

CLAIMS

1. A composition comprising:

a first mRNA construct comprising a first open reading frame (ORF), wherein the first ORF encodes a first antigen, wherein the first antigen is selected from: a pathogenic microbial antigen or a tumor-associated antigen, or an epitope containing fragment thereof;

wherein the first ORF is operatively linked to at least one untranslated region (UTR), wherein the UTR comprises at least a first organ protection sequence (OPS), and wherein the first OPS comprises at least three miRNA target (miRNA) sequences which are all different from each other, comprises at least two micro-RNA (miRNA) target sequences, and wherein each of the at least two three miRNA target sequences are optimised to hybridise with a corresponding miRNA sequence.

2. The composition of claim 1, wherein the first mRNA construct is comprised within or adsorbed to an *in vivo* delivery composition.

- ~~3.~~ The composition of claim 1 or claim 2, wherein the antigen is selected from the group consisting of: a pathogenic microbial protein and a tumor-associated antigen, or an epitope containing fragment thereof.

- ~~43.~~ The composition of claim ~~13~~, wherein the pathogenic microbial ~~protein antigen~~ is selected from the group consisting of: a viral protein; a bacterial protein; a fungal protein; a parasite protein; and or a prion.

- ~~54.~~ The composition of ~~any of claims 1 to 4~~, further comprising a second mRNA construct comprising a second open reading frame (ORF), wherein the second ORF encodes a proinflammatory cytokine.

- ~~65.~~ The composition of claim ~~54~~, wherein the proinflammatory cytokine is selected from the group consisting of: interleukin 1 (IL-1), interleukin 2 (IL-2), interleukin 3 (IL-3), interleukin 4 (IL-4), interleukin 5 (IL-5), interleukin 6 (IL- 6), interleukin 7 (IL- 7), interleukin 8 (IL-8), interleukin 9 (IL-9), interleukin 10 (IL-10), interleukin 11 (IL-11), interleukin 12 (IL-12), interleukin 13 (IL-13), interleukin 14 (IL-14), interleukin 15 (IL-15), interleukin 16 (IL-16), interleukin 17 (IL-17), interleukin 18 (IL-18), interleukin 19 (IL- 19), interleukin 20 (IL-20), interleukin 21 (IL-21), interleukin 22 (IL-22), interleukin 23 (IL-23), interleukin 24 (IL-24), interleukin 25 (IL-25), interleukin 26 (IL-26), interleukin 27 (IL-27), interleukin 28 (IL-28), interleukin 29 (IL-29), interleukin 30 (IL-30), interleukin 31 (IL-31), interleukin 32 (IL-32), interleukin 33 (IL-33), interleukin 35 (IL-35), interleukin 36 (IL-36) IL-12; IL-2; IL-6; IL-8; IFN γ ; IFN α ; IFN β ; TNF α ; and GM-CSF.

- ~~76.~~ The composition of claim ~~54 or claim 6~~, wherein the second mRNA construct is comprised within or adsorbed to a delivery composition.

- ~~87.~~ The composition of ~~any of claims 5 to 75~~, wherein the second ORF codes for an IL-12 protein, or a subunit, derivative, fragment, agonist or homologue thereof.
- ~~98.~~ The composition of claim ~~87~~, wherein the second ORF comprises a sequence at least 90% identical to SEQ ID NO: 59.
- ~~109.~~ The composition of ~~any of claims 45 to 9~~, wherein the second ORF is operatively linked to a second untranslated region (UTR), wherein the UTR comprises a second organ protection sequence (OPS) and wherein the second OPS comprises at least ~~two~~ three micro-RNA (miRNA) target sequences which are all different from each other.
- ~~110.~~ The composition of claim ~~109~~, wherein the at least ~~two~~ three miRNA target sequences are optimised to hybridise with a corresponding miRNA sequence.
- ~~1211.~~ The composition of claim ~~910 or claim 11~~, wherein the first OPS includes at least one different miRNA target sequence to the second OPS.
- ~~1312.~~ The composition of claim ~~910 or claim 11~~, wherein the first OPS and the second OPS include the same miRNA target sequences.
- ~~1413.~~ The composition of ~~any of claims 1 to 13~~, wherein the composition includes a delivery composition that comprises a delivery vector selected from ~~the group consisting of: a particle, such as a polymeric particle; a lipid nanoparticle (LNP), a liposome; a lipidoid particle; and/or a viral vector.~~
- ~~1514.~~ The composition of ~~any of claims 1 to 14~~, wherein the first OPS comprises ~~at least three, at least four, or at least five~~ miRNA target sequences.
- ~~16.~~ The composition of ~~any of claims 1 to 15~~, wherein the first OPS comprises ~~at least three~~ miRNA target sequences ~~which are all different from each other~~.
- ~~1715.~~ The composition of ~~any of claims 1 to 16~~, wherein the first OPS comprises miRNA sequences selected to protect one or more organs or tissues selected from the group consisting of muscle, liver, brain, breast, endothelium, pancreas, colon, kidney, lungs, spleen and skin, heart, gastrointestinal organs, reproductive organs, and esophagus.
- ~~1816.~~ The composition of ~~any of claims 1 to 17~~, wherein the first OPS comprises at least ~~two~~ three miRNA target sequences selected from one or more sequences that bind to: miRNA-122; miRNA-125; miRNA-199; miRNA-124a; miRNA-126; miRNA-98; Let7 miRNA family; miRNA-375; miRNA-141; miRNA-142; miRNA-148a/b; miRNA-143; miRNA-145; miRNA-194; miRNA-200c; miRNA-203a; miRNA-205; miRNA-1; miRNA-133a; miRNA-206; miRNA-34a; miRNA-192; miRNA-194; miRNA-204; miRNA-215; miRNA-30 family; miRNA-877; miRNA-4300; miRNA-4720; and/or miRNA-6761.
- ~~19.~~ The composition of ~~any of claims 1 to 18~~, wherein the first OPS comprises ~~miRNA sequences selected to protect one or more organs selected from the group consisting of muscle, liver, kidney, lungs, spleen, skin, heart, gastrointestinal organs, reproductive organs, and esophagus.~~

~~20. The composition of any of claims 1 to 19, wherein the first OPS comprises at least two miRNA target sequences selected from sequences capable of binding with miRNA-1, miRNA-122, miRNA-30a, miRNA-203a, let7b, miRNA-126, and/or miRNA-192.~~

~~21~~17. The composition of any of claims 1 to 20, wherein the first OPS comprises sequences selected from one or more of SEQ ID NOs: 44-57.

~~22. The composition of any of claims 1 to 21, wherein the first OPS comprises at least two miRNA target sequences selected from sequences capable of binding with miRNA-1, miRNA133a, miRNA206, miRNA-122, miRNA203a, miRNA205, miRNA200c, miRNA30a, and/or let7a/b.~~

~~23. The composition of any of claims 1 to 22, wherein the first OPS comprises at least two miRNA target sequences selected from sequences capable of binding with miRNA-1, miRNA-122, miR-30a and/or miR-203a.~~

~~24. The composition of claim 23, wherein the first OPS comprises miRNA target sequences capable of binding with miRNA-1, miRNA-122, miRNA-30a and miRNA-203a.~~

~~25. The composition of any of claims 1 to 24, wherein the first OPS comprises miRNA target sequences capable of binding with miRNA-122, miRNA-1, miRNA-203a, and miRNA-30a.~~

~~26. The composition of any of claims 1 to 25, wherein the first OPS comprises miRNA target sequences capable of binding with let7b, miRNA-126, and miRNA-30a.~~

~~27. The composition of any of claims 1 to 26, wherein the first OPS comprises miRNA target sequences capable of binding with miRNA-122, miRNA-192, and miRNA-30a.~~

~~28. The composition of any of claims 1 to 27, wherein the first OPS comprises miRNA target sequences capable of binding with miRNA-192, miRNA-30a, and miRNA-124, and two miRNA target sequences capable of binding with miRNA-122.~~

~~29~~18. The composition of any of claims 1 to 28, wherein the antigen comprises a viral protein or an epitope containing fragment thereof.

~~30~~19. The composition of claim ~~29~~18, wherein the antigen comprises is selected from: a coronavirus spike protein, an influenza protein, a respiratory syncytial virus (RSV) protein or a Human Immunodeficiency Virus (HIV) protein, or a variant thereof, or an epitope containing fragment thereof.

~~31. The composition of claim 29, wherein the antigen comprises a variant coronavirus spike protein.~~

~~32. The composition of claim 30 or 31, wherein the coronavirus spike protein is a SARS-CoV-2 spike protein.~~

~~33. The composition of claim 29, wherein the antigen comprises an influenza protein or a variant thereof, or an epitope containing fragment thereof.~~

- ~~34. The composition of claim 33, wherein the influenza protein is selected from the group consisting of a hemagglutinin, a neuraminidase, a matrix-2 and/or a nucleoprotein.~~
- ~~35. The composition of claim 33, wherein the influenza protein is selected from type A influenza, a type B influenza, or a subtype of type A influenza of H1, H2, H3, H4, H5, H6, H7, H8, H9, H10, H11, H12, H13, H14, H15 or H16.~~
- ~~36. The composition of claim 29, wherein the antigen comprises a respiratory syncytial virus (RSV) protein, or a variant thereof, or an epitope containing fragment thereof.~~
- ~~37. The composition of claim 36, wherein the protein of the respiratory syncytial virus is the F glycoprotein or the G glycoprotein.~~
- ~~38. The composition of claim 29, wherein the antigen comprises a Human Immunodeficiency Virus (HIV) protein or an epitope containing fragment thereof.~~
- ~~39. The composition of claim 38, wherein the HIV protein is the glycoprotein 120 neutralizing epitope or glycoprotein 145.~~
- ~~4020. The composition of any of claims 1 to 28, wherein the antigen comprises a protein from the *Mycobacterium tuberculosis* bacterium or an epitope containing fragment thereof.~~
- ~~4121. The composition of claim 4020, wherein the protein from the *Mycobacterium tuberculosis* bacterium is selected from ESAT-6, Ag85B, TB10.4, Rv2626 and/or RpfD-B.~~
- ~~4222. The composition of any of claims 1 to 28, wherein the antigen is a tumor-associated antigen which comprises selected from: a colorectal tumour antigen; a breast tumour antigen; a lung tumour antigen; a liver tumour antigen; or a pancreas tumour antigen.~~
- ~~4323. The composition of any of claims 1 to 28, wherein the antigen is a tumor-associated antigen which is MUC1.~~
- ~~4424. The composition of any of claims 1 to 28, wherein the antigen is a tumor-associated antigen which is a neoantigen.~~
- ~~45. The composition of any of claims 1 to 4 or 14 to 44, wherein the first mRNA construct further comprises a second open reading frame (ORF), wherein the second ORF encodes a proinflammatory cytokine selected from: IFN γ ; IFN α ; IFN β ; TNF α ; IL-12; IL-2; IL-6; IL-8; and GM-CSF.~~
- ~~46. The composition of any of claims 1 to 44, wherein the first mRNA construct further comprises a further open reading frame (ORF), wherein the further ORF encodes an antigen different to the antigen encoded by the first ORF.~~

47. The composition of claim 46, wherein the antigen encoded by the further ORF is selected from: a bacterial protein, a viral protein, or a tumor-associated antigen, or an epitope-containing fragment thereof.
48. The composition of any of claims 10 to 13, wherein the second OPS comprises at least three, at least four, or at least five miRNA target sequences.
49. The composition of any of claims 10 to 13 or 48, wherein the second OPS comprises at least three miRNA target sequences which are all different from each other.
50. The composition of any of claims 10 to 13 or 48 to 49, wherein the second OPS comprises miRNA sequences selected to protect one or more organs or tissues selected from the group consisting of muscle, liver, brain, breast, endothelium, pancreas, colon, kidney, lungs, spleen and skin.
51. The composition of any of claims 10 to 13 or 48 to 50, wherein the second OPS comprises at least two miRNA target sequences selected from one or more sequences that are capable of binding with: miRNA-122; miRNA-125; miRNA-199; miRNA-124a; miRNA-126; Let7 miRNA family; miRNA-375; miRNA-141; miRNA-142; miRNA-148a/b; miRNA-143; miRNA-145; miRNA-194; miRNA-200c; miRNA-203a; miRNA-205; miRNA-1; miRNA-133a; miRNA-206; miRNA-34a; miRNA-192; miRNA-194; miRNA-204; miRNA-215; miRNA-30 family; miRNA-877; miRNA-4300; miRNA-4720; and miRNA-6761.
52. The composition of any of claims 10 to 13 or 48 to 51, wherein the second OPS comprises comprises miRNA sequences selected to protect one or more organs selected from the group consisting of muscle, liver, kidney, lungs, spleen, skin, heart, gastrointestinal organs, reproductive organs, and esophagus.
53. The composition of any of claims 10 to 13 or 48 to 52, wherein the second OPS comprises sequences selected from one or more of SEQ ID NOs: 44-57
54. The composition of any of claims 10 to 13 or 48 to 53, wherein the second OPS comprises at least two miRNA target sequences selected from sequences capable of binding with miRNA-1, miRNA-122, miRNA-30a, miRNA-203a, let7b, miRNA-126, and/or miRNA-192.
55. The composition of any of claims 10 to 13 or 48 to 54, wherein the second OPS comprises at least two miRNA target sequences selected from sequences capable of binding with miRNA-1, miRNA133a, miRNA206, miRNA-122, miRNA203a, miRNA205, miRNA200c, miRNA30a, and/or let7a/b.
56. The composition of any of claims 10 to 13 or 48 to 55, wherein the second OPS comprises at least two miRNA target sequences selected from sequences capable of binding with miRNA-1, miRNA-122, miR-30a and/or miR-203a.

- ~~57. The composition of any of claims 10 to 13 or 48 to 56, wherein the second OPS comprises miRNA target sequences capable of binding with miRNA-1, miRNA-122, miRNA-30a and miRNA-203a.~~
- ~~58. The composition of any of claims 10 to 13 or 48 to 57, wherein the second OPS comprises miRNA target sequences capable of binding with miRNA-122, miRNA-1, miRNA-203a, and miRNA-30a.~~
- ~~59. The composition of any of claims 10 to 13 or 48 to 58, wherein the second OPS comprises miRNA target sequences capable of binding with let7b, miRNA-126, and miRNA-30a.~~
- ~~60. The composition of any of claims 10 to 13 or 48 to 59, wherein the second OPS comprises miRNA target sequences capable of binding with miRNA-122, miRNA-192, and miRNA-30a.~~
- ~~61. The composition of any of claims 10 to 13 or 48 to 60, wherein the second OPS comprises miRNA target sequences capable of binding with miRNA-192, miRNA-30a, and miRNA-124, and two miRNA target sequences capable of binding with miRNA-122.~~
- ~~62. The composition of any of claims 10 to 13 or 48 to 61, wherein the first OPS comprises miRNA target sequences capable of binding with miRNA-1, miRNA-122, miR-30a and miR-203a; and~~
- ~~the second OPS comprises miRNA target sequences capable of binding with miRNA-122, miRNA-192, and/or miRNA-30a.~~
- ~~63. The composition of any of claims 1 to 62, further comprising at least a third mRNA construct comprising at least a third open reading frame (ORF), wherein the third ORF encodes an antigen different to the antigen encoded by the first ORF, and selected from: a bacterial protein, a viral protein, or a tumor-associated antigen, or an epitope containing fragment thereof.~~
- ~~64. The composition of claim 63, wherein the third ORF is operatively linked to at least a third untranslated region (UTR), wherein the UTR comprises at least a third organ protection sequence (OPS), wherein the third OPS protects multiple organs, and wherein the third OPS comprises at least two micro-RNA (miRNA) target sequences, and wherein each of the at least two miRNA target sequences are optimised to hybridise with a corresponding miRNA sequence~~
- ~~65. The composition of claim 63 or 64, wherein the first ORF codes for a coronavirus spike protein or an epitope containing fragment thereof, and the third ORF codes for a viral protein or an epitope containing fragment thereof that comprises all or a part of an influenza protein, or a variant thereof.~~
- ~~66. The composition of any of claims 1 to 65, wherein the composition is suitable for administration intravenously, subcutaneously, intra-muscularly, intranasally, intra-arterially and/or through inhalation.~~

- ~~67. The composition of any of claims 1 to 66 for use in a method of the prevention or treatment of pathogenic disease.~~
- ~~68. The composition for use according to claim 67, wherein the method comprises administering the composition to a subject in need thereof.~~
- ~~69. The composition for use according to claim 67 or 68, wherein the pathogenic disease is caused by a coronavirus.~~
- ~~70. The composition for use according to claim 69, wherein the pathogenic disease is caused by the SARS-CoV-2 virus.~~
- ~~71. A method of increasing a Th1 immune response, comprising administering a composition according to any of claims 8 or 9 to a subject in need thereof.~~
- ~~72. A composition comprising:~~
- ~~at least a first mRNA construct comprising at least a first open reading frame (ORF), wherein the first ORF encodes an antigen selected from: a bacterial protein; and/or a viral protein; and~~
- ~~an second construct comprising at least a second mRNA construct comprising at least one open reading frame (ORF), wherein the ORF encodes a proinflammatory cytokine selected from: IFN γ ; IFN α ; IFN β ; TNF α ; IL-12; IL-2; IL-6; IL-8; and GM-CSF, and wherein the second ORF is operatively linked to at least one untranslated region (UTR), wherein the UTR comprises at least one OPS that protects multiple organs, and wherein the OPS comprises at least two miRNA target sequences, and wherein each of the at least two miRNA target sequences are optimised to hybridise with a corresponding miRNA sequence;~~
- ~~and~~
- ~~an *in vivo* delivery composition;~~
- ~~wherein the first and second constructs are comprised within or adsorbed to the delivery composition.~~
- ~~73. The composition of claim 72, wherein the ORF codes for an IL-12 protein, or a derivative, agonist or homologue thereof~~
- ~~74. The composition of claim 72 or 73, wherein the delivery composition comprises delivery vectors selected from the group consisting of: a particle, such as a polymeric particle; a liposome; a lipidoid particle; and a viral vector.~~
- ~~75. The composition of any of claims 72 to 74, wherein the OPS comprises miRNA sequences selected to protect one or more organs selected from the group consisting of muscle, liver, kidney, lungs, spleen and skin.~~
- ~~76. The composition of any of claims 72 to 75, wherein the OPS comprises sequences selected from one or more of SEQ ID NOs: 44-57.~~

- ~~77. The composition of any of claims 72 to 76, wherein the OPS comprises at least two miRNA target sequences selected from sequences capable of binding with miRNA-1, miRNA-122, miRNA-30a, miRNA-203a, let7b, miRNA-126, and/or miRNA-192.~~
- ~~78. The composition of any of claims 72 to 77, wherein the OPS comprises at least two miRNA target sequences selected from sequences capable of binding with miRNA-1, miRNA133a, miRNA206, miRNA-122, miRNA203a, miRNA205, miRNA200c, miRNA30a, and/or let7a/b.~~
- ~~79. The composition of any of claims 72 to 78, wherein the OPS comprises at least two miRNA target sequences selected from sequences capable of binding with miRNA-1, miRNA-122, miR-30a and/or miR-203a.~~
- ~~80. The composition of any of claims 72 to 79, wherein the OPS comprises miRNA target sequences capable of binding with miRNA-1, miRNA-122, miRNA-30a and miRNA-203a.~~
- ~~81. The composition of any of claims 72 to 80, wherein the OPS comprises miRNA target sequences capable of binding with miRNA-122, miRNA-1, miRNA-203a, and miRNA-30a.~~
- ~~82. The composition of any of claims 72 to 81, wherein the OPS comprises miRNA target sequences capable of binding with let7b, miRNA-126, and miRNA-30a.~~
- ~~83. The composition of any of claims 72 to 82, wherein the OPS comprises miRNA target sequences capable of binding with miRNA-122, miRNA-192, and miRNA-30a.~~
- ~~84. The composition of any of claims 72 to 83, wherein the OPS comprises miRNA target sequences capable of binding with miRNA-192, miRNA-30a, and miRNA-124, and two miRNA target sequences capable of binding with miRNA-122.~~
- ~~85. The composition of any of claims 72 to 84, wherein the antigen comprises a viral protein or an epitope containing fragment thereof.~~
- ~~86. The composition of claim 85, wherein the antigen comprises a coronavirus spike protein.~~
- ~~87. The composition of claim 85, wherein the antigen comprises a variant coronavirus spike protein~~
- ~~88. The composition of claim 86 or 87, wherein the coronavirus spike protein is a SARS-CoV-2 spike protein.~~
- ~~89. The composition of claim 85, wherein the antigen comprises an influenza protein or a variant thereof, or an epitope containing fragment thereof.~~
- ~~90. The composition of claim 89, wherein the influenza protein is selected from the group consisting of a hemagglutinin, a neuraminidase, a matrix-2 and/or a nucleoprotein.~~
- ~~91. The composition of claim 89, wherein the influenza protein is selected from type A influenza, a type B influenza, or a subtype of type A influenza of H1, H2, H3, H4, H5, H6, H7, H8, H9, H10, H11, H12, H13, H14, H15 or H16.~~

92. ~~The composition of claim 85, wherein the antigen comprises a respiratory syncytial virus (RSV) protein, or a variant thereof, or an epitope containing fragment thereof.~~
93. ~~The composition of claim 92, wherein the protein of the respiratory syncytial virus is the F glycoprotein or the G glycoprotein.~~
94. ~~The composition of claim 85, wherein the antigen comprises a Human Immunodeficiency Virus (HIV) protein or an epitope containing fragment thereof.~~
95. ~~The composition of claim 94, wherein the HIV protein is the glycoprotein 120 neutralizing epitope or glycoprotein 145.~~
96. ~~The composition of any of claims 72 to 84, wherein the antigen comprises a protein from the *Mycobacterium tuberculosis* bacterium or an epitope containing fragment thereof.~~
97. ~~The composition of claim 96, wherein the protein from the *Mycobacterium tuberculosis* bacterium is selected from ESAT-6, Ag85B, TB10.4, Rv2626 and/or RpfD-B.~~
98. ~~The composition of any of claims 72 to 96 for use in a method of the prevention of pathogenic disease.~~
99. ~~A method of increasing a Th1 immune response, comprising administering a composition according to claim 73 to a subject in need thereof.~~
100. ~~— A composition comprising:~~
- ~~at least one mRNA construct comprising at least one open reading frame (ORF), wherein the at least one ORF encodes a proinflammatory cytokine selected from: IL-12; IFN γ ; IFN α ; IFN β ; TNF α ; IL-2; IL-6; IL-8; and GM-CSF, and wherein the ORF is operatively linked to at least one untranslated region (UTR), wherein the UTR comprises at least one OPS that protects multiple organs, and wherein the OPS comprises at least two miRNA target sequences, and wherein each of the at least two miRNA target sequences are optimised to hybridise with a corresponding miRNA sequence;~~
- ~~and~~
- ~~an *in vivo* delivery composition;~~
- ~~wherein the mRNA construct is comprised within or adsorbed to the delivery composition.~~
101. ~~The composition according to claim 100, wherein the ORF codes for an IL-12 protein, or a derivative, agonist or homologue thereof.~~
102. ~~The composition according to claim 100 or 101, wherein the delivery composition comprises delivery vectors selected from the group consisting of: a particle, such as a polymeric particle; a liposome; a lipidoid particle; and a viral vector.~~
103. ~~The composition according to any of claims 100 to 102, wherein the OPS comprises miRNA sequences selected to protect one or more organs selected from the group consisting of muscle, liver, kidney, lungs, spleen and skin.~~

- ~~104.—The composition according to any of claims 100 to 104, wherein the OPS comprises sequences selected from one or more of SEQ ID NOs: 44-57.~~
- ~~105.—The composition according to any of claims 100 to 104, wherein the OPS comprises at least two miRNA target sequences selected from sequences capable of binding with miRNA-1, miRNA-122, miRNA-30a, miRNA-203a, let7b, miRNA-126, and/or miRNA-192.~~
- ~~106.—The composition according to any of claims 100 to 105, wherein the OPS comprises at least two miRNA target sequences selected from sequences capable of binding with miRNA-1, miRNA133a, miRNA206, miRNA-122, miRNA203a, miRNA205, miRNA200c, miRNA30a, and/or let7a/b.~~
- ~~107.—The composition according to any of claims 100 to 106, wherein the OPS comprises at least two miRNA target sequences selected from sequences capable of binding with miRNA-1, miRNA-122, miR-30a and/or miR-203a.~~
- ~~108.—The composition according to claim 107, wherein the OPS comprises miRNA target sequences capable of binding with miRNA-1, miRNA-122, miRNA-30a and miRNA-203a.~~
- ~~109.—The composition according to any of claims 100 to 108, wherein the OPS comprises miRNA target sequences capable of binding with miRNA-122, miRNA-1, miRNA-203a, and miRNA-30a.~~
- ~~110.—The composition according to any of claims 100 to 109, wherein the OPS comprises miRNA target sequences capable of binding with let7b, miRNA-126, and miRNA-30a.~~
- ~~111.—The composition according to any of claims 100 to 110, wherein the OPS comprises miRNA target sequences capable of binding with miRNA-122, miRNA-192, and miRNA-30a.~~
- ~~112.—The composition according to any of claims 100 to 111, wherein the OPS comprises miRNA target sequences capable of binding with miRNA-192, miRNA-30a, and miRNA-124, and two miRNA target sequences capable of binding with miRNA-122.~~
- ~~113.—The composition of any of claims 100 to 112, for use in a method of the prevention of pathogenic disease, the method comprising:~~
- ~~administering the composition to a subject in need thereof; and~~
- ~~coadministering a vaccine composition to the subject.~~
- ~~114.—A method of increasing a Th1 immune response, comprising administering a composition according to claim 101 to a subject in need thereof.~~
- ~~115.—A composition comprising the composition of any of claims 100 to 112; and~~
- ~~a vaccine selected from the group consisting of: a toxoid vaccine, a recombinant vaccine, a conjugated vaccine, an RNA-based vaccine, a DNA-based vaccine, a live-attenuated~~

~~vaccine, an inactivated vaccine, a recombinant vector based vaccine, and combinations thereof.~~

~~116.— A method of treating or preventing one or more pathogenic disease or improving an immune response, the method comprising~~

~~administering to a subject in need thereof a composition comprising at least a first mRNA construct comprising at least a first open reading frame (ORF), wherein the first ORF encodes an antigen selected from: a bacterial protein, or a viral protein, or an epitope containing fragment thereof; wherein the first ORF is operatively linked to at least one untranslated region (UTR), wherein the UTR comprises at least a first organ protection sequence (OPS), wherein the OPS protects multiple organs, and wherein the first OPS comprises at least two micro-RNA (miRNA) target sequences, and wherein each of the at least two miRNA target sequences are optimised to hybridise with a corresponding miRNA sequence; and~~

~~an *in vivo* delivery composition;~~

~~wherein the mRNA construct is comprised within or adsorbed to the delivery composition.~~

~~117.— The method of claim 116, further comprising co-administering to the subject a composition comprising at least one mRNA construct comprising at least a second open reading frame (ORF), wherein the second ORF encodes a proinflammatory cytokine selected from: IL-12; IFN γ ; IFN α ; IFN β ; TNF α ; IL-2; IL-6; IL-8; and GM-CSF.~~

~~118.— The method of claim 116 or claim 117, wherein the second ORF codes for an IL-12 protein, or a derivative, agonist or homologue thereof~~

~~119.— The method of any of claims 116 to 118, wherein the second ORF comprises a sequence at least 90% identical to SEQ ID NO: 59.~~

~~120.— The method of any of claims 116 to 119, wherein the second ORF is operatively linked to at least one untranslated region (UTR), wherein the UTR comprises at least a second OPS that protects multiple organs, and wherein the second OPS comprises at least two miRNA target sequences, and wherein each of the at least two miRNA target sequences are optimised to hybridise with a corresponding miRNA sequence.~~

~~121.— The method of claim 120, wherein the first OPS includes a different set of miRNA target sequences to the second OPS.~~

~~122.— The method of claim 120, wherein the first OPS and the second OPS include the same miRNA target sequences.~~

~~123.— The method of any of claims 116 to 122, wherein the delivery composition comprises delivery vectors selected from the group consisting of: a particle, such as a polymeric particle; a liposome; a lipidoid particle; and a viral vector.~~

124. ~~The method of any of claims 116 to 123, wherein the pathogenic disease is caused by a coronavirus.~~
125. ~~The method of claim 124, wherein the pathogenic disease is caused by the SARS-CoV-2 virus.~~
126. ~~The method of claims 124 or 125, wherein the antigen comprises a viral protein or an epitope-containing fragment thereof that comprises all or a part of a coronavirus spike protein.~~
127. ~~The method of claims 124 or 125, wherein the antigen comprises a viral protein or an epitope-containing fragment thereof that comprises all or a part of a variant coronavirus spike protein.~~
128. ~~The method of claims 126 or 127, wherein the coronavirus spike protein is a SARS-CoV-2 spike protein.~~
129. ~~The method of any of claims 116 to 128, wherein the first mRNA construct further comprises a further open reading frame (ORF), wherein the further ORF encodes an antigen different to the antigen encoded by the first ORF.~~
130. ~~The method of any of claims 116 to 128, further comprising co-administering to the subject a third mRNA construct comprising at least a third open reading frame (ORF), wherein the third ORF encodes an antigen different to the antigen encoded by the first ORF.~~
131. ~~A method of preventing one or more pathogenic disease or improving an immune response, the method comprising:~~
- ~~administering a vaccine composition to a subject in need thereof; and~~
- ~~co-administering to the subject an adjuvant composition comprising at least one mRNA construct comprising at least one open reading frame (ORF), wherein the at least one ORF encodes a proinflammatory cytokine selected from: IL-12; IFN γ ; IFN α ; IFN β ; TNF α ; IL-2; IL-6; IL-8; and GM-CSF, and wherein the ORF is operatively linked to at least one untranslated region (UTR), wherein the UTR comprises at least one OPS that protects multiple organs, and wherein the OPS comprises at least two miRNA target sequences, and wherein each of the at least two miRNA target sequences are optimised to hybridise with a corresponding miRNA sequence; and an *in vivo* delivery composition; wherein the mRNA construct is comprised within or adsorbed to the delivery composition.~~
132. ~~The method of claim 131, wherein the vaccine composition is selected from the group consisting of: a toxoid vaccine, a recombinant vaccine, a conjugated vaccine, an RNA-based vaccine, a DNA-based vaccine, a live-attenuated vaccine, an inactivated vaccine, a recombinant-vector based vaccine, and combinations thereof.~~

133. ~~The method of claim 131 or 132, wherein the vaccine composition comprises at least a first mRNA construct comprising at least a first open reading frame (ORF), wherein the first ORF encodes an antigen selected from: a bacterial protein or part thereof, a viral protein or part thereof, and a neoantigen or part thereof; and an *in vivo* delivery composition, wherein the mRNA construct is comprised within or adsorbed to the delivery composition.~~
134. ~~The method of any of claims 117 to 133, wherein coadministering comprises administering the vaccine composition and the adjuvant composition concurrently or consecutively, in either order.~~
135. ~~The method of any of claims 116 to 134, wherein the vaccine composition and/or the adjuvant composition is administered intravenously, subcutaneously, intra-muscularly, intranasally, intra-arterially and/or through inhalation.~~
136. ~~The method of any of claims 116 to 135, wherein the pathogenic disease is caused by an intracellular pathogen.~~
137. ~~The method of any of claims 116 to 136, wherein the pathogenic disease is a latent infection.~~
138. ~~The method of any of claims 116 to 136, wherein the pathogenic disease is an active infection.~~
139. ~~The method of any of claims 116 to 135, wherein the pathogenic disease is caused by an influenza virus.~~
140. ~~The method of any of claims 116 to 135, wherein the pathogenic disease is caused by a coronavirus.~~
141. ~~The method of claim 140, wherein the pathogenic disease is caused by the SARS-CoV-2 virus.~~
142. ~~The method of any of claims 116 to 135, wherein the pathogenic disease is caused by the respiratory syncytial virus (RSV).~~
143. ~~The method of any of claims 116 to 135, wherein the pathogenic disease is caused by the Human Immunodeficiency Virus (HIV).~~
144. ~~The method of any of claims 116 to 135, wherein the pathogenic disease is caused by the Varicella zoster virus (VZV).~~
145. ~~The method of any of claims 116 to 135, wherein the pathogenic disease is caused by the Mycobacterium tuberculosis bacterium.~~
146. ~~A method of treating or preventing cancer, the method comprising administering to a subject in need thereof a first composition comprising at least a first mRNA construct comprising at least a first open reading frame (ORF), wherein the first ORF encodes a tumor associated antigen, or an epitope containing fragment thereof; wherein~~

~~the first ORF is operatively linked to at least one untranslated region (UTR), wherein the UTR comprises at least a first organ protection sequence (OPS), wherein the OPS protects multiple organs, and wherein the first OPS comprises at least two micro-RNA (miRNA) target sequences, and wherein each of the at least two miRNA target sequences are optimised to hybridise with a corresponding miRNA sequence; and~~

~~an *in vivo* delivery composition;~~

~~wherein the mRNA construct is comprised within or adsorbed to the delivery composition.~~

~~147. The method of claim 146, wherein the tumor-associated antigen comprises a colorectal tumour antigen.~~

~~148. The method of claim 146, wherein the tumor-associated antigen is MUC1.~~

~~149. The method of claim 146, wherein the tumor-associated antigen is a neoantigen.~~

~~150. The method of claim 149, wherein the neoantigen is personalised to the subject.~~

~~151. The method of any of claims 146 to 150, further comprising co-administering to the subject a second composition comprising at least one mRNA construct comprising at least a second open reading frame (ORF), wherein the second ORF encodes a proinflammatory cytokine selected from: IL-12; IFN γ ; IFN α ; IFN β ; TNF α ; IL-2; IL-6; IL-8; and GM-CSF.~~

~~152. The method of claim 151, wherein co-administering comprises administering the first composition and the second composition concurrently or consecutively, in either order.~~

~~153. A method of treating or preventing cancer, the method comprising:~~

~~administering a cancer therapeutic vaccine composition to a subject in need thereof; and~~

~~coadministering to the subject a composition comprising at least one mRNA construct comprising at least one open reading frame (ORF), wherein the at least one ORF encodes a proinflammatory cytokine selected from: IL-12; IFN γ ; IFN α ; IFN β ; TNF α ; IL-2; IL-6; IL-8; and GM-CSF, and wherein the ORF is operatively linked to at least one untranslated region (UTR), wherein the UTR comprises at least one OPS that protects multiple organs, and wherein the OPS comprises at least two miRNA target sequences, and wherein each of the at least two miRNA target sequences are optimised to hybridise with a corresponding miRNA sequence; and an *in vivo* delivery composition; wherein the mRNA construct is comprised within or adsorbed to the delivery composition.~~

~~154. The method of claim 153, wherein the cancer therapeutic vaccine composition delivers a tumor-associated antigen to the subject.~~

~~155. The method of claim 154, wherein the tumor-associated antigen is delivered to the subject using a viral vector.~~

~~156. The method of claim 155, wherein the vector is an adenovirus vector.~~

~~157. The method of claim 156, wherein the adenovirus vector is ChAdOx1 or ChAdOx2.~~

25. The composition of claim 1, wherein the first mRNA comprises a second ORF encoding a second antigen, wherein the second antigen is different to the first antigen.

26. The composition of claim 25, wherein the second antigen is selected from: a pathogenic microbial antigen or a tumor-associated antigen, or an epitope containing fragment thereof;

27. The composition of claim 1, further comprising a second mRNA construct comprising a second open reading frame (ORF), wherein the second ORF encodes a second antigen, wherein the second antigen is different to the first antigen.

28. The composition of claim 27, wherein the second antigen is selected from: a pathogenic microbial antigen or a tumor-associated antigen, or an epitope containing fragment thereof.