CLAIMS

1. An mRNA construct comprising at least one open reading frame (ORF), wherein the ORF is operatively linked to at least one untranslated region (UTR), wherein the UTR comprises at least one organ protection sequence (OPS), wherein the OPS sequence comprises at least a first, a second and a third micro-RNA (miRNA) target sequence, and wherein each of the at least a first, second and third the miRNA target sequences are optimised to hybridise with a corresponding miRNA sequence.

2. The mRNA construct of claim 1, wherein the first, second and third miRNA target sequences are all different from each other.

3. The mRNA construct of claim 1, wherein the any one of the first, second and third miRNA sequences is repeated at least twice within the OPS.

4. The mRNA construct of claim 1, wherein the OPS comprises at least a fourth miRNA target sequence.

5. The mRNA construct of claim 4, wherein the fourth miRNA target sequences is different from the first, second and third miRNA target sequences.

6. The mRNA construct of claim 4, wherein the fourth miRNA sequence is repeated at least twice within the OPS.

7. The mRNA construct of claim 4, wherein the OPS comprises at least a fifth micro-RNA (miRNA) target sequence.

8. The mRNA construct of claim 7, wherein the fifth miRNA target sequences is different from the first, second, third and fourth miRNA target sequences.

9. The mRNA construct of claim 8, wherein the fifth miRNA sequence is repeated at least twice within the OPS.

10. The mRNA construct of claim 1, wherein the UTR is positioned 3' to the ORF.

11. The mRNA construct of claim 1, wherein the UTR is positioned 5' to the ORF.

12. The mRNA construct of claim1, wherein the at least a first, second and third the miRNA target sequences are 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 a,b,c; miRNA-877; miRNA-4300; miRNA-4720; and miRNA-6761.

13. The mRNA construct of claim 1, wherein the at least a first, second and third miRNA target sequences are selected from one or more of the sequences of SEQ ID NOs: 44-57.

14. The mRNA construct of claim 1, wherein the OPS reduces or eliminates translation of the ORF in non-diseased cells comprised within one or more organs selected from the group consisting of: liver; pancreas; brain and CNS; kidney; spleen; gut, including oesophagus, stomach, intestine, colon, and rectum; lung; muscle, including myocardium; skin and breast.

15. The mRNA construct of claim 1, wherein the mRNA construct comprises at least a second ORF.

16. The mRNA construct of claim 15, wherein the mRNA construct comprises at least a third ORF.

17. The mRNA construct of claim 1, wherein the ORF encodes an oncolytic virus or therapeutic virulence factor.

18. The mRNA construct of claim 1, wherein the ORF encodes an oncolytic virus viral entry receptor.

19. The mRNA construct of claim 1, wherein the ORF encodes a protein that decreases an anti-viral immune response.

20. The mRNA construct of claim 19, wherein the protein is B18R or a homologue or derivative thereof.

21. The mRNA construct of claim 1, wherein the ORF encodes a protein that binds to and inhibits an immune checkpoint receptor or an activator thereof.

22. The mRNA construct of claim 21, wherein the immune checkpoint receptor or activator thereof is selected from one or more of the group consisting of: CTLA4; LAG3; PD1; and PDL1.

23. The mRNA construct of claim 1, wherein the ORF encodes a pro-inflammatory cytokine or a derivative, agonist or homologue thereof.

24. The mRNA construct of claim 23, wherein the proinflammatory cytokine is selected from: IFNγ; IFNα; IFNβ; TNFα; IL-12; IL-2; IL-6; IL-8; and GM-CSF.

25. The mRNA construct of claim 1, wherein the ORF encodes a protein selected from the group consisting of: EpCAM; anti-CTLA-4; anti-PD1; anti-PDL1; A2A; anti-FGF2; anti-FGFR/FGFR2b; anti-SEMA4D; CCL5; CD137; CD200; CD38; CD44; CSF-1R; CXCL10; CXCL13; endothelin B Receptor; IL-15; IL-21; IL-35; ISRE7; LFA-1; NG2 (also known as SPEG4); a SMAD; STING; TGFβ; and VCAM1.

26. The mRNA construct of claim 1, wherein the ORF encodes a chemokine that attracts T-cells.

27. The mRNA construct of claim 26, wherein the chemokine is selected from the group consisting of: CCL2; CCL3; CCL4; CCL5; CCL20; CCL22; CCL28; CXCL8; CXCL9; CXCL10; CXCL11; CXCL12; and CXCL1.

28. The mRNA construct of claim 1, wherein the ORF encodes a surface-anchored targeting domain that is specific for a T cell marker.

29. The mRNA construct of claim 28, wherein the surface-anchored targeting domain is MR1.

30. The mRNA construct of claim 1, wherein the ORF encodes an antigen.

31. A pharmaceutical composition comprising:

i. at least one mRNA construct comprising at least one open reading frame (ORF), wherein the ORF is operatively linked to at least one untranslated region (UTR), wherein the UTR comprises at least one organ protection sequence (OPS), wherein the OPS sequence comprises at least a first, a second and a third micro-RNA (miRNA) target sequence, and wherein each of the at least a first, second and third the miRNA target sequences are optimised to hybridise with a corresponding miRNA sequence; and

ii. an *in vivo* delivery composition;

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

32. The composition of claim 31, wherein the composition is selected from the group consisting of: a particle; a liposome; a lipidoid particle; and a viral vector.

33. The composition of claim 31, wherein the composition is for use in treating cancer.

34. The composition of claim 31, wherein the composition is for use as a vaccine, or as a vaccine adjuvant.

35. An mRNA construct comprising at least one open reading frame (ORF), wherein the ORF is operatively linked to at least one untranslated region (UTR), wherein the UTR comprises at least one organ protection sequence (OPS), wherein the OPS sequence protects multiple organs, and wherein the OPS comprises at least a first, and at least a second micro-RNA (miRNA) target sequence, and wherein each of the at least a first and second miRNA target sequences are optimised to hybridise with a corresponding miRNA sequence.

36. The mRNA construct of claim 35, wherein the first and second miRNA target sequences are different from each other.

37. The mRNA construct of claim 35, wherein the first and second miRNA target sequences are repeated at least twice within the OPS.

38. The mRNA construct of claim 35, wherein the OPS comprises at least a third miRNA target sequence.

39. The mRNA construct of claim 35, wherein the third miRNA target sequence is different from the first and second miRNA target sequences.

40. The mRNA construct of claim 35, wherein the third miRNA sequence is repeated at least twice within the OPS.

41. The mRNA construct of claim 35, wherein the OPS comprises at least a fourth miRNA target sequence.

42. The mRNA construct of claim 41, wherein the fourth miRNA target sequences is different from the first, second, and third miRNA target sequences.

43. The mRNA construct of claim 41, wherein the fourth miRNA sequence is repeated at least twice within the OPS.

44. The mRNA construct of claim 41, wherein the OPS comprises at least a fifth miRNA target sequence.

45. The mRNA construct of claim 44, wherein the fifth miRNA target sequences is different from the first, second, third and fourth miRNA target sequences.

46. The mRNA construct of claim 44, wherein the fifth miRNA sequence is repeated at least twice within the OPS.

47. The mRNA construct of claim 35, wherein the UTR is positioned 3' to the ORF.

48. The mRNA construct of claim 35, wherein the UTR is positioned 5' to the ORF.

49. The mRNA construct of claim 35, wherein the at least a first and second miRNA target sequences are 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 a,b,c; miRNA-877; miRNA-4300; miRNA-4720; and miRNA-6761.

50. The mRNA construct of claim 35, wherein the at least a first and second miRNA target sequences are selected from one or more of the sequences of SEQ ID Nos: 44-57.

51. The mRNA construct of claim 35, wherein the OPS reduces or eliminates translation of the ORF in non-diseased cells comprised within one or more organs selected

from the group consisting of: liver; pancreas; brain and CNS; kidney; spleen; gut, including oesophagus, stomach, intestine, colon, and rectum; lung; skin and breast.

52. The mRNA construct of claim 35, wherein the mRNA construct comprises at least a second ORF.

53. The mRNA construct of claim 35, wherein the mRNA construct comprises at least a third ORF.

54. The mRNA construct of claim 35, wherein the ORF encodes an oncolytic or therapeutic virus virulence factor.

55. The mRNA construct of claim 35, wherein the ORF encodes an oncolytic virus viral entry receptor.

56. The mRNA construct of claim 35, wherein the viral entry receptor is a nectin.

57. The mRNA construct of claim 35, wherein the ORF encodes a protein that decreases an anti-viral immune response.

58. The mRNA construct of claim 35, wherein the protein is B18R or a homologue or derivative thereof.

59. The mRNA construct of claim 35, wherein the ORF encodes a protein that binds to and inhibits an immune checkpoint receptor or an activator thereof.

60. The mRNA construct of claim 59, wherein the immune checkpoint receptor is selected from: CTLA4; LAG3; and PD1.

61. The mRNA construct of claim 35, wherein the ORF encodes a pro-inflammatory cytokine or a derivative, agonist or homologue thereof.

62. The mRNA construct of claim 61, wherein the proinflammatory cytokine is selected from: IFNγ; IFNα; IFNβ; TNFα; IL-12; IL-2; IL-6; IL-8; and GM-CSF.

63. The mRNA construct of claim 35, wherein the ORF encodes a protein selected from the group consisting of: EpCAM; anti-CTLA-4; anti-PD1; anti-PDL1; A2A; anti-FGF2; anti-FGFR/FGFR2b; anti-SEMA4D; CCL5; CD137; CD200; CD38; CD44; CSF-1R; CXCL10; CXCL13; endothelin B Receptor; IL-15; IL-21; IL-35; ISRE7; LFA-1; NG2 (also known as SPEG4); a SMAD; STING; TGFβ; and VCAM1.

64. The mRNA construct of claim 35, wherein the ORF encodes a chemokine that attracts T-cells.

65. The mRNA construct of claim 64, wherein the chemokine is selected from the group consisting of: CCL2; CCL3; CCL4; CCL5; CCL20; CCL22; CCL28; CXCL8; CXCL9; CXCL10; CXCL11; CXCL12; and XCL1.

66. The mRNA construct of claim 35, wherein the ORF encodes a surface-anchored targeting domain that is specific for a T cell marker.

67. The mRNA construct of claim 66, wherein the surface-anchored targeting domain is MR1.

68. The mRNA construct of claim 35, wherein the ORF encodes an antigen.

69. The mRNA construct of claim 68, wherein the antigen comprises a coronavirus spike protein or a fragment or derivative thereof.

70. A pharmaceutical composition comprising:

    a. at least one mRNA construct comprising at least one open reading frame (ORF), wherein the ORF is operatively linked to at least one untranslated region (UTR), wherein the UTR comprises at least one organ protection

sequence (OPS), wherein the OPS sequence protects multiple organs, and wherein the OPS sequence comprises at least a first and a second micro-RNA (miRNA) target sequence, and wherein each of the at least a first and second miRNA target sequences are optimised to hybridise with a corresponding miRNA sequence; and

b. an *in vivo* delivery composition;

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

71. The composition of claim 70, wherein the composition is selected from the group consisting of: a particle; a liposome; a lipidoid particle; and a viral vector.

72. The composition of claim 70, wherein the composition is for use in treating cancer.

73. The composition of claim 70, wherein the composition is for use as a vaccine or a vaccine adjuvant.

74. An mRNA comprising at least one open reading frame (ORF), wherein the ORF is operatively linked to at least one untranslated region (UTR), wherein the UTR comprises at least one organ protection (OPS) sequence, and wherein the OPS sequence comprises:

a. at least a first organ protection sequence, wherein the first organ protection sequence comprises a sequence that is a target for a first miRNA, and wherein the first organ protection sequence is optimised to hybridise to the first miRNA with a substantially perfect match within cells of a first organ;

b. at least a second organ protection sequence, wherein the second organ protection sequence comprises a sequence that is a target for a second miRNA, and wherein the second organ protection sequence is optimised to hybridise to

the second miRNA with a substantially perfect match within cells of a second organ; and

c. at least a third organ protection sequence, wherein the third organ protection sequence comprises a sequence that is a target for a third miRNA, and wherein the third organ protection sequence is optimised to hybridise to the third miRNA with a substantially perfect match within cells of a third organ;

wherein the first, second and third organ protection sequences are arranged consecutively within the OPS and wherein the cells of the first, second and third organs are non-diseased cells.

75. The mRNA of claim 74, wherein the non-diseased cells are comprised within predominantly healthy tissue.

76. The mRNA of claim 74, wherein the first, second and third miRNA target sequences are selected from one or more of the sequences of SEQ ID Nos: 44-57.

77. The mRNA of claim 74, wherein the ORF codes for an immunomodulator protein.

78. The mRNA of claim 74, wherein the ORF codes for an IL-12 protein, or a derivative, agonist or homologue thereof.

79. The mRNA of claim 78, wherein the mRNA comprises SEQ ID NO: 62.

80. The mRNA of claim 74, wherein the ORF codes for a GM-CSF protein, or a derivative, agonist or homologue thereof.

81. The mRNA of claim 80, wherein the mRNA comprises SEQ ID NO: 64.

82. The mRNA of claim 74 wherein the mRNA comprises SEQ ID NO: 63.

83. A pharmaceutical composition comprising:

i. at least one mRNA of claim 74; and

ii. an *in vivo* delivery composition;

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

84. The composition of claim 83, wherein the composition is selected from the group consisting of: a particle; a liposome; a lipidoid particle; and a viral vector.

85. The composition of claim 83, wherein the composition is for use in treating cancer.

86. The composition of claim 83, wherein the composition is for use as a vaccine or as a vaccine adjuvant.

87. The composition of claim 83, wherein the composition is administered intravenously, subcutaneously, intra-muscularly, intranasally, intra-arterially and/or through inhalation.

88. A vaccine composition comprising:

at least a first mRNA construct comprising at least one open reading frame (ORF), wherein the ORF is operatively linked to at least one untranslated region (UTR), wherein the UTR comprises at least one organ protection sequence (OPS), wherein the OPS sequence protects multiple organs, and wherein the OPS sequence comprises at least a first and a second micro-RNA (miRNA) target sequence, and wherein each of the at least a first and second 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.

89. The vaccine composition of claim 88, wherein the delivery composition is selected from the group consisting of: a particle, such as a polymeric particle; a liposome; a lipidoid particle; and a viral vector.

90. The vaccine composition of claim 88, wherein the ORF encodes an antigen selected from: a bacterial protein; and/or a viral protein.

91. The vaccine composition of claim 90, wherein the antigen comprises a viral protein that comprises all or a part of a coronavirus spike protein.

92. The vaccine composition of claim 91, wherein the coronavirus spike protein is a SARS-CoV-2 spike protein.

93. The vaccine composition of claim 88, further comprising at least a second mRNA construct comprising at least a second open reading frame (ORF), wherein the second ORF encodes a proinflammatory cytokine selected from: IFNγ; IFNα; IFNβ; TNFα; IL-12; IL-2; IL-6; IL-8; and GM-CSF.

94. The vaccine composition of claim 88, wherein the first mRNA further comprises at least a second open reading frame (ORF), wherein the second ORF encodes a proinflammatory cytokine selected from: IFNγ; IFNα; IFNβ; TNFα; IL-12; IL-2; IL-6; IL-8; and GM-CSF.

95. A vaccine composition comprising:

a vaccine construct comprised of 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 wherein the first ORF

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

an adjuvant construct comprised of at least a second mRNA construct comprising at least a second open reading frame (ORF), wherein the second ORF encodes a proinflammatory cytokine selected from: IFNγ; IFNα; IFNβ; TNFα; 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 sequence that protects multiple organs, and wherein the OPS sequence comprises at least a third and a fourth miRNA target sequence, and wherein each of the at least a third and fourth miRNA target sequences are optimised to hybridise with a corresponding miRNA sequence;

and

an *in vivo* delivery composition;

wherein the vaccine and adjuvant constructs are comprised within or adsorbed to the delivery composition.

96. The vaccine composition of claim 95, wherein the second ORF codes for an IL-12 protein, or a derivative, agonist or homologue thereof.

97. The vaccine composition of claim 96, wherein the second ORF comprises SEQ ID NO: 63.

98. The vaccine composition of claim 95, wherein the first ORF codes for a viral protein that comprises all or a part of a coronavirus spike protein.

99. The vaccine composition of claim 98, wherein the coronavirus spike protein is a SARS-CoV-2 spike protein.

100. The composition of claim 95, wherein the composition is administered intravenously, subcutaneously, intra-muscularly, intranasally, intra-arterially and/or through inhalation.