caprylic acid, capric acid, lauric acid, myristic acid, palmitic acid, or stearic acid.~~

~~15. The extracellular vesicle of claim 12, wherein the straight chain fatty acid is palmitic acid.~~

~~16. The extracellular vesicle of claim 2, wherein the vitamin is vitamin E (tocopherol or tocotrienol), vitamin D, vitamin K, riboflavin, niacin, or pyridoxine.~~

~~17. The extracellular vesicle of claim 2, wherein the vitamin is vitamin E (tocopherol or tocotrienol).~~

~~18~~3. The ~~extracellular vesicle~~EV of ~~anyone of claims 1-17~~claim 1 or 2, wherein L_1, L_2, L_3, or any combination thereof is a cleavable linkage comprising a phosphodiester bond or a non-cleavable linkage comprising a phosphorothioate bond.

~~19. The extracellular vesicle of anyone of claims 1-18, wherein L_2 is an optional cleavable linkage comprising a phosphodiester bond or a non-cleavable linkage comprising a phosphorothioate bond.~~

~~20. The extracellular vesicle of anyone of claims 1-19, wherein L_3 is an optional cleavable linkage comprising a phosphodiester bond or a non-cleavable linkage comprising a phosphorothioate bond.~~

~~21~~4. The ~~extracellular vesicle~~EV of any one of claims 1-~~20~~3, wherein the SP_1 optional first spacer and/or the SP_2 an optional second spacer independently comprise an alkyl spacer, a glycol spacer, or a combination thereof.

~~22. The extracellular vesicle of claim 21, wherein the alkyl spacer is C1, C2, C3, C4, C5, C6, C7, C8, C9, C10, C11, C12, C13, C14, or C15.~~

~~23. The extracellular vesicle of claim 21, wherein the alkyl spacer is C3 or C6.~~

~~24. The extracellular vesicle of claim 21, wherein the glycol spacer has 2 (diethylene glycol), 3 (triethylene glycol), 4 (tetraethylene glycol; TEG), 5 (pentaethylene glycol), 6 (hexaethylene glycol; HEG), 7, 8, 9, 10, 11, 12, 13, 14, or 15 glycol units.~~

~~25. The extracellular vesicle of claim 21, wherein the glycol spacer is tetraethylene glycol (TEG) or hexaethylene glycol (HEG).~~

~~26. The extracellular vesicle of any one of claims 1 to 25, wherein each non-cleavable spacer is independently selected from alkyl, diethylene glycol, triethylene glycol, tetraethylene glycol (TEG), hexaethylene glycol (HEG), pentaethylene glycol, polyethylene glycol (PEG), glycerol, diglycerol, triglycerol, tetraglycerol (TG), pentaglycerol, a hexaglycerol (HG), polyglycerol (PG), succinimide, maleimide, or any combination thereof.~~

~~27. The extracellular vesicle of claim 26, wherein the polyethylene glycol (PEG) is characterized by the formula R_1-(O-CH_2-CH_2)$_n$- or R_1-(O-CH_2-CH_2)n-O-, wherein R1 is hydrogen, methyl or ethyl and n is an integer between 1 and 15.~~

~~28. The extracellular vesicle of claim 26, wherein the polyglycerol (PG) is characterized by the formula ((R_1—O—(CH_2—CHOH—CH_2O)$_n$—), wherein R_1 is hydrogen, methyl or ethyl, and n is an integer between 1 and 15.~~

~~29. The extracellular vesicle of anyone of claims 1 to 28, wherein the L_1, L_2, or L_3 cleavable linkage, or any combination thereof, comprises a redox cleavable linker, a reactive oxygen species cleavable linker, a pH dependent cleavable linker, an enzymatic cleavable linker, a protease cleavable linker, an esterase cleavable linker, a phosphatase cleavable linker, a photoactivated cleavable linker, a self-immolative linker, or any combination thereof.~~

~~30. The extracellular vesicle of anyone of claims 1 to 29, wherein the L_1, L_2, or L_3 cleavable linkage, or any combination thereof, comprises a self-immolative linker.~~

~~31. The extracellular vesicle of any one of claims 1 to 30, wherein the L_1, L_2, or L_3 cleavable linkage, or any combination thereof, comprises a cinnamyl group, a naphthyl group, a biphenyl group, a heterocyclic ring, a homoaromatic group, coumarin, furan, thiophene, thiazole, oxazole, isoxazole, pyrrole, pyrazole, pyridine, imidazone, triazole, or any combination thereof.~~

~~32~~5. The ~~extracellular vesicle~~EV of any one of claims 1 to ~~31~~4, wherein the L_1, L_2, or L_3 cleavable linkage, or any combination thereof, has the formula:

-Aa-Yy-

wherein each –A- is independently an amino acid unit or a combination thereof, a is independently an integer from 1 to 15; -Y- is a spacer unit, and y is 0, 1, or 2, wherein -Aa- is a dipeptide, a tripeptide, a tetrapeptide, a pentapeptide, or a hexapeptide, or a combination thereof, wherein each

dipeptide, tripeptide, tetrapeptide, pentapeptide, or hexapeptide in the combination can be the same or different.

~~33. The extracellular vesicle of claim 32, wherein –Aa– is a dipeptide, a tripeptide, a tetrapeptide, a pentapeptide, or a hexapeptide, or a combination thereof, wherein each dipeptide, tripeptide, tetrapeptide, pentapeptide, or hexapeptide in the combination can be the same or different.~~

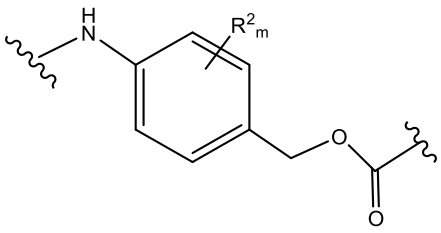
~~34. The extracellular vesicle of claim 33, wherein a is 2 and –Aa– is selected from the group consisting of valine-alanine, valine-citrulline, phenylalanine-lysine, N-methylvaline-citrulline, cyclohexylalanine-lysine, glutamic acid-valine-citrulline, and beta-alanine-lysine.~~

~~35. The extracellular vesicle of claim 33, wherein said –Aa– is valine-alanine, valine-citrulline, or glutamic acid-valine-citrulline.~~

~~36. The extracellular vesicle of any one of claims 31 to 35, wherein y is 1.~~

~~37. The extracellular vesicle of any one of claims 31 to 36, wherein –Y– is a self-immolative spacer.~~

~~38~~6. The ~~extracellular vesicle~~EV of claim ~~37~~5, wherein –Yy- has the formula:



wherein each R_2 is independently C_{1-8} alkyl, -O-(C_{1-8} alkyl), halogen, nitro, or cyano; and m is an integer from 0 to 4.

~~39. The extracellular vesicle of claim 38, wherein m is 0, 1, or 2.~~

~~40. The extracellular vesicle of claim 38, wherein m is 0.~~

~~41. The extracellular vesicle of any one of claims 31 to 40, wherein the L_1, L_2, or L_3 cleavable linkage, or any combination thereof, comprises valine-alanine-p-aminobenzylcarbamate or valine-citrulline-p-aminobenzylcarbamate.~~

~~42. The extracellular vesicle of any one of claims 31 to 36, wherein -Y- is a non self-immolative spacer.~~

~~43. The extracellular vesicle of claim 42, wherein the non self-immolative spacer is -Gly- or -Gly-Gly-.~~

~~44~~7. The ~~extracellular vesicle~~EV of any one of claims 1 to ~~43~~6, wherein the anchoring moiety [AM] comprises a scaffold protein selected from the group consisting of prostaglandin F2 receptor negative regulator (the PTGFRN protein); basigin (the BSG protein); immunoglobulin superfamily member 2 (the IGSF2 protein); immunoglobulin superfamily member 3 (the IGSF3 protein); immunoglobulin superfamily member 8 (the IGSF8 protein); integrin beta-1 (the ITGB1 protein); integrin alpha-4 (the ITGA4 protein); 4F2 cell-surface antigen heavy chain (the SLC3A2 protein); a class of ATP transporter proteins (the ATP1A1, ATP1A2, ATP1A3, ATP1A4, ATP1B3, ATP2B1, ATP2B2, ATP2B3, ATP2B4 proteins); a functional fragment thereof; and any combination thereof.

~~45. The extracellular vesicle of claim 44, wherein the anchoring moiety [AM] and/or the scaffold moiety is Scaffold X.~~

~~46. The extracellular vesicle of claim 45, wherein the Scaffold X is selected from the group consisting of prostaglandin F2 receptor negative regulator (the PTGFRN protein); basigin (the BSG protein); immunoglobulin superfamily member 2 (the IGSF2 protein); immunoglobulin superfamily member 3 (the IGSF3 protein); immunoglobulin superfamily member 8 (the IGSF8 protein); integrin beta-1 (the ITGB1 protein); integrin alpha-4 (the ITGA4 protein); 4F2 cell-~~

~~surface antigen heavy chain (the SLC3A2 protein); a class of ATP transporter proteins (the ATP1A1, ATP1A2, ATP1A3, ATP1A4, ATP1B3, ATP2B1, ATP2B2, ATP2B3, ATP2B4 proteins); a functional fragment thereof; and any combination thereof.~~

~~47. The extracellular vesicle of claim 45, wherein the Scaffold X is PTGFRN protein or a functional fragment thereof.~~

~~48. The extracellular vesicle of claim 45, wherein the Scaffold X comprises an amino acid sequence as set forth in SEQ ID NO:302.~~

~~49~~8. The ~~extracellular vesicle~~EV of claim ~~45~~7, wherein the ~~Scaffold X~~scaffold protein comprises an amino acid sequence at least 50%, at least 60%, at least 70%, at least 80%, at least 85%, at least 90%, at least 95%, at least 96%, at least 97%, at least 98%, at least 99%, or about 100% identical to SEQ ID NO:302.

~~50. The extracellular vesicle of any one of claims 1 to 49, wherein the biologically active molecule [BAM] is linked via an anchoring moiety [AM] to the exterior surface of the EV.~~

~~51. The extracellular vesicle of any one of claims 1 to 50, wherein the biologically active molecule is a polypeptide, a peptide, a polynucleotide (DNA and/or RNA), a chemical compound, or any combination thereof.~~

~~52. The extracellular vesicle of claim 51, wherein the biologically active molecule is a chemical compound.~~

~~53. The extracellular vesicle of claim 52, wherein the chemical compound is a small molecule.~~

~~54. The extracellular vesicle of any one of claims 1 to 53, wherein the biologically active molecule comprises an antisense oligonucleotide (ASO), a siRNA, a miRNA, a shRNA, an mRNA a nucleic acid, or any combination thereof.~~

~~55. The extracellular vesicle of any one of claims 1 to 54, wherein the biologically active molecule comprises a peptide, a protein, an antibody or an antigen binding fragment thereof, or any combination thereof.~~

~~56. The extracellular vesicle of claim 55, wherein the antigen binding fragment thereof comprises scFv, (scFv)2, Fab, Fab', F(ab')2, F(ab1)2, Fv, dAb, and Fd fragment, diabodys, antibody-related polypeptide, or any fragment thereof.~~

~~57~~9. The ~~extracellular vesicle~~EV of any one of claims 1 to ~~85~~4, wherein the biologically active molecule comprises an ASO, wherein the ASO targets a STAT6 transcript, a CEBP/β transcript, a STAT3 transcript, a KRAS transcript, a NRAS transcript, an NLPR3 transcript, or any combination thereof, wherein the biologically active molecule [BAM] is linked via the anchoring moiety [AM] to the exterior surface of the EV.

~~58. The extracellular vesicle of claim 57, wherein the ASO targets a transcript.~~

~~59. The extracellular vesicle of claim 58, wherein the transcript is a STAT6 transcript, a CEBP/β transcript, a STAT3 transcript, a KRAS transcript, a NRAS transcript, an NLPR3 transcript, or any combination thereof.~~

~~60. The extracellular vesicle of any one of claims 1 to 59, wherein the EV is an exosome.~~

~~61. The extracellular vesicle of claim 60, wherein the exosome is a native exosome.~~

~~62. The extracellular vesicle of claim 60, wherein the exosome is an exosome overexpressing PTGFRN or a functional fragment thereof.~~

~~63~~10. A pharmaceutical composition comprising the ~~extracellular vesicle~~EV of any one of claims 1 to ~~62~~ 9 and a pharmaceutically acceptable carrier.

~~64~~11. A kit comprising the EV of any one of claim~~s~~ 1 to ~~62~~ 9 or the pharmaceutical composition of claim ~~63~~ 10 and instructions for use.

~~65~~12. ~~A method of treating or preventing~~Use of the EV of any one of claims 1 to 9 or the pharmaceutical composition of claim 10 in the manufacture of a medicament for the treatment of a disease or disorder in a subject in need thereof ~~comprising administering the EV of any one of claim 1 to 62 or the pharmaceutical composition of claim 63 to the subject~~.

~~66. The method of claim 65, wherein the disease or disorder is a cancer, an inflammatory disorder, a neurodegenerative disorder, a central nervous disease, or a metabolic disease.~~

~~67. The method of claim 65 or 66, wherein the EV is administered intravenously, intraperitoneally, nasally, orally, intramuscularly, subcutaneously, parenterally, or intratumorally.~~

~~68~~13. A method of attaching a biologically active molecule (BAM) to an extracellular vesicle (EV), comprising linking an anchoring moiety (AM) to the EV, wherein the anchoring moiety (AM) is attached to the biologically active moiety (BAM) according to the formula:

$$[AM]\text{-}L_1\text{-}[SP_1]\text{-}L_2\text{-}[SP_2]\text{-}L_3\text{-}[BAM]$$

wherein:

[AM] is the anchoring moiety and is selected from the group of cholesterol-C6, cholesterol-TEG, tocopherol-C8, tocopherol, and palmitate-C6;

L_1 is a cleavable or non-cleavable linkage;

L_2 and L_3 are optional cleavable or non-cleavable linkages, wherein L_1, L_2, L_3, or a combination thereof is a phosphodiester or phosphorothioate bond;

SP_1 is an optional first spacer selected from group of C3, C6, TEG, or HEG; and,

SP_2 is an optional second spacer.

~~69. The method of claim 68, wherein [AM] is cholesterol-C6, cholesterol-TEG, tocopherol-C8, tocopherol, of palmitate-C6.~~

~~70. The method of claim 68 or 69, wherein L_1, L_2, L_3, or a combination thereof is a phosphodiester bond.~~

~~71. The method of any one of claims 68 to 70, wherein SP_1 is C3, C6, TEG, or HEG.~~

~~72. The method of any one of claims 68 to 71, wherein L_1, L_2, L_3, or a combination thereof is a phosphorothioate bond.~~

~~73. The method of any one of claims 68 to 72, wherein SP_2 is C3, C6, TEG or HEG.~~

~~74. The method of any one of claims 68 to 73, wherein L_1, L_2, L_3, or a combination thereof is a phosphorothioate bond.~~

~~75. The method of any one of claims 68 to 74, wherein [BAM] is an antisense oligonucleotide (ASO).~~

~~76~~14. A method of increasing the load density of a biologically active molecule (BAM) attached to an extracellular vesicle (EV), comprising screening a library of anchoring moieties (AM) attached to the biologically active moiety (BAM) according to the formula:

$$[AM]\text{-}L_1\text{-}[SP_1]\text{-}L_2\text{-}[SP_2]\text{-}L_3\text{-}[BAM]$$

wherein:

[AM] is the anchoring moiety selected from the group consisting of cholesterol-C6, cholesterol-TEG, tocopherol-C8, tocopherol, and palmitate-C6;

L_1 is a cleavable or non-cleavable linkage;

L_2 and L_3 are optional cleavable or non-cleavable linkages;

SP_1 is an optional first spacer selected from the group consisting of C3, C6, TEG and HEG; and,

SP_2 is an optional second spacer selected from the group consisting of C3, C6, TEG and HEG.

~~77. The method of claim 76, wherein [AM] is cholesterol-C6, cholesterol-TEG, tocopherol-C8, tocopherol, of palmitate-C6.~~

~~78. The method of claim 76 or 77, wherein L_1, L_2, L_3, or a combination thereof is a phosphodiester bond.~~

~~79. The method of any one of claims 76 to 78, wherein SP_1 is C3, C6, TEG, or HEG.~~

~~80. The method of any one of claims 76 to 79, wherein L_1, L_2, L_3, or a combination thereof is a phosphorothioate bond.~~

~~81. The method of any one of claims 76 to 80, wherein SP_2 is C3, C6, TEG or HEG.~~

~~82. The method of any one of claims 76 to 81, wherein L_1, L_2, L_3, or a combination thereof is a phosphorothioate bond.~~

~~83. The method of any one of claims 76 to 82, wherein [BAM] is an antisense oligonucleotide (ASO).~~

~~84~~15. The method of ~~any of claims 76 to 83~~ claim 14, wherein the load density of a biologically active molecule (BAM) attached to an EV is increased at least about 1-fold, at least about 1.5-fold, at least about 2-fold, at least about 2.5-fold, at least about 3-fold, at last about 4-fold, at least about 5-fold, at least about 6-fold, at least about 7-fold, at least 8-fold, at least about 9-fold, or at least about 10-fold.

~~85~~16. An extracellular vesicle (EV) comprising an antisense oligonucleotide [ASO] covalently linked to the EV via an anchoring moiety [AM] according to the formula:

$$[AM]\text{-}L_1\text{-}[SP_1]\text{-}L_2\text{-}[SP_2]\text{-}L_3\text{-}[ASO]$$

wherein:

[AM] is the anchoring moiety selected from the group consisting of cholesterol-C6, cholesterol-TEG, tocopherol-C8, tocopherol, and palmitate-C6;

L_1 is a phosphodiesterase cleavable linkage;

SP_1 is an optional first spacer selected from the group consisting of C3, C6, TEG and HEG;

L_2 is optional phosphorothioate non-cleavable linkage;

SP_2 is an optional second spacer selected from the group consisting of C3, C6, TEG, and HEG; and,

L_3 is an optional phosphorothioate non-cleavable linkage.

~~85. The EV of claim 84, wherein the EV is an exosome.~~

~~86. The EV of claim 85, wherein the exosome is a native exosome.~~

~~87~~17. The EV of claim ~~86~~16, where the load density of ASO attached to the ~~exosome~~ EV is increased by at least about 1.5-fold, and the average number of ASO molecules per exosome is between about 2000 and about 5500.

~~88. The EV of claim 86, wherein the anchoring moiety [AM] is cholesterol-C6.~~

~~89. The EV of claim 88, wherein the average number of ASO molecules per exosome is 5032+/-386.~~

~~90. The EV of claim 88, wherein the average number of ASO molecules per exosome is between about 4500 and about 5500.~~

~~91. The EV of claim 88, wherein the average number of ASO molecules per exosome is between about 4500 and about 4600, between about 4600 and about 4700, between about 4700 and about 4800, between about 4800 and about 4900, between about 4900 and about 5000, between about 5000 and about 5100, between about 5100 and about 5200, between about 5200 and about 5300, between about 5300 and about 5400, or between about 5400 and about 5500.~~

92. The EV of claim 88, wherein the average number of ASO molecules per exosome is at least about 4500, at least about 4600, at least about 4700, at least about 4800, at least about 4900, at least about 5000, at least about 5100, at least about 5200, at least about 5300, at least about 5400, or at least about 5500.

93. The EV of claim 88, wherein the loading efficiency is 73% to 93%.

94. The EV of claim 88, wherein the loading efficiency is between about 70% and about 95%.

95. The EV of claim 88, wherein the loading efficiency is between about 70% and about 75%, between about 75% and about 80%, between about 80% and about 85%, between about 85% and about 90%, or between about 90% and about 95%.

96. The EV of claim 88, wherein the loading efficiency is at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, or at least about 95%.

97. The EV of claim 86, wherein the anchoring moiety [AM] is cholesterol-TEG.

98. The EV of claim 93, wherein the average number of ASO molecules per exosome is 3991+/-490.

99. The EV of claim 97, wherein the average number of ASO molecules per exosome is between about 3500 and about 4500.

100. The EV of claim 97, wherein the average number of ASO molecules per exosome is between about 3500 and about 3600, between about 3600 and about 3700, between about 3700 and about 3800, between about 3800 and about 3900, between about 3900 and about 4000, between about 4000 and about 4100, between about 4100 and about 4200, between about 4200 and about 4300, between about 4300 and about 4400, or between about 4400 and about 4500.

~~101. The EV of claim 97, wherein the average number of ASO molecules per exosome is at least about 3500, at least about 3600, at least about 3700, at least about 3800, at least about 3900, at least about 4000, at least about 4100, at least about 4200, at least about 4300, at least about 4400, or at least about 4500.~~

~~102. The EV of claim 97, wherein the loading efficiency is 56% to 79%.~~

~~103. The EV of claim 97, wherein the loading efficiency is between about 50% and about 85%.~~

~~104. The EV of claim 97, wherein the loading efficiency is between about 50% and about 55%, between about 55% and about 60%, between about 60% and about 65%, between about 65% and about 70%, between about 70% and about 75%, between about 75% and about 80%, or between about 80% and about 85%.~~

~~105. The EV of claim 97, wherein the loading efficiency is at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, at least about 80%, or at least about 85%.~~

~~106. The EV of claim 86, wherein the anchoring moiety [AM] is tocopherol-C8, tocopherol, or palmitate-C6.~~

~~107. The EV of claim 106, wherein the average number of ASO molecules per exosome is 4241+/-722.~~

~~108. The EV of claim 106, wherein the average number of ASO molecules per exosome is between about 3500 and about 5000.~~

~~109. The EV of claim 106, wherein the average number of ASO molecules per exosome is between about 3500 and about 3600, between about 3600 and about 3700, between about 3700 and about 3800, between about 3800 and about 3900, between about 3900 and about 4000, between about 4000 and about 4100, between about 4100 and about 4200, between about 4200 and about~~

~~4300, between about 4300 and about 4400, between about 4400 and about 4500, between about 4500 and about 4600, between about 4600 and about 4700, between about 4700 and about 4800, between about 4800 and about 4900, or between about 4900 and about 5000.~~

~~110. The EV of claim 106, wherein the average number of ASO molecules per exosome is at least about 3500, at least about 3600, at least about 3700, at least about 3800, at least about 3900, at least about 4000, at least about 4100, at least about 4200, at least about 4300, at least about 4400, at least about 4500, at least about 4600, at least about 4700, at least about 4800, at least about 4900, or at least about 5000.~~

~~111. The EV of claim 106, wherein the loading efficiency is 57% to 73%.~~

~~112. The EV of claim 106, wherein the loading efficiency is between about 50% and about 80%.~~

~~113. The EV of claim 106, wherein the loading efficiency is between about 50% and about 55%, between about 55% and about 60%, between about 60% and about 65%, between about 65% and about 70%, between about 70% and about 75%, or between about 75% and about 80%.~~

~~114. The EV of claim 106, wherein the loading efficiency is at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, at least about 75%, or at least about 80%.~~

18. The EV of any one of claims 1 to 17, wherein the EV is an exosome.

~~115. The EV of claim 84, wherein the exosome is an exosome overexpressing PTGFRN.~~

~~116. The EV of claim 115, where the load density of ASO attached to the exosome is increased by at least about 2-fold.~~

~~117. The EV of claim 115, wherein the anchoring moiety [AM] is cholesterol-C6.~~

~~118. The EV of claim 117, wherein the average number of ASO molecules per exosome is 2442+/-339.~~

~~119. The EV of claim 117, wherein the average number of ASO molecules per exosome is between about 2000 and about 3000.~~

~~120. The EV of claim 117, wherein the average number of ASO molecules per exosome is between about 2000 and about 2100, between about 2100 and about 2200, between about 2200 and about 2300, between about 2300 and about 2400, between about 2400 and about 2500, between about 2500 and about 2600, between about 2600 and about 2700, between about 2700 and about 2800, between about 2800 and about 2900, or between about 2900 and about 3000.~~

~~121. The EV of claim 117, wherein the average number of ASO molecules per exosome is at least about 2000, at least about 2100, at least about 2200, at least about 2300, at least about 2400, at least about 2500, at least about 2600, at least about 2700, at least about 2800, at least about 2900, or at least about 3000.~~

~~122. The EV of claim 117, wherein the loading efficiency is 27% to 46%.~~

~~123. The EV of claim 117, wherein the loading efficiency is between about 25% and about 50%.~~

~~124. The EV of claim 117, wherein the loading efficiency is between about 25% and about 30%, between about 30% and about 35%, between about 35% and about 40%, between about 40% and about 45%, or between about 45% and about 50%.~~

~~125. The EV of claim 117, wherein the loading efficiency is at least about 25%, at least about 30%, at least about 35%, at least about 40%, at least about 45%, or at least about 50%.~~

~~126. The EV of claim 115, wherein the anchoring moiety [AM] is cholesterol-TEG.~~

~~127. The EV of claim 126, wherein the average number of ASO molecules per exosome is 1728+/-264.~~

~~128. The EV of claim 126, wherein the average number of ASO molecules per exosome is between about 1400 and about 2100.~~

~~129. The EV of claim 126, wherein the average number of ASO molecules per exosome is between about 1400 and about 1500, between about 1500 and about 1600, between about 1600 and about 1700, between about 1700 and about 1800, between about 1800 and about 1900, between about 1900 and about 2000, or between about 2000 and about 2100.~~

~~130. The EV of claim 126, wherein the average number of ASO molecules per exosome is at least about 1400, at least about 1500, at least about 1600, at least about 1700, at least about 1800, at least about 1900, at least about 2000, or at least about 2100.~~

~~131. The EV of claim 126, wherein the loading efficiency is 19% to 33%.~~

~~132. The EV of claim 126, wherein the loading efficiency is between about 15% and about 35%.~~

~~133. The EV of claim 126, wherein the loading efficiency is between about 15% and about 20%, between about 20% and about 25%, between about 25% and about 30%, or between about 30% and about 35%.~~

~~134. The EV of claim 126, wherein the loading efficiency is at least about 15%, at least about 20%, at least about 25%, at least about 30%, or at least about 35%.~~

~~135. The EV of claim 115, wherein the anchoring moiety [AM] is tocopherol-C8, tocopherol, or palmitate-C6.~~

~~136. The EV of claim 135, wherein the average number of ASO molecules per exosome is 2979+/-1006.~~

~~137. The EV of claim 135, wherein the average number of ASO molecules per exosome is between about 1900 and about 4000.~~

~~138. The EV of claim 135, wherein the average number of ASO molecules per exosome is between about 1900 and about 2000, between about 2000 and about 2100, between about 2100 and about 2200, between about 2200 and about 2300, between about 2300 and about 2400, between about 2400 and about 2500, between about 2500 and about 2600, between about 2600 and about 2700, between about 2700 and about 2800, between about 2800 and about 2900, between about 2900 and about 3000, between about 3000 and about 3100, between about 3100 and about 3200, between about 3200 and about 3300, between about 3300 and about 3400, between about 3400 and about 3500. between about 3500 and about 3600, between about 3600 and about 3700, between about 3700 and about 3800, between about 3800 and about 3900, or between about 3900 and about 4000.~~

~~139. The EV of claim 135, wherein the average number of ASO molecules per exosome is at least about 1900, at least about 2000, at least about 2100, at least about 2200, at least about 2300, at least about 2400, at least about 2500, at least about 2600, at least about 2700, at least about 2800, at least about 2900, at least about 3000, at least about 3100, at least about 3200, at least about 3300, at least about 3400, at least about 3500, at least about 3600, at least about 3700, at least about 3800, at least about 3900, or at least about 4000.~~

~~140. The EV of claim 135, wherein the loading efficiency is 37% to 68%.~~

~~141. The EV of claim 135, wherein the loading efficiency is between about 30% and about 75%.~~

~~142. The EV of claim 135, wherein the loading efficiency is between about 30% and about 35%, between about 35% and about 40%, between about 40% and about 45%, between about 45% and about 50%, between about 50% and about 55%, between about 55% and about 60%, between about 60% and about 65%, between about 65% and about 70%, or between about 70% and about 75%.~~

143. The EV of claim 135, wherein the loading efficiency is at least about 30%, at least about 35%, at least about 40%, at least about 45%, at least about 50%, at least about 55%, at least about 60%, at least about 65%, at least about 70%, or at least about 75%.

144. An exosome comprising an antisense oligonucleotide [ASO] covalently linked to the exosome via an anchoring moiety [AM] according to the formula:

$$[AM]\text{-}L_1\text{-}[SP_1]\text{-}L_2\text{-}[SP_2]\text{-}L_3\text{-}[BAM]$$

wherein [AM] is cholesterol-TEG; L_1 is a phosphodiesterase cleavable bond; SP_1 is C3; L_2 is a phosphorothioate non-cleavable bond; SP_2 is TEG; and, L_3 is a phosphorothioate non-cleavable bond.

145. The exosome of claim 144, wherein the exosome is a native exosome.

146. The exosome of claim 145, wherein the average number of ASO molecules per exosome is about 4780.

147. The exosome of claim 145, wherein the average number of ASO molecules per exosome is between about 4500 and about 5000.

148. The exosome of claim 145, wherein the average number of ASO molecules per exosome is at least 4500.

149. The exosome of claim 145, wherein the loading efficiency is about 80%.

150. The exosome of claim 145, wherein the loading efficiency is between about 70% and about 90%.

151. The exosome of claim 145, wherein the loading efficiency is at least about 70%.

~~152. The exosome of claim 144, wherein the exosome is an exosome overexpressing PTGFRN.~~

~~153. The exosome of claim 152, wherein the average number of ASO molecules per exosome is about 1659.~~

~~154. The exosome of claim 152, wherein the average number of ASO molecules per exosome is between about 1500 and about 2000.~~

~~155. The exosome of claim 152, wherein the average number of ASO molecules per exosome is at least about 1500.~~

~~156. The exosome of claim 152, wherein the loading efficiency is about 28%.~~

~~157. The exosome of claim 152, wherein the loading efficiency is between about 20% and about 35%.~~

~~158. The exosome of claim 152, wherein the loading efficiency is at least about 20%.~~

~~159~~19. An exosome comprising an antisense oligonucleotide [ASO] covalently linked to the exosome via an anchoring moiety [AM] according to the formula:

$$[AM]\text{-}L_1\text{-}[SP_1]\text{-}L_2\text{-}[BAM]$$

wherein [AM] is cholesterol-TEG; L_1 is a phosphodiesterase cleavable bond; SP_1 is TEG; and L_2 is a phosphorothioate non-cleavable bond.

~~160. The exosome of claim 159, wherein the exosome is a native exosome.~~

~~161. The exosome of claim 160, wherein the average number of ASO molecules per exosome is about 4090.~~

~~162. The exosome of claim 160, wherein the average number of ASO molecules per exosome is between about 3500 and about 4500.~~

~~163. The exosome of claim 160, wherein the average number of ASO molecules per exosome is at least 3500.~~

~~164. The exosome of claim 160, wherein the loading efficiency is about 68%.~~

~~165. The exosome of claim 160, wherein the loading efficiency is at least about 60%.~~

~~166. The exosome of claim 160, wherein the loading efficiency is between about 60% and about 70%.~~

~~167~~20. The exosome of claim ~~159~~18 or 19, wherein the exosome is an exosome overexpressing PTGFRN.

~~168. The exosome of claim 167, wherein the average number of ASO molecules per exosome is about 1890.~~

~~169. The exosome of claim 167, wherein the average number of ASO molecules per exosome is between about 1400 and about 2400.~~

~~170. The exosome of claim 167, wherein the average number of ASO molecules per exosome is at least about 1400.~~

~~171. The exosome of claim 167, wherein the loading efficiency is about 31%.~~

~~172. The exosome of claim 167, wherein the loading efficiency is between about 20% and about 40%.~~

~~173. The exosome of claim 167, wherein the loading efficiency is at least about 20%.~~