CLAIMS

1. An immunostimulatory bacterium, comprising a plasmid that encodes a therapeutic product, wherein:

the bacterium comprises genome modifications, whereby the bacterium does not produce active thymidylate synthase, and requires supplementation for growth; and

the immunostimulatory bacterium lacks flagella and is *msbB*$^-$/*pagP*$^-$.

2. The immunostimulatory bacterium of claim 1, wherein the supplementation for growth comprises thymine, thymine derivatives, thymidine, thymidine derivatives, thymine precursor(s), thymidine precursor(s), or thymidine monophosphate precursor(s).

3. The immunostimulatory bacterium of claim 1 or claim 2, wherein the bacterium comprises genome modifications that reduce or eliminate activation of TLR2, and optionally TLR4 and/or TLR5.

4. An immunostimulatory bacterium, comprising a plasmid that encodes a therapeutic product, wherein;

the bacterium comprises genome modifications, whereby the bacterium does not secrete active asparaginase; and

the bacterium comprises genome modifications that reduce or eliminate activation of TLR2, and optionally TLR4 and/or TLR5.

5. The immunostimulatory bacterium of any of claims 1-4, wherein the genome of the immunostimulatory bacterium is modified by deletion or disruption or modification of all or of a sufficient portion of the gene *ansB* encoding L-asparaginase II, whereby the bacterium is *ansB*$^-$ and does not express active L-asparaginase II.

6. An immunostimulatory bacterium, comprising genome modification(s) that reduce or eliminate activation of TLR2, whereby induction of type I IFN is not inhibited by TLR2, wherein:

the immunostimulatory bacterium comprises genome modification(s) whereby it cannot replicate *in vivo*, but can replicate when grown *in vitro* with nutritional supplementation; and

the genome modification(s) eliminate(s) or inactivate(s) thymidylate synthase, whereby the bacterium is *thyA*$^-$.

7. An immunostimulatory bacterium, comprising genome modification(s) that reduce or eliminate activation of TLR2, whereby induction of type I IFN is not inhibited by TLR2, wherein the immunostimulatory bacterium comprises a plasmid that encodes an interferon, or encodes a modified STING protein that constitutively induces type I interferon, and encodes an antigen or protein from a pathogen or tumor.

8. An immunostimulatory bacterium, comprising a plasmid encoding a therapeutic product, wherein:

the genome of the immunostimulatory bacterium is modified by deletion or disruption of all or of a sufficient portion of a gene or genes, whereby the bacterium has been modified to generate lipopolysaccharide (LPS) with penta-acylated lipid A;

lipopolysaccharide with hexa-acylated lipid A is substantially reduced, by at least 10-fold, compared to the wild-type bacterium, or is absent;

the genome of bacterium is modified to be auxotrophic for an essential nutrient;

the genome of the bacterium is modified, whereby the bacterium itself does not inhibit or prevent induction of type I interferon (IFN) in an infected immune cell; and

the genome of the bacterium is modified, whereby it does not encode or produce active asparaginase and/or thymidylate synthase.

9. An immunostimulatory bacterium, comprising a plasmid encoding a therapeutic product, wherein:

the genome of the immunostimulatory bacterium is modified by deletion or disruption of all or of a sufficient portion of a gene or genes, whereby the bacterium has been modified to generate lipopolysaccharide (LPS) with penta-acylated lipid A;

lipopolysaccharide with hexa-acylated lipid A is substantially reduced, by at least 10-fold, compared to the wild-type bacterium, or is absent;

the genome of the bacterium comprises a modification or modifications that result in a bacterium that does not have flagella;

the wild-type of the bacterium has flagella; and

the genome of bacterium is modified whereby it does not produce active thymidylate synthase, whereby the bacterium is *thyA*$^-$.

10. An immunostimulatory bacterium, comprising a plasmid encoding a therapeutic product, wherein:

the genome of the immunostimulatory bacterium is modified by deletion or disruption of all or of a sufficient portion of a gene or genes, whereby the bacterium lacks flagella;

the unmodified immunostimulatory bacterium has flagella; and

the genome of the bacterium is modified, whereby it does not produce active thymidylate synthase.

11. The immunostimulatory bacterium of claim 9 or claim 10, wherein genome modifications comprise deletions, insertions, and/or replacements whereby the bacterium is *thyA*$^-$.

12. The immunostimulatory bacterium of any of claims 1-11, wherein the genome is modified so that the bacterium lacks curli fimbriae.

13. The immunostimulatory bacterium of any of claims 1-12, wherein the bacterium comprises genome modifications that reduce or eliminate activation of TLR4 and/or TLR5.

14. The immunostimulatory bacterium of any of claims 1-13, wherein:

the genome modifications result in a bacterium that does not have flagella; and

the wild-type of the bacterium has flagella.

15. The immunostimulatory bacterium of any of claims 1-14, wherein the bacterium does not produce curli fimbriae.

16. The immunostimulatory bacterium of any of claims 1-15, wherein genome modifications result in penta-acylated lipopolysaccharides.

17. The immunostimulatory bacterium of any of claims 4-16, wherein the immunostimulatory bacterium lacks flagella and is *msbB*$^-$/*pagP*$^-$.

18. An immunostimulatory bacterium, comprising genome modifications that reduce or eliminate activation of TLR2, whereby induction of type I IFN is not inhibited by TLR2, wherein:

the immunostimulatory bacterium can replicate *in vivo* in a eukaryotic host; and

the immunostimulatory bacterium comprises a plasmid that encodes a tumor-associated antigen, or encodes a tumor antigen and a STING protein, or encodes a tumor-associated antigen and interferon alpha, or encodes a tumor-associated antigen and interferon beta.

19. The immunostimulatory bacterium of any of claims 1-18, wherein the bacterium encodes a STING protein that is a modified STING protein that has increased induction of type I interferon compared to the unmodified human STING protein.

20. The immunostimulatory bacterium of claim 19, wherein the modified STING protein is a modified STING protein of any of claims 406-431.

21. The immunostimulatory bacterium of claim 20, wherein the modified STING protein comprises the replacement N154S/R284G.

22. The immunostimulatory bacterium of any of claims 1-21, wherein a therapeutic product encoded in the plasmid is part of a cytosolic DNA/RNA sensor pathway that leads to expression of type I interferon (IFN), or the encoded product is interferon-alpha or is interferon-beta, or the encoded product is both IFN-alpha and IFN-beta.

23. The immunostimulatory bacterium of claim 22, wherein the therapeutic product that is part of a cytosolic DNA/RNA sensor pathway that leads to expression of type I interferon (IFN) is a STING protein.

24. The immunostimulatory bacterium of any of claims 1-23, wherein the plasmid encodes an antigen, epitope(s), or protein from a pathogen or a tumor.

25. An immunostimulatory bacterium, comprising a plasmid encoding a combination of heterologous products, wherein:

the genome of the immunostimulatory bacterium is modified by deletion or disruption of all or of a sufficient portion of a gene or genes, whereby the bacterium has attenuated recognition by TLR2, and optionally one or both of TLR4 and TLR5;

one product is part of a cytosolic DNA/RNA sensor pathway that leads to expression of type I interferon (IFN); and

a second product that is an antigen, an epitope or epitopes from is antigen, or is protein for immunization against the pathogen or tumor.

26. The immunostimulatory bacterium of claim 25, wherein the genome of the bacterium is modified whereby the bacterium does not have curli fimbriae.

27. An immunostimulatory bacterium, comprising nucleic acid operatively linked to a prokaryotic promoter, wherein:

the nucleic acid encodes RNA that lacks sequences necessary for translation by a prokaryote, whereby the RNA is produced in the bacterium;

the encoded RNA lacks a Shine-Dalgarno sequence, and/or comprises an Internal Ribosome Entry Site (IRES), and/or a translational read through 2A peptide; and

the immunostimulatory bacterium comprises genomic modifications whereby the bacterium infects tissue-resident myeloid cells, and does not infect epithelial cells.

28. An immunostimulatory bacterium, comprising nucleic acid operatively linked to a prokaryotic promoter, wherein:

the nucleic acid comprises RNA that lacks sequences necessary for translation by a prokaryote; and

the immunostimulatory bacterium comprises genomic modifications whereby the bacterium infects tissue-resident myeloid cells, and does not infect epithelial cells.

29. The immunostimulatory bacterium of claim 28, wherein the RNA lacks a Shine-Dalgarno sequence.

30. The immunostimulatory bacterium of any of claims 27-29, wherein the 2A peptide is one or more of T2A, P2A, E2A, or F2A.

31. The immunostimulatory bacterium of any of claims 1-30, wherein:

the nucleic acid encoding a therapeutic product is operatively linked to a prokaryotic promoter, wherein:

the nucleic acid encodes RNA that lacks sequences necessary for translation by a prokaryote, whereby the RNA is produced in the bacterium, wherein:

the RNA lacks a Shine-Dalgarno sequence, and comprises an Internal Ribosome Entry Site (IRES), or a translational read through 2A peptide.

32. The immunostimulatory bacterium of any of claims 27-31, wherein the prokaryotic promoter is a bacterial promoter or a bacteriophage promoter.

33. The immunostimulatory bacterium of claim 32, wherein the promoter is a bacteriophage promoter.

34. The immunostimulatory bacterium of claim 32 or claim 33, wherein the immunostimulatory bacterium encodes a phage RNA polymerase.

35. The immunostimulatory bacterium of claim 32, wherein the promoter is selected from a promoter comprising any of SEQ ID NOs: 393-396, respectively:

attatgtcttgacatgtagtgagtgggctggtataatgcagcaag, or

ttatgcttgacgctgcgtaaggtttttgttataatacaccaag, or

attatgtcttgacatgtagtgagtgggctggtaaatgcagcaag, or

gatcccggagttcatgcgtgatgcaatgaaagtgccgttctacttcggtgggacctcactgcttatcgttgttgtcgtgattatggactttat
ggctcaagtgcaaactctgatgatgtccagtcagtatgagtctgcattgaagaaggcgaacctgaaaggctacggccgttaattggtcg
cctgagaagttacggagagtaaaaatgaaagttcgtgcttccgtcaagaaattatgccgtaactgcaaaatcgttaagcgtgatggtgtc
atccgtgtgatttgcagtgccgagccgaagcataaacagcgccaaggctgatttttttcgcatatttttcttgcaaagttgggttgagctggc
tagattagccagccaatcttttgtatgtctgtacgtttccatttgagtatcctgaaaacgggctttcagcatggtacgtacatattaaatagta
ggagtgcatagtggcccgtatagcaggcattaacattcctgatcagaaacacgccgtgatcgcgttaacttcgatctacggtgtcggca
agacccgttctaaagccatcctggctgcagcgggtatcgctgaaaatgttaagatcctctagatttaagaaggagatatacat
(*Salmonella* rpsm promoter).

36. The immunostimulatory bacterium of any of claims 27-35, wherein the immunostimulatory bacterium comprises genomic modifications whereby the bacterium infects tissue-resident myeloid cells, and does not infect epithelial cells, wherein the genome modifications result in bacteria that are *msbB*$^{-}$/*pagP*$^{-}$.

37. The immunostimulatory bacterium of any of claims 27-~~claim~~ 36, wherein:

the bacterium lacks flagella; and

the bacterium without the genomic modifications comprises flagella.

38. An immunostimulatory bacterium, comprising a plasmid encoding a therapeutic product, wherein infection of a macrophage by the bacterium converts a human M2 macrophage to an M1 or M1-like phenotype macrophage.

39. The immunostimulatory bacterium of claim 38, wherein the therapeutic product is part of a cytosolic DNA/RNA sensor pathway that leads to expression of type I interferon (IFN).

40. The immunostimulatory bacterium of claim 39, wherein the expression of the type I IFN is constitutive.

41. The immunostimulatory bacterium of claim 39 or claim 40, wherein the therapeutic product is a gain-of-function (GOF) variant of the therapeutic product that is part of the cytosolic DNA/RNA sensor pathway, wherein the variant GOF product does not require cytosolic nucleic acids, nucleotides, dinucleotides, or cyclic dinucleotides to result in expression of type I IFN.

42. The immunostimulatory bacterium of any of claims 39-41, wherein the product is a variant STING protein.

43. The immunostimulatory bacterium of any of claims 38-42, wherein infection by the bacterium converts human M2 macrophages into M1-like type I IFN producing cells.

44. The immunostimulatory bacterium of any of claims 1-43 that lacks flagella, wherein the wild-type bacterium has flagella, and is *pagP*$^{-}$/*msbB*$^{-}$.

45. The immunostimulatory bacterium of claim 44 that is a *Salmonella* strain.

46. The immunostimulatory bacterium of any of claims 1-45, wherein the therapeutic product is an anti-cancer therapeutic.

47. The immunostimulatory bacterium of any of claims 1-45, wherein the therapeutic product is an anti-viral therapeutic or an anti-pathogenic bacterial therapeutic.

48. The immunostimulatory bacterium of claim 47, wherein the anti-viral therapeutic inhibits a viral enzyme or inhibits viral replication.

49. The immunostimulatory bacterium of claim 47, wherein the therapeutic is an anti-viral therapeutic is a viral antigen whose expression results in an immune-protective response against a virus, or the anti-viral therapeutic is an antibody that binds to or interacts with a viral antigen, whereby a virus is inhibited or blocked, or anti-viral immunity results.

50. The immunostimulatory bacterium of claim 47, wherein the therapeutic is an anti-bacterial therapeutic that is a bacterial antigen whose expression results in an immune-protective response against the bacterial pathogen, or the anti-bacterial therapeutic is an antibody that binds to or interacts with a bacterial antigen, whereby the pathogenic bacterium is inhibited or blocked, or anti-pathogenic bacterium immunity results.

51. The immunostimulatory bacterium of any of claims 47-50, wherein the immunostimulatory bacterium encodes an anti-viral therapeutic for treating a virus or infectious agent that causes persistent infection.

52. The immunostimulatory bacterium of any of claims 47-49 and 51, wherein the anti-viral therapeutic is a viral antigen or epitope of an antigen, and the antigen comprises a viral surface protein, or a viral nucleocapsid protein, or a viral nonstructural protein, or a virus open reading frame protein.

53. The immunostimulatory bacterium of claim 51, wherein the virus or infectious agent causes chronic infection.

54. The immunostimulatory bacterium of claim 51, wherein the virus or infectious agent causes latent infection.

55. The immunostimulatory bacterium of claim 51, wherein the virus or infectious agent causes slow infection.

56. The immunostimulatory bacterium of claim 51, wherein the virus or infectious agent is selected from among T-Cell leukemia viruses, Epstein-Barr virus, cytomegalovirus, herpesviruses, varicella zoster virus, measles virus, papovaviruses, prions, hepatitis virus type A, B, C, D and E, adenoviruses, parvoviruses, human immunodeficiency virus (HIV), coronaviruses, smallpox virus, poliovirus, influenza virus, rotavirus, yellow fever virus, mumps virus, rubella virus, and papillomaviruses.

57. The immunostimulatory bacterium of claim 51, wherein the virus is HIV or is a hepatitis virus.

58. The immunostimulatory bacterium of claim 51, wherein the infectious agent is a prion or a protozoan.

59. The immunostimulatory bacterium of any of claims 47-58, wherein the therapeutic product is a viral surface antigen or portion thereof sufficient to produce an immune response in a host.

60. The immunostimulatory bacterium of any of claims 51-59, wherein the therapeutic product interferes with viral gene expression or replication.

61. The immunostimulatory bacterium of any of claims 1-60, wherein the bacterium encodes an immunostimulatory protein.

62. The immunostimulatory bacterium of claim 61, wherein the immunostimulatory protein is a Stimulator of Interferon Genes (STING) protein, a modified STING protein, a cytokine, a chemokine, or a co-stimulatory receptor or ligand.

63. The immunostimulatory bacterium of any of claims 1-62, wherein the bacterium comprises a genomic modification whereby it lacks flagella.

64. The immunostimulatory bacterium of any of claims 1-63, wherein the bacterium comprises a genomic modification whereby it is *pagP*$^-$ or *msbB*$^-$/*pagP*$^-$.

65. The immunostimulatory bacterium of any of claims 1-64, wherein:

the bacterium comprises a bacterial genomic modification whereby it does not express asparaginase or activate the synthesis of secreted asparaginase, and/or

the genome of the immunostimulatory bacterium is modified by deletion or disruption of all or of a sufficient portion of the gene *ansB* encoding L-asparaginase II, whereby the bacterium is *ansB*$^-$ and does not express active L-asparaginase II.

66. The immunostimulatory bacterium claim 65, wherein the immunostimulatory bacterium is an anti-cancer therapeutic that colonizes tumors and/or the tumor microenvironment, whereby the *ansB*$^-$ phenotype reduces or eliminates production of active asparaginase

67. An immunostimulatory bacterium, comprising nucleic acid operatively linked to a prokaryotic promoter, wherein:

the nucleic acid comprises RNA that lacks sequences necessary for translation by a prokaryote, whereby the RNA is produced in the bacterium, but cannot be translated by the bacterium;

the bacterium has genomic modifications whereby infection is restricted to myeloid cells; and

the RNA encodes a therapeutic product or is a therapeutic product.

68. An RNA delivery system, comprising an immunostimulatory bacterium that primarily or solely infects myeloid cells and that comprises RNA encoded by the bacterium under control of a prokaryotic promoter, wherein:

the RNA lacks regulatory sequences necessary for translation by the bacterium; and

the RNA encodes a therapeutic product or is a therapeutic product.

69. The immunostimulatory bacterium of claim 67 or the RNA delivery system of claim 68, wherein the transcribed RNA lacks a Shine-Dalgarno sequence.

70. The immunostimulatory bacterium of claim 67 or the RNA delivery system of claim 68, wherein the transcribed RNA lacks a Shine-Dalgarno sequence and comprises a Kozak consensus sequence.

71. The immunostimulatory bacterium or RNA delivery system of claim 70, wherein the Kozak consensus sequence is ACCAUGG (SEQ ID NO: 397).

72. The immunostimulatory bacterium or RNA delivery system of any of claims 67-70, wherein the bacterium lacks flagella and contains a genome modification, whereby it is *pagP*$^-$/*msbB*$^-$.

73. The immunostimulatory bacterium or RNA delivery system of any of claims 67-72, wherein the RNA encoding the therapeutic product or that is the therapeutic product is encoded on a plasmid.

74. The immunostimulatory bacterium or RNA delivery system of any of claims 67-73 wherein the nucleic acid encoding the RNA is operatively linked to a prokaryotic promoter that is inducible.

75. The immunostimulatory bacterium or RNA delivery system of any of claims 67-73, wherein the nucleic acid encoding the RNA is operatively linked to a prokaryotic promoter that is constitutive.

76. The immunostimulatory bacterium or RNA delivery system of any of claims 67-75, wherein the nucleic acid encoding the RNA comprises an Internal Ribosome Entry Site (IRES).

77. An immunostimulatory bacterium or RNA delivery system of any of claims 1-76, wherein the genome of the immunostimulatory bacterium is modified by deletion or disruption of all or of a sufficient portion of the gene *ansB*, encoding L-asparaginase II, whereby the bacterium is *ansB*$^-$ and does not express active L-asparaginase II.

78. An immunostimulatory bacterium or RNA delivery system of any of claims 1-77, wherein the genome of the immunostimulatory bacterium is modified by deletion or disruption of all or of a sufficient portion of the gene *ansB*, encoding L-asparaginase II, and by deletion or disruption of all or of a sufficient portion of the gene *csgD*, whereby the bacterium is *ansB*$^-$ and does not express active L-asparaginase II, and is *csgD*$^-$ and does not activate the synthesis of curli fimbriae.

79. The immunostimulatory bacterium or RNA delivery system of any of claims 1-78, wherein the bacterial genome further comprises deletion of or disruption of all or of a sufficient portion of the genes encoding the flagella, whereby the bacterium is flagellin$^-$ and does not produce flagella, wherein the wild-type bacterium has flagella.

80. The immunostimulatory bacterium or RNA delivery system of claim 79, wherein the genome of the bacterium is further modified by deletion or disruption of all or of

a sufficient portion of the gene *csgD*, whereby the bacterium is *csgD*$^-$ or has another or additional modification in the genome whereby biofilm formation is impaired.

81. The immunostimulatory bacterium or RNA delivery system of claim 79, wherein the genome of the bacterium is further modified by deletion or disruption of all or of a sufficient portion of genes, whereby the bacterium is *csgD*$^-$/*msbB*$^-$/*pagP*$^-$.

82. The immunostimulatory bacterium or RNA delivery system of any of claims 69-81, wherein the bacterium comprises modification of the genome, whereby the bacterium lacks flagella.

83. An immunostimulatory bacterium, comprising genome modifications whereby the bacterium lacks flagella, and is *lppA*$^-$/*lppB*$^-$, and optionally is *csgD*$^-$.

84. The immunostimulatory bacterium of any of claims 1-83, wherein the bacterium is auxotrophic for purines.

85. The immunostimulatory bacterium of any of claims 1-83, wherein the bacterium is auxotrophic for adenosine or is auxotrophic for adenosine, adenine, and ATP.

86. The immunostimulatory bacterium of any of claims 1-85, wherein the bacterium is *purI*$^-$.

87. The immunostimulatory bacterium of any of claims 1-86, wherein the bacterium is *pagP*$^-$.

88. The immunostimulatory bacterium of any of claims 1-87, wherein the bacterium is *asd*$^-$ or *thyA*$^-$ or both.

89. The immunostimulatory bacterium of any of claims 1-88 that is aspartate-semialdehyde dehydrogenase$^-$ (*asd*$^-$), wherein the bacterium is *asd*$^-$ by virtue of disruption of or deletion of all or a portion of the endogenous gene encoding aspartate-semialdehyde dehydrogenase (*asd*), whereby endogenous *asd* is not expressed or functional enzyme is not produced, or is *thyA*$^-$ by virtue of the disruption of or deletion of all or a portion of the endogenous gene or genes, whereby endogenous thymidylate synthase is not expressed or functional enzyme is not produced.

90. An immunostimulatory bacterium that is aspartate-semialdehyde dehydrogenase$^-$ (*asd*$^-$), wherein:

the bacterium is *asd*$^-$ by virtue of disruption of or deletion of all or a portion of the endogenous gene encoding aspartate-semialdehyde dehydrogenase (*asd*), whereby endogenous *asd* is not expressed or functional enzyme is not produced; and

the bacterium is *thyA*$^-$ by virtue of the disruption of or deletion of all or a portion of the endogenous gene or genes, whereby endogenous thymidylate synthase is not expressed or functional enzyme is not produced.

91. The immunostimulatory bacterium of claim 90, wherein the unmodified bacterium is a *Salmonella* bacterium.

92. The immunostimulatory bacterium of any of claims 1-91 that encodes aspartate-semialdehyde dehydrogenase (*asd*) on the plasmid under control of a bacterial promoter.

93. The immunostimulatory bacterium of any of claims 1-92, wherein the bacterium is *msbB*$^-$.

94. The immunostimulatory bacterium of any of claims 1-93 that is *asd*$^-$,

purI$^-$, *msbB*$^-$, flagellin$^-$ and *pagP*$^-$.

95. The immunostimulatory bacterium of any of claims 1-94 that is *asd*$^-$, *csgD*$^-$, *purI*$^-$, *msbB*$^-$, flagellin$^-$ and *pagP*$^-$; or *thyA*$^-$, *csgD*$^-$, *purI*$^-$, *msbB*$^-$, flagellin$^-$ and *pagP*

96. The immunostimulatory bacterium of any of claims 1-95 that is *ansB*$^-$, *asd*$^-$, *csgD*$^-$, *purI*$^-$, *msbB*$^-$, flagellin$^-$ and *pagP*$^-$; or *ansB*$^-$, *thyA*$^-$, *csgD*$^-$, *purI*$^-$, *msbB*$^-$, flagellin$^-$ and *pagP*$^-$

97. The immunostimulatory bacterium of any of claims 1-96, wherein an encoded therapeutic product is an anti-cancer therapeutic.

98. The immunostimulatory bacterium of any of claims 1-97, wherein the plasmid encodes a modified STING and IL-15 or IL-15/IL-15R alpha chain complex, wherein the STING constitutively induces type I IFN in the absence of cGAS and/or any STING ligands.

99. The immunostimulatory bacterium any of claims 1-98, wherein the bacterium is *ansB*$^-$, *thyA*$^-$, *csgD*$^-$, *purI*$^-$, *msbB*$^-$, flagellin$^-$ and *pagP*$^-$.

100. The immunostimulatory bacterium of any of claims 1-99, wherein nucleic acid encoding the therapeutic product is operably linked to nucleic acid encoding a secretion signal, whereby, when expressed, the therapeutic product is secreted.

101. The immunostimulatory bacterium of any of claims 1-100, wherein an encoded therapeutic product is an anti-viral product.

102. The immunostimulatory bacterium of any of claims 1-100, wherein the encoded therapeutic product is a viral antigen.

103. The immunostimulatory bacterium of any of claims 100-102, wherein the encoded therapeutic product is an anti-viral antibody.

104. The immunostimulatory bacterium of any of claims 100-103, wherein:

the encoded therapeutic product is an anti-viral product; and

the virus that is selected is one that causes chronic infections or latent infections.

105. The immunostimulatory bacterium of any of claims 100-104, wherein:

the encoded therapeutic product is an anti-viral product; and

the virus is selected from among a hepatitis virus, a herpes virus, a varicella zoster virus, a poxvirus, a measles virus, and a retrovirus.

106. The immunostimulatory bacterium of any of claims 1-105, wherein the number of copies of the plasmid is greater than 150.

107. The immunostimulatory bacterium of any of claims 1-105, wherein the number of copies of the plasmid is 150 copies or fewer, or is less than or equal to 150.

108. The immunostimulatory bacterium of any of claims 1-105, wherein the plasmid is present in low copy number, and low copy number is less than 25 or less than 20 or less than about 25 or less than about 20 copies.

109. The immunostimulatory bacterium of any of claims 1-108, wherein an encoded therapeutic product is a nucleic acid or a protein.

110. The immunostimulatory bacterium of claim 109, wherein the encoded therapeutic product is a protein.

111. The immunostimulatory bacterium of any of claims 1-110, wherein the plasmid encodes two or more therapeutic products.

112. The immunostimulatory bacterium of any of claims 109-111, wherein the encoded therapeutic product(s) on the plasmid is/are anti-cancer treatment(s).

113. The immunostimulatory bacterium of any of claims 109-111, wherein the encoded therapeutic product(s) on the plasmid is/are anti-viral treatment(s).

114. The immunostimulatory bacterium of claim 112 or claim 113, wherein the bacterium encodes two or more products selected from among a cytokine, a protein that constitutively induces a type I IFN, and a co-stimulatory receptor or molecule.

115. The immunostimulatory bacterium of claim 114, wherein the co-stimulatory molecule lacks a cytoplasmic domain.

116. The immunostimulatory bacterium of any of claims 1-115, wherein the nucleic acid encoding one or more of the therapeutic product or products comprises nucleic acid encoding a signal for secretion of the therapeutic product(s) from a cell comprising the bacterium.

117. The immunostimulatory bacterium of any of claims 1-116, wherein the nucleic acid encoding the product on the plasmid is operatively linked to regulatory sequences recognized by a eukaryotic host

118. The immunostimulatory bacterium of any of claims 1-117, wherein the immunostimulatory bacterium encodes two or more products, and expression of each product is under control of a separate promoter, or expression of all is under control of a single promoter, and each product is separated by nucleic acid encoding a 2A peptide to effect separate translation of each encoded therapeutic product.

119. The immunostimulatory bacterium of claim 118, wherein the nucleic acid encodes a T2A, F2A, E2A, or P2A peptide to effect separate expression of therapeutic products expressed under control of a single promoter.

120. The immunostimulatory bacterium of any of claims 1-119, wherein the eukaryotic promoter is an RNA polymerase II promoter or an RNA polymerase III promoter.

121. The immunostimulatory bacterium of claim 120, wherein the promoter is an RNA polymerase II promoter that is a viral promoter or a mammalian RNA polymerase II promoter.

122. The immunostimulatory bacterium of claim 121, wherein the promoter is a viral promoter selected from among a cytomegalovirus (CMV) promoter, an SV40 promoter, an Epstein Barr virus (EBV) promoter, a herpes virus promoter, and an adenovirus promoter.

123. The immunostimulatory bacterium of any of claims 1-121, wherein the promoter that controls expression of one or more of the encoded therapeutic products or heterologous proteins on the plasmid is an elongation factor-1 (EF-1) alpha promoter, or an MND promoter, or a UBC promoter, or a PGK promoter, or a CAG promoter.

124. The immunostimulatory bacterium of any of claims 1-121, wherein the promoter that controls expression of one or more of the encoded therapeutic products or heterologous proteins on the plasmid is an EF-1 alpha, an adenovirus 2 or 5 late, a CMV, an SV40, an MND, a PGK, an EIF4A1, a CAG, or a CD68 promoter.

125. The immunostimulatory bacterium of any of claims 1-121, wherein the promoter that controls expression of one or more of the encoded therapeutic products or heterologous proteins on the plasmid is a viral promoter that is a late promoter.

126. The immunostimulatory bacterium of any of claims 1-125, wherein the plasmid comprises regulatory sequences that comprise a terminator and/or promoter(s) selected from among SV40, hGH, BGH, MND, chicken beta-globulin, and rbGlob (rabbit globulin) genes, to control expression of the therapeutic product(s).

127. The immunostimulatory bacterium of any of claims 1-126, wherein the encoded therapeutic product(s) is/are operatively linked to a signal sequence for secretion from a cell containing the plasmid.

128. The immunostimulatory bacterium of any of claims 1-127, wherein the plasmid that encodes the therapeutic product comprises a construct that includes an enhancer, a promoter, the open reading frame encoding the therapeutic product or heterologous protein, and a polyA tail.

129. The immunostimulatory bacterium of any of claims 1-128, wherein the plasmid comprises a construct that includes an enhancer, a promoter, an IRES, the open reading frame encoding the therapeutic product or heterologous protein, and a polyA tail.

130. The immunostimulatory bacterium of any of claims 1-129, wherein the plasmid comprises a construct that includes an enhancer, a promoter, an IRES, a localization sequence, the open reading frame encoding the therapeutic product or heterologous protein, and a polyA tail.

131. The immunostimulatory bacterium of claim 130, wherein the construct on the plasmid encoding the therapeutic product or heterologous protein comprises a Woodchuck Hepatitis Virus (WHP) Posttranscriptional Regulatory Element (WPRE) or a Hepatitis B virus Posttranscriptional Regulatory Element (HPRE).

132. The immunostimulatory bacterium of any of claims 1-131, wherein the plasmid contains nucleic acid encoding a therapeutic product that is part of a cytosolic DNA/RNA sensor pathway that leads to expression of type I interferon (IFN), or a variant of the therapeutic product.

133. The immunostimulatory bacterium of claim 132, wherein the therapeutic product in its unmodified form senses or interacts directly or indirectly with cytosolic nucleic acids, nucleotides, dinucleotides, or cyclic dinucleotides, to induce expression of type I IFN, and the variant protein induces expression of type I IFN in the absence of the sensing or interacting with the cytosolic nucleic acids, nucleotides, dinucleotides, or cyclic dinucleotides.

134. The immunostimulatory bacterium of claim 132, wherein the therapeutic product is a variant that, when expressed in a subject, leads to constitutive expression of type I IFN.

135. The immunostimulatory bacterium of claim 132, wherein the therapeutic product is a gain-of-function (GOF) variant that does not require cytosolic nucleic acids, nucleotides, dinucleotides, or cyclic dinucleotides to result in expression of type I IFN.

136. The immunostimulatory bacterium of any of claims 1-135, wherein the therapeutic product is selected from among STING, RIG-I, MDA-5, IRF-3, IRF-5, IRF-7, IRF-8, TRIM56, RIP1, Sec5, TRAF3, TRAF2, TRAF6, STAT1, LGP2, DDX3, DHX9, DDX1, DDX9, DDX21, DHX15, DHX33, DHX36, DDX60, and SNRNP200.

137. The immunostimulatory bacterium of any of claims 1-135, wherein the therapeutic product is selected from among TRIM56, RIP1, Sec5, TRAF3, TRAF2, TRAF6,

STAT1, LGP2, DDX3, DHX9, DDX1, DDX9, DDX21, DHX15, DHX33, DHX36, DDX60, and SNRNP200.

138. The immunostimulatory bacterium of any of claims 132-137, wherein the therapeutic product is a variant that has increased activity, or that results in constitutive expression of type I interferon (IFN).

139. The immunostimulatory bacterium of any of claims 1-138, wherein the plasmid encodes a gain-of-function, constitutively active variant of a protein that, in humans, promotes or causes interferonopathies.

140. The immunostimulatory bacterium of any of claims 132-139, wherein the therapeutic product is a variant that comprises a mutation that eliminates a phosphorylation site in the protein to thereby reduce nuclear factor kappa-light-chain-enhancer of activated B cell (NF-κB) signaling.

141. The immunostimulatory bacterium of any of claims 132-140, wherein the therapeutic product that induces type I IFN is STING, RIG-I, IRF-3, or MDA5; or wherein the therapeutic product that induces type I IFN is IRF-5, or IRF-8.

142. The immunostimulatory bacterium of any of claims 132-141, wherein:

the therapeutic product that induces expression of type I IFN is a variant thereof that has increased activity or constitutive activity; and

the therapeutic product is STING, RIG-I, IRF-3, IRF-5, IRF-8, or MDA5.

143. The immunostimulatory bacterium of any of claims 132-142, wherein the therapeutic product is a variant of STING, RIG-I, IRF-3, IRF-5, IRF-8, or MDA5 that comprises a gain-of-function mutation resulting in increased expression of type I IFN.

144. The immunostimulatory bacterium of any of claims 132-143, wherein the therapeutic product is a variant of STING, RIG-I, IRF-3, IRF-5, IRF-8, or MDA5 in which one or more serine (S) or threonine (T) residue(s) that is/are phosphorylated as a consequence of viral infection, is/are replaced with an aspartic acid (D), whereby the resulting variant is a phosphomimetic that constitutively induces type I IFN.

145. The immunostimulatory bacterium of any of claims 132-144, wherein:

the therapeutic product is IRF-3 that has one or more replacement(s) at residues at positions 396, 398, 402, 404 and 405, with reference to SEQ ID NO:312; and

the residues are replaced with aspartic acid residues.

146. The immunostimulatory bacterium of claim 145, wherein IRF-3 comprises the replacement S396D with reference to SEQ ID NO:312.

147. The immunostimulatory bacterium of claim 145, wherein IRF-3 comprises the replacements S396D/S398D/S402D/T404D/S405D with reference to SEQ ID NO:312.

148. The immunostimulatory bacterium of any of claims 132-147, wherein the therapeutic product is selected from among STING, RIG-I, MDA-5, IRF-3, IRF-7, IRF-5, IRF-8, TRIM56, RIP1, Sec5, TRAF3, TRAF2, TRAF6, STAT1, LGP2, DDX3, DHX9, DDX1, DDX9, DDX21, DHX15, DHX33, DHX36, DDX60, and SNRNP200.

149. The immunostimulatory bacterium of any of claims 132-148, wherein:

the therapeutic product that senses cytosolic DNA/RNA is a variant STING, MDA5, RIG-I or IRF-3; and

unmodified STING has the sequence set forth in any of SEQ ID NOs: 305-309, unmodified MDA5 has the sequence set forth in SEQ ID NO: 310, unmodified RIG-I has the

sequence set forth in SEQ ID NO: 311, and unmodified IRF-3 has the sequence set forth in SEQ ID NO: 312.

150. The immunostimulatory bacterium of any of claims 132-149, wherein the therapeutic product is selected from among STING, MDA5, IRF-3, and RIG-I, and comprises a gain-of-function mutation(s) that renders the STING, MDA5, IRF-3, IRF-5, IRF-8, or RIG-I constitutively active, whereby expression of type I IFN is constitutive.

151. The immunostimulatory bacterium of claim 149 or claim 150, wherein the mutations are selected as follows:

a) in STING, with reference to SEQ ID NOs: 305-309, one or more selected from among: S102P, V147L, V147M, N154S, V155M, G166E, C206Y, G207E, S102P/F279L, F279L, R281Q, R284G, R284S, R284M, R284K, R284T, R197A, D205A, R310A, R293A, T294A, E296A, R197A/D205A, S272A/Q273A, R310A/E316A, E316A, E316N, E316Q, S272A, R293A/T294A/E296A, D231A, R232A, K236A, Q273A, S358A/E360A/S366A, D231A/R232A/K236A/R238A, S358A, E360A, S366A, R238A, R375A, N154S/R284G, and S324A/S326A;

b) in MDA5, with reference to SEQ ID NO:310, one or more of: T331I, T331R, A489T, R822Q, G821S, A946T, R337G, D393V, G495R, R720Q, R779H, R779C, L372F, and A452T;

c) in RIG-I, with reference to SEQ ID NO:311, one or both of E373A and C268F; and

d) in IRF-3, with reference to SEQ ID NO:312, S396D.

152. The immunostimulatory bacterium of any of claims 132-151, wherein the therapeutic product is a variant STING that contains one or more amino replacement(s) selected, with reference to SEQ ID NOs: 305-309, from among: S102P, V147L, V147M, N154S, V155M, G166E, C206Y, G207E, S102P/F279L, F279L, R281Q, R284G, R284S, R284M, R284K, R284T, R197A, D205A, R310A, R293A, T294A, E296A, R197A/D205A, S272A/Q273A, R310A/E316A, E316A, E316N, E316Q, S272A, R293A/T294A/E296A, D231A, R232A, K236A, Q273A, S358A/E360A/S366A, D231A/R232A/K236A/R238A, S358A, E360A, S366A, R238A, R375A, N154S/R284G, and S324A/S326A, and conservative replacements thereof.

153. The immunostimulatory bacterium of any of claims 114 and 132-152, wherein the type I IFN is an interferon-α or interferon-β.

154. The immunostimulatory bacterium of any of claims 1-153 that encodes a bi-specific antibody.

155. The immunostimulatory bacterium claim 154, wherein the bi-specific antibody is a bi-specific T-cell engager.

156. The immunostimulatory bacterium of any of claims 1-155, wherein the plasmid encodes a bi-specific T-cell engager antibody that binds DLL3 and CD3.

157. The immunostimulatory bacterium of claim 156, wherein the bi-specific T-cell engager antibody comprises a heavy chain and light chain of an anti-DLL3 antibody and of an anti-CD3 antibody.

158. The immunostimulatory bacterium of claim 156 or 157, wherein the bi-specific T-cell engager antibody is selected from among those encoded in the constructs designated SC16.15, SC16.34, and SC16.56, which encode variable heavy and variable light chains of antibodies that bind each of DLL3 and CD3, and whose sequences are set forth in

SEQ ID NOs.485-491, or humanized variants thereof, and variants that have at least 95% sequence identity thereto.

159. The immunostimulatory bacterium of claim 157 or claim 158, wherein the bi-specific T-cell engager antibody comprises combinations of a) - f), whereby the resulting construct can bind to each of DLL3 and CD3:

a) a light chain that comprises amino acid residues 154-260 of SEQ ID NO: 487, or a humanized variant thereof, or a variant having at least 95 % sequence identity thereto; and

b) a heavy chain that comprises the sequence of amino acid residues set forth as amino acid residues 22-138 of SEQ ID NO: 487, or a humanized variant thereof, or a variant having at least 95 % sequence identity thereto; and

c) a light chain that comprises a sequence of amino acid residues set forth as amino acid residues 155-261 of SEQ ID NO: 489, or a humanized variant thereof, or a variant having at least 95 % sequence identity thereto; and

d) a heavy chain that comprises a sequence of amino acid residues set forth as amino acid residues 22-139 of SEQ ID NO: 489, or a humanized variant thereof, or a variant having at least 95 % sequence identity thereto; and

e) a heavy and light chain, wherein:

the light chain comprises a sequence of amino acid residues set forth as amino acid residues 155-261 of SEQ ID NO: 485, or a humanized variant thereof, or a variant having at least 95 % sequence identity thereto; and

the heavy chain comprises a sequence of amino acid residues set forth as amino acid residues 22-139 of SEQ ID NO: 485, or a humanized variant thereof, or a variant having at least 95 % sequence identity thereto; and

f) a heavy and light chain of an anti-CD3 antibody, wherein:

the light chain of the anti-CD3 antibody comprises a sequence of amino acid residues set forth as amino acid residues 398-504 of SEQ ID NO: 485, or a humanized variant thereof, or a variant having at least 95 % sequence identity thereto, or a humanized variant thereof, or a variant having at least 95 % sequence identity thereto; and

the heavy chain of the anti-CD3 antibody comprises a sequence of amino acid residues set forth as amino acid residues 267-382 of SEQ ID NO: 485, or a humanized variant thereof, or a variant having at least 95 % sequence identity thereto.

160. The immunostimulatory bacterium of any of claims 156-159, wherein the encoded bi-specific T-cell engager antibody construct comprises a leader sequence.

161. The immunostimulatory bacterium of claim 160, wherein the leader sequence is an IgGK leader sequence.

162. The immunostimulatory bacterium of any of claims 156-161, wherein:

the bispecific antibody comprises a Gly-Ser linker linking one or more light and heavy chains; and

a Gly-Ser linker linking the anti-DLL3 and anti-CD3 portions of the bi-specific T-cell engager antibody.

163. The immunostimulatory bacterium of claim 162, wherein the linker comprises the sequence of amino acids set forth as residues 383-397 of SEQ ID NO: 485.

164. The immunostimulatory bacterium of any of claims 156-163, wherein the bi-specific T-cell engager antibody comprises a flag tag.

165. The immunostimulatory bacterium of claim 164, wherein the flag tag comprises the sequence of amino acids set forth as residues 505-512 of SEQ ID NO: 485.

166. The immunostimulatory bacterium of any of claims 156-165, comprising a nucleic acid construct encoding a leader sequence, the heavy and light chain of an anti-DLL antibody, and the heavy and light chain of an anti-CD3 antibody, and optionally one or more peptide linkers, and optionally a flag tag.

167. The immunostimulatory bacterium of any of claims 156-166, wherein the encoded bi-specific T-cell engager antibody construct comprises the sequence of amino acid residues set forth in any of SEQ ID NOs: 485-491, or a humanized variant thereof, or a variant having at least 95 % sequence identity thereto, and sequences having at least 95% sequence identity thereto.

168. The immunostimulatory bacterium of any of claims 1-167, wherein the plasmid encodes a tumor-associated antigen.

169. The immunostimulatory bacterium of any of claims 1-168, wherein the immunostimulatory bacterium encodes a modified STING protein that constitutively induces type I interferon.

170. The immunostimulatory bacterium of claim 169, wherein the STING protein comprises the replacements N154S, or R284G, or N154S/R284G.

171. The immunostimulatory bacterium of any of claims 1-170, wherein the plasmid encodes IL-15 or an IL-15/IL-15R alpha chain complex.

172. The immunostimulatory bacterium of any of claims 1-171, wherein the plasmid encodes the combination of a modified STING, IL-15/IL-15R alpha chain complex, a tumor-associated antigen and or a bi-specific T-cell engager antibody.

173. The immunostimulatory bacterium of any of claims 1-172, wherein the plasmid encodes an immunostimulatory protein that confers or contributes to an anti-tumor immune response in the tumor microenvironment that is selected from among one or more of: IL-2, IL-7, IL-12p70 (IL-12p40 + IL-12p35), IL-15, IL-2 that has attenuated binding to IL-2Ra, IL-15/IL-15R alpha chain complex (IL-15Rα-IL-15sc), IL-18, IL-21, IL-23, IL-36γ, IL-2 that is modified so that it does not bind to IL-2Ra, CXCL9, CXCL10, CXCL11, interferon-α, interferon-β, interferon-γ, CCL3, CCL4, CCL5, proteins that are involved in or that effect or potentiate recruitment and/or persistence of T cells, CD40, CD40 ligand (CD40L), CD28, OX40, OX40 ligand (OX40L), 4-1BB, 4-1BB ligand (4-1BBL), members of the B7-CD28 family, CD47 antagonists, an anti-IL-6 antibody or IL-6 binding decoy receptor, TGF-beta polypeptide antagonists, and members of the tumor necrosis factor receptor (TNFR) superfamily.

174. The immunostimulatory bacterium of claim 173, wherein:

the immunostimulatory protein is a co-stimulatory molecule selected from among CD40, CD40 ligand (CD40L), CD28, OX40, OX40 ligand (OX40L), 4-1BB, and a 4-1BB ligand (4-1BBL) that optionally is truncated and lacking a cytoplasmic domain for expression on an antigen-presenting cell (APC); and

the truncated gene product is capable of constitutive immunostimulatory signaling to a T-cell through co-stimulatory receptor engagement and is unable to counter-regulatory signal to the antigen-presenting cell (APC) due to a deleted cytoplasmic domain.

175. The immunostimulatory bacterium of claim 173 or claim 174, wherein the immunostimulatory protein that confers or contributes to an anti-tumor immune response in the tumor microenvironment is a cytokine or a chemokine.

176. The immunostimulatory bacterium of any of claims 173-175, wherein the immunostimulatory protein that confers or contributes to an anti-tumor immune response in the tumor microenvironment is a co-stimulatory molecule or cytoplasmic domain-deleted form thereof.

177. The immunostimulatory bacterium of claim 176, wherein the immunostimulatory protein that confers or contributes to an anti-tumor immune response in the tumor microenvironment is selected from among 4-1BBL, CD80, CD86, CD27L, CD24L, B7RP1, and OX40L.

178. The immunostimulatory bacterium of any of claims 1-177, wherein the plasmid encodes a therapeutic product that is a TGF-beta polypeptide antagonist.

179. The immunostimulatory bacterium of any of claims 1-178, wherein the therapeutic product is an antibody or antigen-binding fragment thereof.

180. The immunostimulatory bacterium of claim 179, wherein the antibody or antigen-binding fragment thereof is an antigen-binding fragment that is selected from among a Fab, Fab', $F(ab')_2$, single-chain Fv (scFv), Fv, dsFv, nanobody, diabody fragment, and a single-chain antibody.

181. The immunostimulatory bacterium of claim 179 or claim 180, wherein the antibody or antigen-binding fragment thereof is humanized or is human.

182. The immunostimulatory bacterium of any of claims 179-181, wherein the antibody or antigen-binding fragment thereof is an antagonist of PD-1, PD-L1, CTLA-4, VEGF, VEGFR2, CD24, or IL-6.

183. The immunostimulatory bacterium of any of claims 1-182, wherein the plasmid encodes two or more therapeutic products selected from among:

a) an immunostimulatory protein that confers or contributes to an anti-tumor immune response in the tumor microenvironment;

b) one or more of a protein that is part of a cytosolic DNA/RNA sensor pathway that leads to expression of type I interferon (IFN), or a variant thereof that has increased activity to increase expression of type I IFN, or a variant thereof that results in constitutive expression of a type I IFN; and

c) an anti-cancer antibody or antigen-binding portion thereof.

184. The immunostimulatory bacterium of claim 183, wherein the immunostimulatory protein is a co-stimulatory molecule that lacks a cytoplasmic domain or a sufficient portion thereof, for expression on an antigen-presenting cell (APC), whereby the truncated co-stimulatory molecule is capable of constitutive immunostimulatory signaling to a T-cell through co-stimulatory receptor engagement and is unable to counter-regulatory signal to the antigen presenting cell (APC).

185. An immunostimulatory bacterium, comprising a plasmid that encodes two or more therapeutic products under control of a single promoter, wherein:

the therapeutic products are selected from among:

a) an immunostimulatory protein that confers or contributes to an anti-tumor immune response in the tumor microenvironment;

b) one or more of a protein that is part of a cytosolic DNA/RNA sensor pathway that leads to expression of type I interferon (IFN), or a variant thereof that has increased activity to increase expression of type I IFN, or a variant thereof that results in constitutive expression of a type I IFN; and

c) an anti-cancer antibody or antigen-binding portion thereof; and

the encoding nucleic acids are separated by an IRES sequence or 2A peptides, and each nucleic acid encoding each product is optionally operatively linked to nucleic acid encoding a signal sequence, whereby, upon translation of the encoded mRNA, each product is separately expressed and secreted from a cell comprising the bacterium and/or plasmid.

186. The immunostimulatory bacterium of claim 185, wherein the immunostimulatory protein is a co-stimulatory molecule that lacks a cytoplasmic domain or a sufficient portion thereof, for expression on an antigen-presenting cell (APC), whereby the truncated co-stimulatory molecule is capable of constitutive immunostimulatory signaling to a T-cell through co-stimulatory receptor engagement and is unable to counter-regulatory signal to the antigen presenting cell (APC).

187. The immunostimulatory bacterium of any of claims 1-186, wherein the plasmid encodes at least two therapeutic products selected from among a cytokine, a protein that constitutively induces a type I IFN, a co-stimulatory molecule, and an anti-cancer antibody or antigen-binding portion thereof.

188. The immunostimulatory bacterium of any of claims 1-187, wherein the immunostimulatory bacterium comprises a plasmid that encodes at least two therapeutic products selected from among a cytokine, a protein that constitutively induces a type I IFN, a co-stimulatory molecule, and an anti-cancer antibody or antigen-binding portion thereof, and also encodes an antigen or an antigenic protein.

189. The immunostimulatory bacterium of claim 188, wherein the antigen is a tumor-associated antigen.

190. The immunostimulatory bacterium of claim 189, wherein the tumor-associated antigen is an oncofetal antigen, an oncoviral antigen, and overexpressed/accumulated antigen, a cancer-Testis antigen, a linear restricted antigen, a mutated antigen, a post-translationally altered antigen, or an idiotypic antigen.

191. The immunostimulatory bacterium claim 190, wherein the tumor-associated antigen is selected from among the following antigens:

Category of Tumor-Associated Antigen (TAA)	Name / Family Name of TAA
Oncofetal	Carcinoembryonic antigen (CEA)
	Immature laminin receptor
	Tumor-associated glycoprotein 72 (TAG-72)
Oncoviral	HPV E6, HPV E7
Overexpressed/Accumulated	BING-4
	Epidermal Growth Factor Receptor (EGFR)
	Wilms' Tumor Protein
	Calcium-activated chloride channel 2
	Cyclin-B1

	9D7
	Epithelial cell adhesion molecule (EpCAM)
	Ephrin type-A receptor 3 (EphA3)
	Human epidermal growth factor receptor 2 (HER2/Neu)
	Telomerase
	Mesothelin
	Stomach-cancer–associated protein tyrosine phosphatase 1 (SAP-1)
	Survivin
Cancer-Testis	BAGE (B melanoma antigen) family
	CAGE family
	GAGE family
	MAGE (melanoma antigen) family
	SAGE (sarcoma antigen) family
	PAGE family
	XAGE family
	CT9, CT10
	New York esophageal squamous cell carcinoma 1 (NY-ESO-1), LAGE-1
	Preferentially expressed antigen in melanoma (PRAME)
	synovial sarcoma/X breakpoint 2 (SSX-2)
Lineage-Restricted	Melanoma antigen recognized by T-cells 1 (Melan-A/MART-1)
	gp100/Pmel17
	Tyrosinase
	Tyrosinase related protein (TRP)-1, TRP-2
	P.polypeptide
	Melanocortin 1 receptor (MC1R)
	Prostate-specific antigen (PSA)
Mutated	β-catenin
	BRCA1, BRCA2
	Cyclin dependent kinase 4 (CDK4)
	Chronic Myelogenous Leukemia Tumor Antigen 66 (CML66)
	Fibronectin
	Melanoma antigen recognized by T-cells 2

	(MART-2)
	p53
	Ras
	TGF-β receptor type II (TGF-βRII)
Post-Translationally Altered	Mucin 1, Cell Surface Associated (MUC1)
Idiotypic	Immunoglobulin (Ig), T-cell Receptor (TCR)

192. The immunostimulatory bacterium any of claims 1-191 that is an anti-cancer therapeutic.

193. The immunostimulatory bacterium of claim 192, wherein the encoded payloads are expressed under control of a eukaryotic promoter.

194. The immunostimulatory bacterium any of claims 1-193, that comprises the genome modifications whereby the bacterium is flagellin$^-$, *asd*$^-$, *msbB*$^-$, *pagP*$^-$, *and csgD*$^-$, *or is ansB*$^-$, *asd*$^-$, *csgD*$^-$, *purI*$^-$, *msbB*$^-$, flagellin$^-$, and *pagP*$^-$.

195. The immunostimulatory bacterium of any of claims 194 that comprises genome modification whereby the bacterium is *thyA*$^-$, *asd*$^-$, *csgD*$^-$, *purI*$^-$, *msbB*$^-$, flagellin$^-$, and *pagP*$^-$.

196. The immunostimulatory bacterium of any of claims 1-195, wherein the immunostimulatory bacterium is a vaccine for treating or preventing a cancer or infection from a pathogen.

197. The immunostimulatory bacterium of claim 196, wherein the encoded payloads are expressed under control of a prokaryotic promoter, and the nucleic acid encoding the payloads comprise translational regulatory signals that are recognized by eukaryotic ribosomes, and not by bacterial ribosomes.

198. The immunostimulatory bacterium of any of claims 1-197, wherein the plasmid in the immunostimulatory bacterium encodes an antigen or protein or epitope(s) thereof from a pathogen.

199. The immunostimulatory bacterium of claim 198, wherein the pathogen causes chronic viral infections, such as infections by hepatitis viruses, herpes viruses, varicella zoster virus (VZV), Epstein-Barr virus, human immunodeficiency virus (HIV), human T-cell leukemia virus (HTLV), Respiratory Syncytial Virus (RSV), and measles virus; or is a virus or other pathogen chronically infect subjects; or is a pathogen that causes acute infections, such as initial infections with chronic influenza and coronaviruses, such as Severe Acute Respiratory Syndrome coronavirus (SARS-CoV), Middle East Respiratory Syndrome coronavirus (MERS-CoV), and Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2, which causes COVID-19).

200. The immunostimulatory bacterium of claim 199, wherein the plasmid encodes an encode an antigen from a pathogen or an epitope or combination of epitopes thereof, such as an antigen from an essential viral protein, such as, for example, in the case of a coronavirus, an antigen from the Nucleocapsid, M and/or S proteins, which can result in neutralizing antibodies, and the enhancement of long-lived circulating and tissue-resident CD8+ T-cells.

201. The immunostimulatory bacterium of any of claims 198-200, wherein nucleic acid encoding the antigen, epitope, or antigenic protein is operatively linked to a prokaryotic promoter recognized by the bacterium; and the encoding sequence includes regulatory sequences for translation that are recognized by eukaryotic ribosomes, whereby the bacterium cannot translate the encoded RNA, or the encoding sequence does not include a Shine Dalgarno sequence that is recognized by the bacterial ribosomes so that the encoded mRNA is not translated; and the mRNA is delivered to the eukaryotic host cell into which the bacterium is delivered.

202. The immunostimulatory bacterium of any of claims 1-201, wherein:

the plasmid encodes two or more therapeutic products under control of a single promoter; and

expression of the nucleic acid encoding at least two or all of the products is under control of a single promoter, and the nucleic acid encoding each product is separated by nucleic acid encoding 2A polypeptides, whereby, upon translation, each product is separately expressed.

203. The immunostimulatory bacterium of any of claims 198-202, wherein nucleic acid encoding one or more of the therapeutic products is operatively linked to nucleic acid encoding a sequence that directs secretion of the expressed product(s).

204. The immunostimulatory bacterium of any of claims 1-203, wherein:

the therapeutic product is a co-stimulatory molecule with a cytoplasmic domain deletion for expression on an antigen-presenting cell (APC); and

the truncated gene product is capable of constitutive immunostimulatory signaling to a T-cell through co-stimulatory receptor engagement, and is unable to counter-regulatory signal to the APC due to the cytoplasmic domain deletion.

205. The immunostimulatory bacterium of claim 204, wherein the co-stimulatory molecule that lacks a cytoplasmic domain is 4-1BBL, CD80, CD86, CD27L, B7RP1, CD24L, or OX40L.

206. The immunostimulatory bacterium of any of claims 1-205 that encodes two or more therapeutic products, wherein at least one product is selected from a) and at least one is selected from b), wherein:

a) is IL-2, IL-7, IL-12p70 (IL-12p40 + IL-12p35), IL-15, IL-23, IL-36 gamma, IL-2 that has attenuated binding to IL-2Ra, IL-15/IL-15R alpha chain complex (IL-15Rα-IL-15sc), IL-18, IL-2 that is modified so that it does not bind to IL-2Ra, CXCL9, CXCL10, CXCL11, interferon-α, interferon-β, CCL3, CCL4, CCL5, proteins that are involved in or that effect or potentiate recruitment and/or persistence of T cells, CD40, CD40 Ligand (CD40L), OX40, OX40 Ligand (OX40L), 4-1BB, 4-1BB Ligand (4-1BBL), members of the B7-CD28 family, TGF-beta polypeptide antagonists, or members of the tumor necrosis factor receptor (TNFR) superfamily; and

b) is STING, RIG-I, MDA-5, IRF-3, IRF-5, IRF-7, IRF-8, TRIM56, RIP1, Sec5, TRAF3, TRAF2, TRAF6, STAT1, LGP2, DDX3, DHX9, DDX1, DDX9, DDX21, DHX15, DHX33, DHX36, DDX60, or SNRNP200.

207. The immunostimulatory bacterium of any of claims 1-206 that encodes or further encodes one or more of a TGF-beta inhibitory antibody, a TGF-beta binding decoy receptor, an anti-IL-6 antibody, and an IL-6 binding decoy receptor.

208. The immunostimulatory bacterium of any of claims 1-207 that encodes one or more of the following combinations of therapeutic products:

IL-2 and IL-12p70;

IL-2 and IL-21;

IL-2, IL-12p70, and a STING GOF variant;

IL-2, IL-21, and a STING GOF variant;

IL-2, IL-12p70, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt), where Δcyt is a deleted cytoplasmic domain;

IL-2, IL-21, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

IL-15/IL-15Rα, and a STING GOF variant;

IL-15/IL-15Rα, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

IL-15/IL-15Rα and IL-12p70;

IL-15/IL-15Rα and IL-21;

IL-15/IL-15Rα, IL-12p70, and a STING GOF variant;

IL-15/IL-15Rα, IL-21, and a STING GOF variant;

IL-15/IL-15Rα, IL-12p70, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

IL-15/IL-15Rα, IL-21, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

IL-12p70 and IL-21;

IL-12p70, IL-21, and a STING GOF variant;

IL-12p70, IL-21, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

IL-12p70 and a STING GOF variant;

IL-12p70, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

IL-12p70 and IL-18;

IL-12p70, IL-18, and a STING GOF variant;

IL-12p70, IL-18, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

a TGF-β decoy receptor, IL-2, and IL-12p70;

a TGF-β decoy receptor, IL-2, and IL-21;

a TGF-β decoy receptor, IL-2, IL-12p70, and a STING GOF variant;

a TGF-β decoy receptor, IL-2, IL-21, and a STING GOF variant;

a TGF-β decoy receptor, IL-2, IL-12p70, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

a TGF-β decoy receptor, IL-2, IL-21, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

a TGF-β decoy receptor, IL-15/IL-15Rα, and a STING GOF variant;

a TGF-β decoy receptor, IL-15/IL-15Rα, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

a TGF-β decoy receptor, IL-15/IL-15Rα, and IL-12p70;

a TGF-β decoy receptor, IL-15/IL-15Rα, and IL-21;

a TGF-β decoy receptor, IL-15/IL-15Rα, IL-12p70, and a STING GOF variant;

a TGF-β decoy receptor, IL-15/IL-15Rα, IL-21, and a STING GOF variant;

a TGF-β decoy receptor, IL-15/IL-15Rα, IL-12p70, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

a TGF-β decoy receptor, IL-15/IL-15Rα, IL-21, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

a TGF-β decoy receptor, IL-12p70, and IL-21;

a TGF-β decoy receptor, IL-12p70, IL-21, and a STING GOF variant;

a TGF-β decoy receptor, IL-12p70, IL-21, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

a TGF-β decoy receptor and IL-12p70;

a TGF-β decoy receptor, IL-12p70, and a STING GOF variant;

a TGF-β decoy receptor, IL-12p70, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

a TGF-β decoy receptor, IL-12p70, and IL-18;

a TGF-β decoy receptor, IL-12p70, IL-18, and a STING GOF variant;

a TGF-β decoy receptor, IL-12p70, IL-18, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

a TGF-β decoy receptor and a STING GOF variant;

an anti-CTLA-4 antibody, IL-2, and IL-12p70;

an anti-CTLA-4 antibody, IL-2, and IL-21;

an anti-CTLA-4 antibody, IL-2, IL-12p70, and a STING GOF variant;

an anti-CTLA-4 antibody, IL-2, IL-21, and a STING GOF variant;

an anti-CTLA-4 antibody, IL-2, IL-12p70, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

an anti-CTLA-4 antibody, IL-2, IL-21, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

an anti-CTLA-4 antibody, IL-15/IL-15Rα, and a STING GOF variant;

an anti-CTLA-4 antibody, IL-15/IL-15Rα, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

an anti-CTLA-4 antibody, IL-15/IL-15Rα, and IL-12p70;

an anti-CTLA-4 antibody, IL-15/IL-15Rα, and IL-21;

an anti-CTLA-4 antibody, IL-15/IL-15Rα, IL-12p70, and a STING GOF variant;

an anti-CTLA-4 antibody, IL-15/IL-15Rα, IL-21, and a STING GOF variant;

an anti-CTLA-4 antibody, IL-15/IL-15Rα, IL-12p70, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

an anti-CTLA-4 antibody, IL-15/IL-15Rα, IL-21, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

an anti-CTLA-4 antibody, IL-12p70, and IL-21;

an anti-CTLA-4 antibody, IL-12p70, IL-21, and a STING GOF variant;

an anti-CTLA-4 antibody, IL-12p70, IL-21, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

an anti-CTLA-4 antibody and IL-12p70;

an anti-CTLA-4 antibody, IL-12p70, and a STING GOF variant;

an anti-CTLA-4 antibody, IL-12p70, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

an anti-CTLA-4 antibody, IL-12p70, and IL-18;

an anti-CTLA-4 antibody, IL-12p70, IL-18, and a STING GOF variant;

an anti-CTLA-4 antibody, IL-12p70, IL-18, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

an anti-CTLA-4 antibody and a STING GOF variant;

a CD40 agonist, IL-2, and IL-12p70;

a CD40 agonist, IL-2, and IL-21;

a CD40 agonist, IL-2, IL-12p70, and a STING GOF variant;

a CD40 agonist, IL-2, IL-21, and a STING GOF variant;

a CD40 agonist, IL-2, IL-12p70, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

a CD40 agonist, IL-2, IL-21, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

a CD40 agonist, IL-15/IL-15Rα, and a STING GOF variant;

a CD40 agonist, IL-15/IL-15Rα, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

a CD40 agonist, IL-15/IL-15Rα, and IL-12p70;

a CD40 agonist, IL-15/IL-15Rα, and IL-21;

a CD40 agonist, IL-15/IL-15Rα, IL-12p70, and a STING GOF variant;

a CD40 agonist, IL-15/IL-15Rα, IL-21, and a STING GOF variant;

a CD40 agonist, IL-15/IL-15Rα, IL-12p70, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

a CD40 agonist, IL-15/IL-15Rα, IL-21, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

a CD40 agonist, IL-12p70, and IL-21;

a CD40 agonist, IL-12p70, IL-21, and a STING GOF variant;

a CD40 agonist, IL-12p70, IL-21, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

a CD40 agonist and IL-12p70; a CD40 agonist, IL-12p70, and a STING GOF variant;

a CD40 agonist, IL-12p70, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

a CD40 agonist, IL-12p70, and IL-18;

a CD40 agonist, IL-12p70, IL-18, and a STING GOF variant;

a CD40 agonist, IL-12p70, IL-18, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

a tumor-associated antigen;

a CD40 agonist and a STING GOF variant.

209. The immunostimulatory bacterium of claim 208, further encoding a tumor-associated antigen.

210. The immunostimulatory bacterium of claim 208 or claim 209, wherein the STING gain-of-function (GOF) variant is/are selected from among any set forth in claims 149-153.

211. An immunostimulatory bacterium or a cell, encoding one or more of the following combinations of therapeutic products:

IL-2 and IL-12p70;

IL-2 and IL-21;

IL-2, IL-12p70, and a STING GOF variant;

IL-2, IL-21, and a STING GOF variant;

IL-2, IL-12p70, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt), where Δcyt is a deleted cytoplasmic domain;

IL-2, IL-21, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

IL-15/IL-15Rα, and a STING GOF variant;

IL-15/IL-15Rα, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

IL-15/IL-15Rα and IL-12p70;

IL-15/IL-15Rα and IL-21;

IL-15/IL-15Rα, IL-12p70, and a STING GOF variant;

IL-15/IL-15Rα, IL-21, and a STING GOF variant;

IL-15/IL-15Rα, IL-12p70, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

IL-15/IL-15Rα, IL-21, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

IL-12p70 and IL-21;

IL-12p70, IL-21, and a STING GOF variant;

IL-12p70, IL-21, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

IL-12p70 and a STING GOF variant;

IL-12p70, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

IL-12p70 and IL-18;

IL-12p70, IL-18, and a STING GOF variant;

IL-12p70, IL-18, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

a TGF-β decoy receptor, IL-2, and IL-12p70;

a TGF-β decoy receptor, IL-2, and IL-21;

a TGF-β decoy receptor, IL-2, IL-12p70, and a STING GOF variant;

a TGF-β decoy receptor, IL-2, IL-21, and a STING GOF variant;

a TGF-β decoy receptor, IL-2, IL-12p70, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

a TGF-β decoy receptor, IL-2, IL-21, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

a TGF-β decoy receptor, IL-15/IL-15Rα, and a STING GOF variant;

a TGF-β decoy receptor, IL-15/IL-15Rα, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

a TGF-β decoy receptor, IL-15/IL-15Rα, and IL-12p70;

a TGF-β decoy receptor, IL-15/IL-15Rα, and IL-21;

a TGF-β decoy receptor, IL-15/IL-15Rα, IL-12p70, and a STING GOF variant;

a TGF-β decoy receptor, IL-15/IL-15Rα, IL-21, and a STING GOF variant;

a TGF-β decoy receptor, IL-15/IL-15Rα, IL-12p70, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

a TGF-β decoy receptor, IL-15/IL-15Rα, IL-21, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

a TGF-β decoy receptor, IL-12p70, and IL-21;

a TGF-β decoy receptor, IL-12p70, IL-21, and a STING GOF variant;

a TGF-β decoy receptor, IL-12p70, IL-21, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

a TGF-β decoy receptor and IL-12p70;

a TGF-β decoy receptor, IL-12p70, and a STING GOF variant;

a TGF-β decoy receptor, IL-12p70, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

a TGF-β decoy receptor, IL-12p70, and IL-18;

a TGF-β decoy receptor, IL-12p70, IL-18, and a STING GOF variant;

a TGF-β decoy receptor, IL-12p70, IL-18, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

a TGF-β decoy receptor and a STING GOF variant;

an anti-CTLA-4 antibody, IL-2, and IL-12p70;

an anti-CTLA-4 antibody, IL-2, and IL-21;

an anti-CTLA-4 antibody, IL-2, IL-12p70, and a STING GOF variant;

an anti-CTLA-4 antibody, IL-2, IL-21, and a STING GOF variant;

an anti-CTLA-4 antibody, IL-2, IL-12p70, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

an anti-CTLA-4 antibody, IL-2, IL-21, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

an anti-CTLA-4 antibody, IL-15/IL-15Rα, and a STING GOF variant;

an anti-CTLA-4 antibody, IL-15/IL-15Rα, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

an anti-CTLA-4 antibody, IL-15/IL-15Rα, and IL-12p70;

an anti-CTLA-4 antibody, IL-15/IL-15Rα, and IL-21;

an anti-CTLA-4 antibody, IL-15/IL-15Rα, IL-12p70, and a STING GOF variant;

an anti-CTLA-4 antibody, IL-15/IL-15Rα, IL-21, and a STING GOF variant;

an anti-CTLA-4 antibody, IL-15/IL-15Rα, IL-12p70, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

an anti-CTLA-4 antibody, IL-15/IL-15Rα, IL-21, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

an anti-CTLA-4 antibody, IL-12p70, and IL-21;

an anti-CTLA-4 antibody, IL-12p70, IL-21, and a STING GOF variant;

an anti-CTLA-4 antibody, IL-12p70, IL-21, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

an anti-CTLA-4 antibody and IL-12p70;

an anti-CTLA-4 antibody, IL-12p70, and a STING GOF variant;

an anti-CTLA-4 antibody, IL-12p70, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

an anti-CTLA-4 antibody, IL-12p70, and IL-18;

an anti-CTLA-4 antibody, IL-12p70, IL-18, and a STING GOF variant;

an anti-CTLA-4 antibody, IL-12p70, IL-18, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

an anti-CTLA-4 antibody and a STING GOF variant;

a CD40 agonist, IL-2, and IL-12p70;

a CD40 agonist, IL-2, and IL-21;

a CD40 agonist, IL-2, IL-12p70, and a STING GOF variant;

a CD40 agonist, IL-2, IL-21, and a STING GOF variant;

a CD40 agonist, IL-2, IL-12p70, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

a CD40 agonist, IL-2, IL-21, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

a CD40 agonist, IL-15/IL-15Rα, and a STING GOF variant;

a CD40 agonist, IL-15/IL-15Rα, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

a CD40 agonist, IL-15/IL-15Rα, and IL-12p70;

a CD40 agonist, IL-15/IL-15Rα, and IL-21;

a CD40 agonist, IL-15/IL-15Rα, IL-12p70, and a STING GOF variant;

a CD40 agonist, IL-15/IL-15Rα, IL-21, and a STING GOF variant;

a CD40 agonist, IL-15/IL-15Rα, IL-12p70, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

a CD40 agonist, IL-15/IL-15Rα, IL-21, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

a CD40 agonist, IL-12p70, and IL-21;

a CD40 agonist, IL-12p70, IL-21, and a STING GOF variant;

a CD40 agonist, IL-12p70, IL-21, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

a CD40 agonist and IL-12p70;**

a CD40 agonist, IL-12p70, and a STING GOF variant;

a CD40 agonist, IL-12p70, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

a CD40 agonist, IL-12p70, and IL-18;

a CD40 agonist, IL-12p70, IL-18, and a STING GOF variant;

a CD40 agonist, IL-12p70, IL-18, a STING GOF variant, and 4-1BBL (including 4-1BBLΔcyt);

a CD40 agonist and a STING GOF variant;

a bi-specific T-cell engager (BiTe) + a STING protein, a BiTe + IL-15, a BiTe + IL-15 + a STING protein, where the BiTe targets DLL3, EGFR, Her2, CEA, Mesothelin, PSMA, EpCAM, CD74, Folate Receptor, Nectin4, EphA2, CA-IX, B7H3, Siglec-15, Muc1, or Lewis Y antigen;

a tumor antigen(s) + STING gain-of-function variant;

a therapeutic composition of a tumor antigen(s) and IL-15;

a therapeutic composition of a tumor antigen(s) + IL-15 + a STING gain-of-function variant;

one or more antigens and an IFN;

one or more antigens and an IFNα;

one or more antigens, and IFNα2 or an IFNα1-16;

one or more antigens and any of IFNα1-16;

one or more antigens and IFN-β;

one or more antigens, IFNα2, and IFN-β;

one or more antigens and an IRF3 GOF variant with the mutation S396D;

one or more antigens, IFNα2 or an IFNα1-16, and an IRF3 GOF variant with the mutation S396D;

IFNalpha2 + IRF3-S396D;

IFNα1-16 + IRF3-S396D;

IFNalpha2 + IFN-beta;

IFNα1-16 + IFN-beta

FLT-3L, or sialidase, or IL-12p35, or Azurin, or a membrane anchored IL-2, IL-12, IL-12p35, IL-21, IL-15, FLT-3L, alone or in combination with other immunostimulatory proteins; and

a TLR8 agonist, where the agonist is polyU or polyU/G, a microRNA, or miR-21, alone or in combination with any of the immunostimulatory proteins.

212. The immunostimulatory bacterium of any of claims 202-211, further encoding a tumor-associated antigen.

213. The immunostimulatory bacterium of any of claims 1-212, wherein the plasmid encodes a tumor-associated antigen as set forth in claim 191.

214. The immunostimulatory bacterium of any of claims 1-213, wherein an encoded therapeutic product is a bi-specific T-cell engager.

215. The immunostimulatory bacterium claim 214, wherein the bi-specific T-cell engager binds Delta-like ligand 3 (DLL3) and CD3.

216. The immunostimulatory bacterium of any of claims 1-215, encoding a cytokine and a modified or variant STING protein.

217. The immunostimulatory bacterium of claim 215, wherein the STING protein is a STING protein of any of claims 406-436.

218. The immunostimulatory bacterium of claim 215 or claim 216, wherein the cytokine is IL-15/IL-15R alpha chain complex, or IL-15, or IL-12.

219. The immunostimulatory bacterium of any of claims 215-218, wherein the cytokine is IL-15/IL-15R alpha chain complex, or IL-15.

220. The immunostimulatory bacterium any of claims 215-219, wherein the STING protein is a chimeric STING protein that comprises a human STING protein with the CTT from Tasmanian devil, or is a chimeric STING that comprises a human STING protein with the CTT from Tasmanian devil and having one or more gain-of-function mutations.

221. The immunostimulatory bacterium of any of claims 215-220, wherein the STING protein comprises a gain-of-function mutation that is N154S, or R284G, or N154S/R284G.

222. The immunostimulatory bacterium or cell of any of claims 214-221, wherein the STING gain-of-function variant is selected from among any set forth in any of claims 405-430.

223. The immunostimulatory bacterium of any of claims 1-191, wherein an encoded therapeutic product comprises an Fc domain.

224. The immunostimulatory bacterium of any of claims 1-221, wherein an encoded therapeutic product comprises the B7 protein transmembrane domain.

225. The immunostimulatory bacterium any of claims 1-224 wherein a encoded therapeutic product is a tumor-associated antigen.

226. The immunostimulatory bacterium of any of claims 1-225, wherein an encoded product is a bi-specific T-cell engager antibody.

227. The immunostimulatory bacterium of any of claims 1-226, wherein an encoded therapeutic product is GPI-anchored.

228. The immunostimulatory bacterium of any of claims 1-227, wherein an encoded therapeutic product comprises human serum albumin or its derivatives thereof that increase serum half-life of the encoded product.

229. The immunostimulatory bacterium of any of claims 1-228, wherein an encoded therapeutic product comprises a fusion to collagen.

230. An immunostimulatory bacterium of any of claims 1- 229 that is a strain designated as YS1646Δasd/ΔFLG/ΔpagP/ΔansB/ΔcsgD/F-ΔpurI, or YS1646Δasd/ΔFLG/ΔpagP/ΔansB/ΔcsgD/F-ΔpurI/ΔthyA.

231. A genome modified bacterium, comprising genome modifications, whereby the response by toll-like receptors (TLRs) 2, 4, and 5 is reduced compared to the bacterium without the genome modifications, wherein:

the bacterium comprises further genomic modifications whereby it is auxotrophic for a required nutrient or factor so that it is unable to replicate in a eukaryotic host, but can replicate *in vitro* when supplied with the nutrient or factor;

the bacterium comprises a plasmid containing nucleic acid encoding a product, or comprises RNA encoding the product;

the product encoded by the nucleic acid or RNA is an antigenic sequence or sequences from pathogen that is a pathogenic virus, bacterium, or parasite, or is a tumor antigen, whereby, upon expression of the encoded antigen in the host, the host develops an immune-protective response or immunizing response against the pathogenic virus, bacterium, parasite, or tumor antigen, or the product is a therapeutic product;

expression of the antigenic sequence(s) is/are under control of a prokaryotic promoter so that RNA encoding the antigen(s) is produced in the bacterium;

nucleic acid encoding the antigen comprises regulatory sequences that inhibit or prevent translation of encoded RNA by bacterial ribosomes, but that does not inhibit or prevent translation of the encoded RNA by eukaryotic host ribosomes, whereby translation is de-coupled from transcription in the bacterium;

the resulting bacterium is selective for infecting phagocytic cells when administered to a eukaryotic subject, and delivers the nucleic acid into the phagocytic cells, wherein the RNA is translated; and

232. The bacterium of claim 231, wherein the nucleic acid encoding the antigenic sequence(s) comprises an internal ribosomal entry site (IRES) sequence, whereby host cell translation is facilitated or enhanced, and bacterial translation is inhibited or prevented.

233. The bacterium of claim 232, wherein the IRES is a Vascular Endothelial Growth Factor and Type 1 Collagen Inducible Protein (VCIP) IRES.

234. The bacterium of claim 232 or claim 233, wherein the nucleic acid encoding the antigen(s) comprises a VCIP or other IRES that inhibits or reduces translation in the bacterium, and permits and optionally promotes or enhances translation in a eukaryotic host.

235. The bacterium of any of claims 231-233, wherein the IRES or the VCIP IRES is included in the plasmid, at a position that is 3' of the promoter and 5' of the antigen(s) coding sequence.

236. The bacterium of any of claims 233-235, wherein the sequence of the VCIP IRES is set forth in SEQ ID NO:434.

237. The bacterium of any of claims 231-236, wherein the pathogen is a bacterium or a virus.

238. The bacterium of any of claims 231-237, wherein the encoded antigen is a tumor antigen.

239. The bacterium of any of claims 231-238, wherein the bacterium is a vaccine to prevent or treat a viral infection or a bacterial infection.

240. The bacterium of claim 236, wherein the pathogen is selected from among viruses that causes chronic viral infections.

241. The bacterium of claim 240, wherein the infections are selected from among infections by hepatitis viruses, herpes viruses, varicella zoster virus (VZV), Epstein-Barr virus, human immunodeficiency virus (HIV), human T-cell leukemia virus (HTLV), Respiratory Syncytial Virus (RSV), measles virus, and other viruses that chronically infect subjects.

242. The bacterium of any of claims 239-241, wherein the infection is an acute infection.

243. The bacterium of claim 242, wherein the infection is an infection by Severe Acute Respiratory Syndrome coronavirus (SARS-CoV), Middle East Respiratory Syndrome coronavirus (MERS-CoV), or Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2, which causes COVID-19).

244. The bacterium of any of claims 231-243, wherein the pathogen is a species of *Escherichia, Staphylococcus, Pseudomonas*, *Actinobacteria*, *Archaeobacteria*, *Mycobacteria* or *Porphyromonas*.

245. The bacterium of any of claims 231-243, wherein the pathogen is *P. gingivalis*, SARS-CoV, or *E. coli*, or Haemophilus influenza.

246. The bacterium of any of claims 231-245, wherein the plasmid in the bacterium further encodes an immunostimulatory protein or other adjuvant.

247. The bacterium of claim 246, wherein the plasmid encodes a combination of immunostimulatory proteins or other therapeutic proteins.

248. The bacterium of claim 247 wherein the immunostimulatory protein is a STING protein.

249. The bacterium of claim 248, wherein the STING protein comprises a gain-of-function mutation and/or is a chimeric STING protein.

250. The bacterium of claim 248 or claim 249, wherein the STING protein is the STING protein of any of claims 406-436.

251. The bacterium of any of claims 231-250, wherein the bacterium comprises a plasmid that encodes a combination of therapeutic products.

252. The bacterium of claim 250, that is an immunostimulatory bacterium as described in any of claims 1-251.

253. The bacterium of any of claims 231-252, wherein:

the immunostimulatory protein(s) and/or other therapeutic proteins are encoded in the plasmid as part of a polycistronic sequence with expression of the antigen under control of a prokaryotic promoter recognized by the bacterium; or

the immunostimulatory protein(s) and/or other therapeutic proteins are encoded on the plasmid under control of a eukaryotic promoter recognized by the eukaryotic host.

254. The bacterium of any of claims 231-253, wherein the bacterium comprises mRNA encoding the antigen(s) and any other proteins expressed under control of a prokaryotic promoter that are produced by culturing the bacterium *in vitro*.

255. The bacterium of any of claims 231-254 that comprises genome modifications whereby the bacterium lacks flagella and produces LPS with pent-acylated lipid A.

256. The bacterium of any of claims 231-255 that is *asd*$^-$ or *thyA*$^-$ or both.

257. The bacterium of any of claims 231-256 that is one or both o adenosine auxotroph, and *csgD*$^-$, and is optionally *ansB*$^-$.

258. The bacterium of any of claims 231-257 that comprises nucleic acid encoding a TLR8 agonist.

259. The bacterium of claim 258, wherein the TLR8 agonist is polyU, polyU/G, a microRNA, or miR-21.

260. The bacterium of any of claims 231-259 that is *msbB*$^-$/*pagP*$^-$, lacks flagella, and is *asd*$^-$ or *thyA*$^-$ or both *asd*$^-$ and *thyA*$^-$.

261. The bacterium of any of claims 1-260 that is a species or strain of *Escherichia*, *Listeria*, *Mycobacteria,* or *Salmonella.*

262. The bacterium of any of claims 1-261 that is a strain of *Salmonella.*

263. The bacterium of claim 262 that is a *Salmonella typhimurium* strain.

264. The bacterium of claim 262 or claim 263, wherein the unmodified *Salmonella* is a wild-type strain, or the unmodified *Salmonella* strain is attenuated.

265. The bacterium of any of claims 1-264, wherein the bacterium is derived from strain VNP20009 or YS1646, or from strain ATCC 14028, or from a strain having all of the identifying characteristics of strain ATCC 14028.

266. The bacterium of any of claims 231-265, wherein the genome modification is one or more of a deletion, insertion, disruption, and other modification in a gene, whereby the product encoded by the gene is not produced or, as produced, is inactive.

267. The bacterium of any of claims 231-266, wherein the prokaryotic promoter is a bacterial promoter or a bacterial phage promoter.

268. The bacterium of any of claims 231-267, wherein the eukaryotic host is a human.

269. A vaccine, comprising the bacterium of any of claims 1-268 in an amount and in a vehicle for administration into a subject to elicit an adaptive immune response in a subject.

270. The vaccine of claim 269 that is formulated as an aerosol, or as a powder, or as a tablet, or a suppository.

271. The vaccine of any of claims 269 or claim 270 that formulated for oral administration, nasal administration, inhalation administration, rectal administration, vaginal administration, intraocular administration, intracranial administration, intradermal administration, or intramuscular administration.

272. A vaccine, comprising nucleic acid encoding an antigen from a protein from a virus or a protein from a virus corona virus formulated for nasal or pulmonary inhalation, wherein the vaccine does not sufficiently activate TRL2, whereby the vaccine induces type I IFN.

273. The vaccine of claim 272, wherein the virus is a corona virus.

274. The vaccine of claim 273, wherein the virus is a corona virus that is SARS-COV2.

275. The vaccine of any of claims 272-274 that also does not activate a TLR4 and/or TRL5 response sufficient to decease or inhibit type I IFN.

276. A vaccine, comprising nucleic acid that encodes an antigen or protein or epitope from a pathogen or tumor, wherein:

the vaccine elicits an immune response against the pathogen or tumor;

the pathogen is a respiratory pathogen that infects the respiratory system including the lungs and/or naso-pharynx;

the tumor is a lung tumor;

the vaccine is formulated for inhalation through the nose or lungs;

the vaccine delivers the nucleic acid to phagocytic macrophages to convert the immunosuppressive phagocytic macrophages to immunostimulatory, phagocytic macrophages that are capable of in situ antigen cross-presentation to CD8+ T-cells, and of migration to lymph nodes to prime CD4+ and CD8+ T-cells; and

the vaccine does not activate TLR2, and/or TLR4 and/or TLR5 response sufficient to decease or inhibit type I IFN.

277. The vaccine of claim 276 that also does not activate a TLR4 <u>and</u> ~~and/or~~ TRL5 response sufficient to decease or inhibit type I IFN.

278. The vaccine of claim 276 or claim 277 that does not activate TLR2/4/5 sufficiently to decrease or inhibit type IFN.

279. The vaccine of any of claims 272-278 wherein the vaccine elicits an immune response against a virus.

280. The vaccine of claim 279, wherein the pathogen is a virus.

281. The vaccine of claim 269-280, wherein the pathogen is an RNA virus.

282. The vaccine of claim 281, wherein the virus is a corona virus or influenza virus.

283. The vaccine of claim 282, wherein the virus is a corona virus.

284. The vaccine of claim 283, wherein the virus is a SARS virus.

285. The vaccine of claim 284, wherein the virus is a SARS-COV2 virus

286. The vaccine of claim 269-285, wherein the antigen, protein, or epitope is a viral antigen, protein, or epitope.

287. The vaccine of claim 286, wherein the protein is a capsid or nucleoprotein.

288. The vaccine of any of claims 269-287, wherein the virus is SARS-COV2, and the protein or epitope is or is from a protein designated or encoded by S1, S2, Envelope (E), Membrane (M), Nucleocapsid (N), ORF3a, ORF6, ORF7a, ORF7b, and ORF8.

289. The vaccine of any of claims 269-288, wherein the virus is SARS-COV2, and the protein or epitope is or is from or is a spike protein.

290. The vaccine of any of claims 269-289, wherein the vaccine comprises mRNA encoding the protein or antigen.

291. The vaccine of claim 290, wherein the mRNA is modified to increase stability of the mRNA or the stability of the encoded protein or antigen or epitope.

292. The vaccine of claim 290, wherein the mRNA encodes a modified viral protein, wherein the modification alters the structure of the protein to alter interaction with host cell proteins.

293. The vaccine of any of claims 269-292 that is a delivery vehicle that comprises nucleic acid that encodes an antigen or protein from a pathogen, or encodes a tumor antigen.

294. The vaccine of any of claims 269-293 that comprises an immunostimulatory bacterium, wherein the bacterium comprises genome modifications, whereby it has penta-acylated lipopolysaccharides (LPS), and lacks flagella, wherein wild-type bacterium has flagella.

295. The vaccine of claim 294, wherein the immunostimulatory bacterium has a genome modification(s), whereby it does not produce curli fimbriae.

296. The vaccine of claim 294 or claim 295, wherein the immunostimulatory bacterium comprises a plasmid that encodes an antigen against a pathogen or a tumor antigen.

297. The vaccine of claim 296, wherein the plasmid encodes a therapeutic product is part of a cytosolic DNA/RNA sensor pathway that leads to expression of type I interferon (IFN).

298. The vaccine of claim 297 wherein the product is STING, IRF3,IRF5, IRF7, IRF8, MDA5, RIG-I or a modified form thereof that comprises a gain-of-function mutation, whereby expression of the type I interferon is constitutive.

299. The immunostimulatory bacterium or vaccine of any of claims 1-298 that is an attenuated bacterium or is a Gram-negative bacterium, or is a Gram-positive bacterium.

300. The immunostimulatory bacterium or vaccine of any of claims 1-299, wherein the bacterium is a strain of *Salmonella*, *Shigella*, *E. coli*, *Bifidobacteriae*, *Rickettsia*, *Vibrio*, *Listeria*, *Klebsiella*, *Bordetella*, *Neisseria*, *Aeromonas*, *Francisella*, *Cholera*, *Corynebacterium*, *Citrobacter*, *Chlamydia*, *Haemophilus*, *Brucella*, *Mycobacterium*,

Mycoplasma, *Legionella*, *Rhodococcus*, *Pseudomonas*, *Helicobacter*, *Bacillus*, or *Erysipelothrix*, or *Archaeobacteria,* an attenuated strain thereof or a modified strain thereof of any of the preceding list of bacterial strains.

301. The immunostimulatory bacterium or vaccine of any of claims 1-299 wherein the bacterium is *Rickettsia rickettsiae*, *Rickettsia prowazekii*, *Rickettsia tsutsugamuchi*, *Rickettsia mooseri*, *Rickettsia sibirica*, *Bordetella bronchiseptica*, *Neisseria meningitidis*, *Neisseria gonorrhoeae*, *Aeromonas eucrenophila*, *Aeromonas salmonicida*, *Francisella tularensis*, *Corynebacterium pseudotuberculosis*, *Citrobacter freundii*, *Chlamydia pneumoniae*, *Haemophilus somnus*, *Brucella abortus*, *Mycobacterium intracellulare*, *Mycobacterium tuberculosis, Staphylococcus aureus, Legionella pneumophila*, *Rhodococcus equi*, *Pseudomonas aeruginosa*, *Helicobacter mustelae*, *Vibrio cholerae*, *Bacillus subtilis*, *Erysipelothrix rhusiopathiae*, *Yersinia enterocolitica*, *Rochalimaea quintana*, or *Agrobacterium tumerfacium*.

302. The immunostimulatory bacterium or vaccine of any of claims 1-301 that is a strain of *Salmonella*.

303. The immunostimulatory bacterium or vaccine of claim 302 that is a *Salmonella typhimurium* strain.

304. The immunostimulatory bacterium or vaccine of claim 302 or claim 303, wherein the unmodified *Salmonella* is a wild-type strain.

305. The immunostimulatory bacterium or vaccine of claim 302 or claim 303, wherein the unmodified *Salmonella* strain is attenuated.

306. The immunostimulatory bacterium or vaccine of any of claims 1-305, wherein the immunostimulatory bacterium is derived from strain VNP20009 or YS1646, or strain ATCC 14028, or a strain having all of the identifying characteristics of strain ATCC 14028.

307. The immunostimulatory bacterium or vaccine of any of claims 301-305 that is *ansB*$^-$, *asd*$^+$, *csgD*$^-$, *purI*$^-$, *msbB*$^-$, flagellin$^-$, and *pagP*$^-$ or that is *ansB*$^-$, *thyA*$^-$, *csgD*$^-$, *purI*$^-$, *msbB*$^-$, flagellin$^-$, and *pagP*$^-$.

308. The immunostimulatory bacterium or vaccine of any of claims 1-307, wherein the bacterium encodes and expresses the gene resistance to complement killing (*rck*).

309. The immunostimulatory bacterium or vaccine of claim 308, wherein the *rck* gene is a *Salmonella rck* gene.

310. The immunostimulatory bacterium or vaccine of claim 308 or claim 309 that is an *E. coli* strain.

311. A pharmaceutical composition, comprising the immunostimulatory bacterium or bacterium of vaccine of any of claims 1-310 in a pharmaceutically acceptable vehicle.

312. The pharmaceutical composition of claim 311 that is formulated for systemic administration.

313. The pharmaceutical composition of claim 311 or claim 312 that is formulated for parenteral administration, or intravenous administration, or intramuscular administration, or intratumoral administration, or intraperitoneal administration, or oral administration, or rectal administration, or vaginal administration, or intraocular administration, or intradermal administration, or intracranial administration, or mucosal administration, or administration by inhalation into the mouth or nose.

314. A method of treatment of cancer that comprises a solid tumor or a hematological malignancy in a subject, comprising administering the immunostimulatory bacterium, bacterium or vaccine of any of claims 1-310, or the pharmaceutical composition of any of claims 311-313.

315. A method of immunization, comprising administering the vaccine of any of claims 269-298.

316. Use of the immunostimulatory bacterium, bacterium, virus, or vaccine of any of claims 1-310 or the pharmaceutical composition of any of claims 311-313, for the treatment of a cancer that comprises a solid tumor or a hematological malignancy in a subject.

317. The immunostimulatory bacterium, bacterium, or virus, or vaccine of any of claims 1-310 or the pharmaceutical composition of any of claims 311-313 for use for the treatment of or immunization against cancer that comprises a solid tumor or a hematological malignancy in a subject, or for immunization against a pathogen.

318. The method, use, immunostimulatory bacterium, or pharmaceutical composition, or vaccine of any of claims 314-317, wherein the subject is a human.

319. The method, use, immunostimulatory bacterium, or pharmaceutical composition, or vaccine of any of claims 314-318, wherein the subject has a cancer that comprises a solid tumor or comprises a hematological malignancy.

320. The method, use, immunostimulatory bacterium, pharmaceutical composition, or vaccine of any of claims 314-319, wherein the treatment comprises combination therapy in which a second anti-cancer agent or treatment is administered.

321. The method, use, immunostimulatory bacterium, vaccine, or pharmaceutical composition of claim 320, wherein the second anti-cancer agent or treatment is administered before, concomitantly with, after, or intermittently with, the immunostimulatory bacterium, or pharmaceutical composition.

322. The method, use, immunostimulatory bacterium, vaccine, or pharmaceutical composition of claim 320 or claim 321, wherein the second anti-cancer agent or treatment is an immunotherapy.

323. The method, use, immunostimulatory bacterium, vaccine, or pharmaceutical composition of any of claims 314-322, wherein administration of the immunostimulatory bacterium, or pharmaceutical composition or vaccine is parenteral.

324. The method, use, immunostimulatory bacterium, vaccine, or pharmaceutical composition of any of claims 314-322 wherein administration of the immunostimulatory bacterium, or pharmaceutical composition, or vaccine is oral, or rectal, or by aerosol into the lung and/or nose, or mucosal, or intracranial, or intradermal, or intratumoral.

325. The method, use, immunostimulatory bacterium, vaccine, or pharmaceutical composition of any of claims 314-324, wherein administration of the immunostimulatory bacterium, or vaccine or pharmaceutical composition is intravenously, intramuscularly, intranasally, or subcutaneously.

326. The method, use, immunostimulatory bacterium, pharmaceutical composition, or vaccine of any of claims 314-325, wherein the cancer is selected from among leukemia, lymphoma; gastric cancer; and cancer of the breast, heart, lung, small intestine, colon, spleen, kidney, bladder, head and neck, colorectum, ovary, prostate, brain, pancreas, skin, bone, bone marrow, blood, thymus, uterus, testicles, cervix, and liver.

327. The method, use, immunostimulatory bacterium, vaccine, or pharmaceutical composition of any of claim 314-326, wherein the immunotherapy comprises administration of an anti-PD-1, or anti-PD-L1, or anti-CTLA-4 antibody.

328. The method, use, immunostimulatory bacterium, vaccine, or pharmaceutical composition of any of claims 314-327, wherein the immunostimulatory bacterium is a *Salmonella*, *Shigella*, *Listeria*, or *E. coli* species.

329. The method, use, immunostimulatory bacterium, vaccine, or pharmaceutical composition of any of claims 314-328, wherein the immunostimulatory bacterium is a *Salmonella* species.

330. The method, use, immunostimulatory bacterium, vaccine, or pharmaceutical composition of any of claims 314-329, wherein the immunostimulatory bacterium is a *Salmonella typhimurium* strain.

331. The method, use, immunostimulatory bacterium, vaccine, or pharmaceutical composition of any of claims 314-330, wherein administration of the immunostimulatory bacterium is by intraperitoneal or intratumoral administration.

332. The method, use, immunostimulatory bacterium, vaccine, or pharmaceutical composition of any of claims 314-331, wherein the subject has metastatic cancer.

333. The method, use, immunostimulatory bacterium, vaccine, or pharmaceutical composition of any of claims 314-332, comprising administering a second anti-cancer treatment, wherein the second treatment is selected from among anti-PD-1, anti-CTLA-4, anti-PD-L1, anti-IL-6, anti-Siglec-15, anti-VEGF, anti-CD73, and anti-CD38 antibodies.

334. The method, use, immunostimulatory bacterium, vaccine, or pharmaceutical composition of any of claims 314-333, comprising administering a second or further anti-cancer treatment, wherein the second or further treatment is selected from among a poly (ADP-ribose) polymerase (PARP) inhibitor, a histone deacetylase (HDAC) inhibitor, a chemotherapy agent, an anti-EGFR antibody, a CAR-T cell, an anti-Her2 antibody, an anti-mesothelin antibody, and an anti-B-cell maturation antigen (BCMA) antibody.

335. A method of treatment of a viral infection or infection with another infectious pathogen, comprising administering the immunostimulatory bacterium or vaccine of any of claims 1-310, wherein the immunostimulatory bacterium or vaccine comprises or encodes an antigen, protein, or epitope thereof from the virus or pathogen.

336. The method of claim 335, wherein the immunostimulatory bacterium encodes the antigen, protein or epitope thereof under control of a promoter recognized by the bacterium; and the immunostimulatory bacterium comprises a genome modification(s), whereby it does not replicate *in vivo*.

337. The immunostimulatory bacterium or vaccine of any of claims 1-310, or method of claim 335 and 336 for use for treating a viral infection or infection with another infectious agent.

338. A method of immunizing to prevent (reduce the risk of) infection by a virus or other infectious agent, comprising administering an immunizing dose of the immunostimulatory bacterium or vaccine of any of claims 1-310, wherein a product encoded by the immunostimulatory bacterium is an anti-viral or anti-pathogen therapeutic or antigen, epitope, or protein.

339. The immunostimulatory bacterium or vaccine of any of claims 1-310 for use for immunizing against, to protect against, or to reduce the severity of or reduce the risk of

infection by a virus or another infectious agent, wherein a produced encoded by the immunostimulatory bacterium is an anti-viral or anti-pathogen therapeutic or antigen, epitope, or protein.

340. The immunostimulatory bacterium or vaccine or method of any of claims 335-339, wherein the virus or infectious agent is a virus.

341. The immunostimulatory bacterium, or vaccine, or pharmaceutical composition, or method, or use of any of claims 1-340, wherein the immunostimulatory bacterium comprises a plasmid that encodes RNA operably linked to a promoter recognized by a polymerase present in the bacterium, wherein, upon infection of a eukaryotic host cell, the RNA is released into the cytoplasm of the eukaryotic host.

342. The immunostimulatory bacterium, or vaccine, or pharmaceutical composition, or method, or use of claim 341, wherein the RNA released into the cytoplasm of the eukaryotic host is mRNA.

343. The immunostimulatory bacterium, or vaccine, or pharmaceutical composition, or method, or use of claim 341 or claim 342, wherein the promoter is an inducible promoter.

344. The immunostimulatory bacterium, or vaccine, or pharmaceutical composition, or method, or use of any of claims 341-343, wherein the immunostimulatory bacterium also encodes a polymerase that recognizes the promoter.

345. The immunostimulatory bacterium, or vaccine, or pharmaceutical composition, or method, or use of any of claims 341-344, wherein the polymerase is a T7 RNA polymerase.

346. The immunostimulatory bacterium, or vaccine, or pharmaceutical composition, or method, or use of any of claims 341-345, wherein the immunostimulatory bacterium is *asd*$^-$ or is *thyA*$^-$ or both.

347. The immunostimulatory bacterium or vaccine of any of claims 1-310, for use for treating a tumor or a viral infection, wherein the bacterium encodes an anti-cancer or anti-viral therapeutic product or antigen, protein, or epitope or combinations thereof form the virus or tumor.

348. A method of treatment of cancer or a viral infection, comprising administering the RNA delivery system of any of claims 68-80 to a subject with cancer and/or a viral infection, or the immunostimulatory bacterium or vaccine of any of claims 1-310 that encodes a tumor-associated antigen or viral antigen, protein or epitope.

349. A method of converting an M2 macrophage to an M1 or M1-like phenotype, comprising administering the immunostimulatory bacterium of any of claims 38-82 to a subject with a condition, disease, or disorder treated by enhancing an anti-viral or anti-tumor immune response.

350. Use of the immunostimulatory bacterium of any of claims 38-82, or the immunostimulatory bacterium of any of claims 38-82, to convert an M2 macrophage to an M1 or M1-like phenotype macrophage in a subject with a condition, disease, or disorder treated by enhancing an anti-viral or anti-tumor immune response

351. The method of claim 349 or use or bacterium of claim 350, wherein the disease, disorder, or condition is a cancer and/or a viral or other pathogen infection.

352. A method of delivering RNA encoding a therapeutic product, comprising administering an immunostimulatory bacterium of any of claims 16-25 for treatment of a disease, condition, or disorder.

353. Use of an immunostimulatory bacterium of any of claims 68-82, or the immunostimulatory bacterium of any of claims 68-82, for use for delivering RNA encoding a therapeutic product for treatment of a disease, condition, or disorder.

354. The method of claim 352 or the use or bacterium of claim 353, wherein the disease, disorder, or condition is a cancer and/or a viral or other pathogen infection.

355. A pharmaceutical composition, comprising the bacterium of any of claims 231-310 in a pharmaceutically acceptable vehicle.

356. The pharmaceutical composition of claim 355 that is formulated as vaccine, as a liquid, powder, or tablet.

357. The bacterium or pharmaceutical composition of any of claims 231-313, 355, and 356, for use for treating or preventing (reducing the risk of developing) a disease or condition or infection or cancer.

358. A method for treating or preventing (reducing the risk of developing) a disease or condition or infection or cancer, comprising administering the bacterium or pharmaceutical composition of any of claims 231-313, 355 and 356.

359. A method of delivering RNA, comprising administering the bacterium or pharmaceutical composition of any of claims 231-310, and 355-357.

360. The bacterium of any of claims 231-310 and 355-357, for use for delivering RNA.

361. The method of claim 359 or the bacterium of claim 360, wherein the RNA is mRNA.

362. The bacterium of any of claims 231-310 and 355-357, wherein the product is a therapeutic product, and the plasmid in the bacterium encodes the product to produce mRNA that is not translated by the bacterium.

363. A method of delivering RNA to a subject, comprising administering the bacterium of claim 362.

364. The bacterium of claim 362, for use for delivering RNA to a subject.

365. A bacterium for use for delivering RNA to a subject, comprising a plasmid encoding a heterologous product, wherein:

the nucleic acid encoding the heterologous product is linked to a promoter recognized by the bacterium; and

the nucleic acid encoding the product comprises eukaryotic sequences for translation that are not recognized by the bacterium, whereby the bacterium produces RNA, but does not translate the RNA.

366. The bacterium of claim 365 that is an immunostimulatory bacterium of any of claims 1-310, wherein the nucleic acid encoding the RNA encodes a therapeutic product.

367. The bacterium of claim 365 or claim 366, wherein the bacterium encodes an antigen or protein from a pathogen or tumor for eliciting an immune response against the antigen or protein.

368. A modified Stimulator of Interferon Genes (STING) protein from a non-human species, where the non-human STING is one that has lower NF-κB signaling activity compared to human STING, and, optionally, higher type I interferon (IFN) pathway signaling activity compared to human STING, wherein:

the non-human STING protein is modified to include a mutation or mutations so that it has increased activity or acts constitutively in the absence of cytosolic nucleic acids;

the mutations are insertions, deletions, and/or replacements of amino acids; and

the STING protein optionally has a deletion or disruption of the TRAF6 binding site.

369. A modified Stimulator of Interferon Genes (STING) protein from a non-human species, or a chimeric human STING protein and modifications thereof, comprising one or more mutation(s) associated with gain-of-function (GOF) that result in the constitutive activation of the encoded STING protein and/or enhanced sensitivity, or increased affinity or binding to endogenous ligands, whereby the STING protein is modified by one or more of an insertion, deletion, and replacement of an amino acid or amino acids;

the STING protein has IFN-beta signaling activity, and attenuated nuclear factor kappa-light-chain-enhancer of activated B cell (NF-κB) signaling activity, compared to human STING; and

the mutation or mutations result in increased STING activity or constitutive activity in inducing IFN-beta production.

370. The modified STING protein of claim 368 or claim 369, wherein the human STING protein comprises the sequence set forth in any of SEQ ID NOs:305-309, or is a human allelic variant thereof with at least 98% sequence identity to the sequence of amino acids set forth in any of SEQ ID NOs:305-309.

371. The modified STING protein of any of claims 368-370, wherein:

the STING protein is a chimera comprising replacement of a C-terminal tail (CTT) region in a STING protein from a first species, with the CTT of a STING protein from a second species;

the STING protein of the second species has lower NF-κB signaling activity than the NF-κB signaling activity of human STING; and

the TRAF6 binding site in the CTT optionally is deleted.

372. The modified STING protein of any of claims 368-371, wherein the mutation or mutations is/are any that correspond to those associated with the auto-inflammatory disease STING-associated vasculopathy (SAVI).

373. A modified Stimulator of Interferon Genes (STING) protein that is a chimera, comprising replacement of the CTT (C-terminal tail) region in a STING protein from a first species, with the CTT of a STING protein from a second species, wherein:

the STING protein of the second species has lower NF-κB signaling activity than the NF-κB signaling activity of human STING; and

the TRAF6 binding site in the CTT optionally is deleted.

374. The modified STING protein of any of claims 368-373, wherein the human STING protein comprises the sequence set forth in any of SEQ ID NOs:305-309, or is a human allelic variant thereof with at least 98% sequence identity to the sequence of amino acids set forth in any of SEQ ID NOs:305-309.

375. The modified STING protein of any of claims 368-373, wherein the first species is human, and the second species is selected from among Tasmanian devil, marmoset, cattle, cat, ostrich, boar, bat, manatee, crested ibis, coelacanth, mouse, and ghost shark.

376. The modified STING protein of any of claims 368-375, wherein the type I IFN signaling activity is at least or at least about 30% that of a wild type human STING protein.

377. The modified STING protein of any of claims 368-376, wherein the NF-κB signaling activity is less than 30%, less than 20%, less than 15%, less than 10%, or less than 5% that of wild type human STING NF-κB signaling activity.

378. The modified STING protein of any of claims 368-377, wherein the non-human species or second species is selected from among Tasmanian devil, marmoset, cattle, cat, ostrich, boar, bat, manatee, crested ibis, coelacanth, mouse, and ghost shark.

379. The modified STING protein of any of claims 368-378, wherein the modification of STING is a mutation or mutations that correspond, by reference to and alignment with human STING, to a mutation that occurs in an interferonopathy, wherein the sequence of human STING with which alignment is effected is set forth in any of SEQ ID NOs:305-309.

380. The modified STING protein of any of claims 368-379 that comprises replacement of the C-terminal tail (CTT) with the CTT from a STING protein that has reduced NF-κB signaling activity compared to the NF-κB signaling activity of human STING.

381. The modified STING protein of claim 380, wherein the replacing CTT is from a Tasmanian devil, marmoset, cattle, cat, ostrich, boar, bat, manatee, crested ibis, coelacanth, mouse, or ghost shark STING protein.

382. The modified STING protein of claim 380, wherein the replacing CTT is from a Tasmanian devil, marmoset, cattle, cat, ostrich, boar, bat, manatee, crested ibis, coelacanth, mouse, or ghost shark STING protein, and it replaces the human STING CTT.

383. The modified STING protein of claim 381 or claim 382, wherein the replacing CTT is selected from among the following species, and has a sequence:
Tasmanian devil RQEEFAIGPKRAMTVTTSSTLSQEPQLLISGMEQPLSLRTDGF SEQ ID NO:371,
Marmoset EEEEVTVGSLKTSEVPSTSTMSQEPELLISGMEKPLPLRSDLF SEQ ID NO:372,
Cow EREVTMGSTETSVMPGSSVLSQEPELLISGLEKPLPLRSDVF SEQ ID NO:373,
Cat EREVTVGSVGTSMVRNPSVLSQEPNLLISGMEQPLPLRTDVF SEQ ID NO:374,
Ostrich RQEEYTVCDGTLCSTDLSLQISESDLPQPLRSDCL SEQ ID NO:375,
Boar EREVTMGSAETSVVPTSSTLSQEPELLISGMEQPLPLRSDIF SEQ ID NO:376,
Bat EKEEVTVGTVGTYEAPGSSTLHQEPELLISGMDQPLPLRTDIF SEQ ID NO:377,
Manatee EREEVTVGSVGTSVVPSPSSPSTSSLSQEPKLLISGMEQPLPLRTDVF SEQ ID NO:378,
Crested ibis CHEEYTVYEGNQPHNPSTTLHSTELNLQISESDLPQPLRSDCF SEQ ID NO:379,
Coelacanth
(variant 1) QKEEYFMSEQTQPNSSSTSCLSTEPQLMISDTDAPHTLKRQVC SEQ ID NO:380,
Coelacanth
(variant 2) QKEEYFMSEQTQPNSSSTSCLSTEPQLMISDTDAPHTLKSGF SEQ ID NO:381,
Ghost shark LTEYPVAEPSNANETDCMSSEPHLMISDDPKPLRSYCP SEQ ID NO:383, and
Mouse EKEEVTMNAPMTSVAPPPSVLSQEPRLLISGMDQPLPLRTDLI SEQ ID NO:384,

or allelic variants of each of these sequences, having at least 98% sequence identity thereto.

384. The modified STING protein of claim 382 or claim 383, wherein the human CTT comprises the sequence EKEEVTVGSLKTSAVPSTSTMSQEPELLISGMEKPLPLRTDFS (SEQ ID NO:370), or is an allelic variant having at least 98% sequence identity thereto.

385. The modified STING protein of any of claims 373-384, wherein the modified STING protein is a chimera in which the human STING CTT is replaced with a CTT from the Tasmanian devil STING.

386. The modified STING protein of claim 385, wherein the C-terminal tail (CTT) from the Tasmanian devil STING comprises the sequence: RQEEFAIGPKRAMTVTTSSTLSQEPQLLISGMEQPLSLRTDGF (SEQ ID NO:371), or is an allelic variant having at least 98% sequence identity thereto.

387. The modified STING protein of any of claims 368-386, comprising a deletion or disruption of the TRAF6 binding site.

388. The modified STING protein of claim 387, wherein the STING protein is a human STING protein, and the TRAF6 binding site comprises the amino acid residues DFS at the C-terminus.

389. The modified STING protein of any of claims 368-388, comprising a modification that increases type I interferon signaling activity, or that renders the activity constitutive in the absence of cytosolic nucleic acids.

390. The modified STING protein of claim 389, wherein the modification corresponds, by reference to and alignment with human STING, to a mutation that occurs in an interferonopathy, wherein the human STING protein has the sequence set forth in any of SEQ ID NOs:305-309.

391. The modified STING protein of any of claims 368-390, wherein the modification is one or more amino acid replacements that correspond(s) to one or more of S102P, V147L, V147M, N154S, V155M, G166E, C206Y, G207E, S102P/F279L, F279L, R281Q, R284G, R284S, R284M, R284K, R284T, R197A, D205A, R310A, R293A, T294A, E296A, R197A/D205A, S272A/Q273A, R310A/E316A, E316A, E316N, E316Q, S272A, R293A/T294A/E296A, D231A, R232A, K236A, Q273A, S358A/E360A/S366A, D231A/R232A/K236A/R238A, S358A, E360A, S366A, R238A, R375A, and S324A/S326A, with reference to the sequence of human STING, as set forth in any of SEQ ID NOs:305-309.

392. The modified STING protein of claim 391 that comprises a replacement corresponding to C206Y or R284G, with reference to the sequence of human STING, as set forth in any of SEQ ID NOs:305-309.

393. The modified STING protein of claim 392 that is a Tasmanian devil, marmoset, cattle, cat, ostrich, boar, bat, manatee, crested ibis, coelacanth, mouse, or ghost shark STING protein.

WHAT IS CLAIMED:

1. An immunostimulatory bacterium, comprising a plasmid that encodes a therapeutic product or products, wherein:

the bacterium comprises genome modifications, whereby the bacterium does not produce active thymidylate synthase, and requires supplementation for growth;

the genome of the immunostimulatory bacterium is modified, whereby the bacterium lacks flagella; and

the unmodified bacterium comprises flagella.

2. The immunostimulatory bacterium of claim 1, wherein:

a therapeutic product is a variant protein that is part of the cytosolic DNA/RNA sensor pathway;

the variant protein comprises amino acid modifications whereby expression of type I interferon (IFN) is constitutive when the protein is expressed in or is in a eukaryotic cell; and

amino acid modifications comprise one or more of an amino acid insertion, deletion, and replacement.

3. The immunostimulatory bacterium of claim 1, wherein:

a therapeutic product is a modified STING, IRF3, IRF5, IRF7, IRF8, MDA5, or RIG-I protein that comprises amino acid modifications, whereby expression of type I interferon (IFN) is constitutive; and

the modifications comprise one or more of an amino acid replacement, insertion, and deletion.

4. The immunostimulatory bacterium of claim 3, wherein the amino acid modifications are selected as follows:

a) in STING, with reference to SEQ ID NO: 305-309, one or more selected from among: S102P, V147L, V147M, N154S, V155M, G166E, C206Y, G207E, S102P/F279L, F279L, R281Q, R284G, R284S, R284M, R284K, R284T, R197A, D205A, R310A, R293A, T294A, E296A, R197A/D205A, S272A/Q273A, R310A/E316A, E316A, E316N, E316Q, S272A, R293A/T294A/E296A, D231A,

R232A, K236A, Q273A, S358A/E360A/S366A, D231A/R232A/K236A/R238A, S358A, E360A, S366A, R238A, R375A, N154S/R284G, and S324A/S326A;

b) in MDA5, with reference to SEQ ID NO:310, one or more of: T331I, T331R, A489T, R822Q, G821S, A946T, R337G, D393V, G495R, R720Q, R779H, R779C, L372F, and A452T;

c) in RIG-I, with reference to SEQ ID NO:311, one or both of E373A and C268F; and

d) in IRF-3, with reference to SEQ ID NO:312, S396D.

5. The immunostimulatory bacterium of any of claims 1-4, wherein the immunostimulatory bacterium comprises a plasmid that encodes an interferon, or encodes a modified STING protein that constitutively induces type I interferon, and encodes an antigen or protein from a pathogen or a tumor-associated antigen.

6. The immunostimulatory bacterium of any of claims 1-5, wherein the genome of the immunostimulatory bacterium is modified by deletion or disruption of all or of a sufficient portion of a gene or genes, whereby the bacterium produces lipopolysaccharide (LPS) with penta-acylated lipid A.

7. The immunostimulatory bacterium of any of claims 1-6, wherein the genome of the bacterium is modified so that the bacterium lacks curli fimbriae.

8. The immunostimulatory bacterium of any of claims 1-7, wherein the therapeutic product(s) is/are encoded by nucleic acid that is operatively linked to a prokaryotic promoter.

9. The immunostimulatory bacterium of claim 8, wherein the nucleic acid encoding the therapeutic product or products is transcribed in the bacterium, but cannot be translated by the bacterium.

10. The immunostimulatory bacterium of any of claims 1-7, wherein the therapeutic product(s) is/are encoded by nucleic acid that is operatively linked to a eukaryotic promoter.

11. The immunostimulatory bacterium of any claims 1-10, wherein the plasmid further comprises nucleic acid encoding an antigen from a pathogen or a tumor-associated antigen.

12. The immunostimulatory bacterium of claim 11, wherein the tumor-associated antigen is an oncofetal antigen, an oncoviral antigen, an overexpressed/accumulated antigen, a cancer-testis antigen, a linear restricted antigen, a mutated antigen, a post-translationally altered antigen, or an idiotypic antigen.

13. The immunostimulatory bacterium of any of claims 1-12 that comprises genome modifications whereby the bacterium lacks flagella, is *msbB*$^{-}$/*pagP*$^{-}$, and lacks curli fimbriae, wherein genome modifications include deletions, insertions, replacements, and transpositions.

14. The immunostimulatory bacterium of claim 13 that comprises modifications that render the bacterium *asd*$^{-}$, whereby the bacterium does not replicate *in vivo*, and comprises nucleic acid encoding aspartate dehydrogenase (*asd*) on the plasmid under control of a prokaryotic promoter for growth of the bacteria *in vitro*.

15. An immunostimulatory bacterium, comprising a plasmid encoding a therapeutic product or products, wherein:

nucleic acid encoding the therapeutic product(s) is operatively linked to a prokaryotic promoter; and

the therapeutic product(s) encoded by the plasmid is/are selected from:

a tumor-associated antigen; or

a tumor-associated antigen and a modified STING protein that constitutively induces type I interferon; or

a tumor-associated antigen and interferon alpha, or a tumor-associated antigen and interferon beta.

16. The immunostimulatory bacterium of claim 15, wherein the tumor-associated antigen is an oncofetal antigen, an oncoviral antigen, an overexpressed/accumulated antigen, a cancer-Testis antigen, a linear restricted

antigen, a mutated antigen, a post-translationally altered antigen, or an idiotypic antigen.

17. The immunostimulatory bacterium of claim 16, wherein the tumor-associated antigen (TAA) is selected from among the following antigens:

a) an oncofetal antigen selected from among carcinoembryonic antigen (CEA), immature laminin receptor, and tumor-associated glycoprotein 72 (TAG-72);

b) an oncoviral TAA selected from HPV E6 and HPV E7;

c) an overexpressed/accumulated TAA selected from among epidermal Growth Factor Receptor (EGFR), Wilms' tumor protein, calcium-activated chloride channel 2, cyclin-B1, 9D7, epidermal cell adhesion molecule (EpCAM), Ephrin type-A receptor 3 (EphA3), human epidermal growth factor receptor 2 (HER2/Neu), telomerase, mesothelin, stomach-cancer–associated protein tyrosine phosphatase 1 (SAP-1), and survivin;

d) a cancer testis TAA selected from among BAGE (B melanoma antigen) family, CAGE family, GAGE family, MAGE (melanoma antigen) family, SAGE (sarcoma antigen) family, PAGE family, XAGE family, CT9, CT10, New York esophageal squamous cell carcinoma 1 (NY-ESO-1), LAGE-1, preferentially expressed antigen in melanoma (PRAME), and synovial sarcoma/X breakpoint 2 (SSX-2);

e) a linear-restricted TAA selected from melanoma antigen recognized by T-cells 1 (Melan-A/MART-1), gp100/Pmel17, tyrosinase, tyrosine-related protein (TRP)-1, TRP-2, polypeptide, melanocortin 1 receptor (MC1R), and prostate-specific antigen (PSA);

f) a mutated TAA selected from among β-catenin, BRCA1, BRCA2, cyclin dependent kinase 4 (CDK4), chronic myelogenous leukemia tumor antigen 66 (CML66), fibronectin, melanoma antigen recognized by T-cells 2 (MART-2), p53, Ras, and TGF-β receptor type II (TGF-βRII);

g) a post-translationally altered TAA that is mucin 1, cell surface associated (MUC1); and

h) an idiotypic TAA that is immunoglobulin Ig or T-cell Receptor (TCR).

18. The immunostimulatory bacterium of any of claims 1-17 that comprises genome modifications whereby the bacterium is *pagP*$^{-}$/*msbB*$^{-}$ and lacks flagella, wherein the wild-type bacterium has flagella.

19. The immunostimulatory bacterium of any of claims 1-18 that is a *Salmonella* strain.

20. An immunostimulatory bacterium, comprising a plasmid containing nucleic acid encoding a therapeutic product, wherein:

the nucleic acid encoding the therapeutic product is operatively linked to a prokaryotic promoter; and

the bacterium comprises genome modifications that reduce or eliminate recognition of the bacterium by or activation of TLR2, and optionally TLR4 and/or TLR5, whereby induction of type I IFN is not inhibited compared to the bacterium without the genome modifications.

21. The immunostimulatory bacterium of claim 20, wherein the nucleic acid encodes RNA that cannot be translated by prokaryote ribosomes, but can be translated by eukaryotic ribosomes, whereby the bacterium, when cultured *in vitro,* comprises RNA transcribed from the nucleic acid encoding the therapeutic product.

22. The immunostimulatory bacterium of any of claims 8, 15, 20 and 21, wherein the nucleic acid encodes RNA that lacks a Shine-Dalgarno sequence and/or includes an Internal Ribosome Entry Site (IRES), and/or a translational read through 2A peptide.

23. The immunostimulatory bacterium of any of claims 20-22, wherein the nucleic acid encodes a modified STING protein that constitutively induces type I interferon, and encodes a tumor-associated antigen and/or an antigen from a pathogen.

24. An immunostimulatory bacterium, comprising a plasmid encoding a combination of heterologous products, wherein:

the genome of the immunostimulatory bacterium is modified by deletion or disruption of all or of a sufficient portion of a gene or genes, whereby the bacterium has attenuated recognition by TLR2, and optionally attenuated recognition of one or both of TLR4 and TLR5;

one plasmid encoded product is a protein that is part of a cytosolic DNA/RNA sensor pathway that leads to expression of type I interferon (IFN) and the product is modified whereby expression of type I interferon is constitutive; and

a second encoded product is an antigen, an epitope or epitopes from an antigen, a protein for immunization against a pathogen or tumor, an anti-viral therapeutic, or an anti-pathogenic bacteria therapeutic.

25. The immunostimulatory bacterium of claim 24, wherein the genome of the bacterium is modified whereby the bacterium does not have curli fimbriae, if the wild-type bacterium contains flagella, the bacterium lacks flagella, and the bacterium has penta-acylated lipid A.

26. The immunostimulatory bacterium of any of claims 1-25, wherein:

the bacterium comprises genome modifications, whereby the phenotype of the resulting bacterium is selected from among modifications comprising:

a) *asd*$^-$, *csgD*$^-$, *purI*$^-$, *msbB*$^-$, flagellin$^-$, and *pagP*$^-$;

b) *thyA*$^-$, *csgD*$^-$, *purI*$^-$, *msbB*$^-$, flagellin$^-$, and *pagP*;

c) *ansB*$^-$, *asd*$^-$, *csgD*$^-$, *purI*$^-$, *msbB*$^-$, flagellin$^-$, and *pagP*;

d) *ansB*$^-$, *thyA*$^-$, *csgD*$^-$, *purI*$^-$, *msbB*$^-$, flagellin$^-$, and *pagP*$^-$; and

e) *asd*$^-$, *ansB*$^-$, *thyA*$^-$, *csgD*$^-$, *purI*$^-$, *msbB*$^-$, flagellin$^-$, and *pagP*$^-$,

wherein, if the bacterium is *asd*$^-$, it optionally encodes aspartate dehydrogenase (*asd*) on the plasmid under control of a prokaryotic promoter for expression of *asd in vitro*.

27. The immunostimulatory bacterium of any of claims 24-26, wherein a therapeutic product encoded on the plasmid is an anti-viral therapeutic or an anti-pathogenic bacteria therapeutic.

28. The immunostimulatory bacterium of any of claims 24-27, wherein a therapeutic product encoded on the plasmid is an anti-viral therapeutic that is a viral

antigen whose expression results in an immune-protective response against a virus, or is an antibody that binds to or interacts with a viral antigen, whereby a virus is inhibited or blocked, or anti-viral immunity results.

29. The immunostimulatory bacterium of any of claims 24-28, wherein:

the encoded protein that is part of a cytosolic DNA/RNA sensor pathway is a modified STING protein that constitutively induces type I interferon; and

another encoded product or products is/are a tumor-associated antigen and/or an antigen from a pathogen.

30. The immunostimulatory bacterium of claim 29, wherein the encoded products are encoded as a polycistronic message under control of a single prokaryotic promoter for expression in the bacterium.

31. The immunostimulatory bacterium of any of claims 1-30 that encodes a therapeutic, wherein the therapeutic is an anti-bacterial therapeutic that is a bacterial antigen whose expression results in an immune-protective response against the bacterial pathogen, or the anti-bacterial therapeutic is an antibody that binds to or interacts with a bacterial antigen, whereby the pathogenic bacterium is inhibited or blocked, or anti-pathogenic bacterium immunity results.

32. The immunostimulatory bacterium of any of claims 1-30, wherein the immunostimulatory bacterium encodes a therapeutic for treating an infectious agent that causes persistent infection, or for treating an infectious agent that causes chronic infection, or for treating an infectious agent that causes latent infection, or for treating an infectious agent that causes slow infection.

33. The immunostimulatory bacterium of claim 32, wherein the infectious agent is a virus selected from among T-Cell leukemia viruses, Epstein-Barr virus, cytomegalovirus, herpesviruses, varicella zoster virus, measles virus, papovaviruses, hepatitis virus type A, B, C, D and E, adenoviruses, parvoviruses, human immunodeficiency virus (HIV), coronaviruses, smallpox virus, poliovirus, influenza

virus, rotavirus, yellow fever virus, mumps virus, rubella virus, and papillomaviruses; or is a bacterium; or is a prion; or is a protozoan.

34. The immunostimulatory bacterium of any of claims 1-33 that is a strain designated as YS1646Δ*asd*/ΔFLG/Δ*pagP*/Δ*ansB*/Δ*csgD*/F-Δ*purI*, or YS1646Δ*asd*/ΔFLG/Δ*pagP*/Δ*ansB*/Δ*csgD*/F-Δ*purI*/Δ*thyA*, wherein F-Δ*purI* refers to a deletion of the full-length *purI* gene.

35. An immunostimulatory bacterium, comprising a plasmid containing nucleic acid operatively linked to a prokaryotic promoter, wherein:

the nucleic acid comprises DNA that lacks sequences necessary for translation by a prokaryote or comprises sequences that prevent translation by a prokaryote, whereby the RNA encoded by the DNA is produced in the bacterium, but cannot be translated by the bacterium;

the RNA encodes a therapeutic product or is a therapeutic product;

the bacterium has genomic modifications whereby infection is substantially or is restricted to phagocytic cells; and

the genome of the immunostimulatory bacterium is modified by deletion or disruption of all or of a sufficient portion of the gene *ansB*, encoding L-asparaginase II, whereby the bacterium is $ansB^-$ and does not express active L-asparaginase II.

36. The immunostimulatory bacterium of claim 35, wherein the genome of the bacterium is modified by deletion or disruption of all or of a sufficient portion of the gene *csgD*, whereby the bacterium is $csgD^-$ and does not activate the synthesis of curli fimbriae.

37. The immunostimulatory bacterium of claim 35 or 36, wherein the genome of the bacterium is further modified by deletion or disruption of all or of a sufficient portion of genes, whereby the bacterium is $ansB^-/csgD^-/msbB^-/pagP^-$.

38. An immunostimulatory bacterium, comprising a plasmid encoding a therapeutic product, wherein:

the product is a bi-specific T-cell engager antibody that binds DLL3 and CD3;

the immunostimulatory bacterium lacks flagella and comprises LPS that is penta-acylated; and

the wild-type bacterium comprises flagella.

39. The immunostimulatory bacterium of claim 38, wherein the bi-specific T-cell engager antibody comprises a heavy chain and light chain of an anti-DLL3 antibody and of an anti-CD3 antibody.

40. The immunostimulatory bacterium of claim 38 or 39, wherein the bi-specific T-cell engager antibody comprises combinations of a) - f), whereby the resulting construct can bind to each of DLL3 and CD3:

a) a light chain that comprises amino acid residues 154-260 of SEQ ID NO: 487, or a humanized variant thereof, or a variant having at least 95 % sequence identity thereto; and

b) a heavy chain that comprises the sequence of amino acid residues set forth as amino acid residues 22-138 of SEQ ID NO: 487, or a humanized variant thereof, or a variant having at least 95 % sequence identity thereto; and

c) a light chain that comprises a sequence of amino acid residues set forth as amino acid residues 155-261 of SEQ ID NO: 489, or a humanized variant thereof, or a variant having at least 95 % sequence identity thereto; and

d) a heavy chain that comprises a sequence of amino acid residues set forth as amino acid residues 22-139 of SEQ ID NO: 489, or a humanized variant thereof, or a variant having at least 95 % sequence identity thereto; and

e) a heavy and light chain, wherein:

the light chain comprises a sequence of amino acid residues set forth as amino acid residues 155-261 of SEQ ID NO: 485, or a humanized variant thereof, or a variant having at least 95 % sequence identity thereto; and

the heavy chain comprises a sequence of amino acid residues set forth as amino acid residues 22-139 of SEQ ID NO: 485, or a humanized variant thereof, or a variant having at least 95 % sequence identity thereto; and

f) a heavy and light chain of an anti-CD3 antibody, wherein:

the light chain of the anti-CD3 antibody comprises a sequence of amino acid residues set forth as amino acid residues 398-504 of SEQ ID NO: 485, or

a humanized variant thereof, or a variant having at least 95 % sequence identity thereto; and

the heavy chain of the anti-CD3 antibody comprises a sequence of amino acid residues set forth as amino acid residues 267-382 of SEQ ID NO: 485, or a humanized variant thereof, or a variant having at least 95 % sequence identity thereto.

41. An immunostimulatory bacterium, comprising a plasmid that encodes two or more therapeutic products under control of a single promoter, wherein:

the therapeutic products are selected from among:

a) an immunostimulatory protein that confers or contributes to an anti-tumor immune response in the tumor microenvironment;

b) one or more of a protein that is part of a cytosolic DNA/RNA sensor pathway, wherein the protein is a variant that results in constitutive expression of a type I IFN; and

c) an anti-cancer antibody or antigen-binding portion thereof; and

the encoding nucleic acids are separated by an IRES sequence or 2A peptides, and each nucleic acid encoding each product is optionally operatively linked to nucleic acid encoding a signal sequence, whereby, upon translation of the encoded mRNA, each product is separately expressed and secreted from a cell comprising the bacterium and/or plasmid.

42. The immunostimulatory bacterium of claim 41, wherein the immunostimulatory protein is a co-stimulatory molecule that lacks a cytoplasmic domain or a sufficient portion thereof, for expression on an antigen-presenting cell (APC), whereby the truncated co-stimulatory molecule is capable of constitutive immunostimulatory signaling to a T-cell through co-stimulatory receptor engagement and is unable to counter-regulatory signal to the antigen presenting cell (APC).

43. The immunostimulatory bacterium of claim 41 or claim 42, wherein the immunostimulatory bacterium comprises a plasmid that encodes the at least two therapeutic products, wherein the products are selected from among a cytokine, a protein that constitutively induces a type I IFN, a co-stimulatory molecule, and an

anti-cancer antibody or antigen-binding portion thereof, and also encodes an antigen or an antigenic protein.

44. An immunostimulatory bacterium that is a strain designated as YS1646Δ*asd*/ΔFLG/Δ*pagP*/Δ*ansB*/Δ*csgD*/F-Δ*purI*, or YS1646Δ*asd*/ΔFLG/Δ*pagP*/Δ*ansB*/Δ*csgD*/F-Δ*purI*/Δ*thyA*, wherein F-Δ*purI* refers to deletion of the full-length of the *purI* gene.

45. A genome modified bacterium, comprising genome modifications, whereby the response by toll-like receptors (TLRs) 2, 4, and 5 is reduced compared to the bacterium without the genome modifications, wherein:

the bacterium comprises further genomic modifications whereby it is auxotrophic for a required nutrient or factor so that it is unable to replicate in a eukaryotic host, but can replicate *in vitro* when supplied with the nutrient or factor;

the bacterium comprises a plasmid containing nucleic acid encoding a product, or the bacterium comprises RNA encoding the product;

the product encoded by the nucleic acid or RNA is an antigenic sequence or sequence from a pathogen that is a pathogenic virus, bacterium, prion, or parasite, or is a tumor-associated antigen, whereby, upon expression of the encoded antigenic sequence in the host, the host develops an immune-protective response or immunizing response against the pathogenic virus, bacterium, prion, parasite, or tumor-associated antigen, or the product is a therapeutic product against a pathogen or tumor;

expression of the antigenic sequence(s) is/are under control of a prokaryotic promoter so that RNA encoding the product is produced in the bacterium;

nucleic acid encoding the antigen comprises regulatory sequences that inhibit or prevent translation of the encoded RNA by bacterial ribosomes, but that do not inhibit or prevent translation of the encoded RNA by eukaryotic host ribosomes, whereby translation is de-coupled from transcription in the bacterium; and

the resulting bacterium is selective for infecting phagocytic cells when administered to a eukaryotic subject, and delivers the nucleic acid into the phagocytic cells, wherein the RNA is translated into the product.

46. The bacterium of claim 45 that comprises nucleic acid encoding a TLR8 agonist.

47. The bacterium of claim 45 or 46 that is *msbB*$^{-}$/*pagP*$^{-}$, lacks flagella, and is *asd*$^{-}$ or *thyA*$^{-}$ or both *asd*$^{-}$ and *thyA*$^{-}$.

48. The bacterium of any of claims 1-18 and 20-47 that is a species or strain of *Escherichia*, *Listeria*, *Mycobacteria,* or *Salmonella.*

49. A vaccine, comprising nucleic acid that encodes an antigen or protein or epitope from a pathogen or tumor, wherein:

the vaccine elicits an immune response against the pathogen or tumor;

the pathogen is a respiratory pathogen that infects the respiratory system including the lungs and/or naso-pharynx;

the tumor is a lung tumor;

the vaccine is formulated for inhalation through the nose or lungs;

the vaccine delivers the nucleic acid to phagocytic macrophages to convert the immunosuppressive phagocytic macrophages to immunostimulatory, phagocytic macrophages that are capable of in situ antigen cross-presentation to CD8+ T-cells, and of migration to lymph nodes to prime CD4+ and CD8+ T-cells; and

the vaccine does not activate a TLR2, TLR4 and/or TRL5 response sufficient to decease or inhibit type I IFN.

50. The vaccine of claim 49, wherein the pathogen is a virus.

51. The vaccine of claim 49 or 50, wherein the virus is a corona virus or influenza virus.

52. A pharmaceutical composition, comprising the bacterium of any of claims 1-48 in a pharmaceutically acceptable vehicle.

53. The bacterium of any of claims 1-48 or pharmaceutical composition of claim 52, wherein the bacterium is a *Salmonella typhimurium*.

54. The bacterium of any of claims 1-48 and 53 or vaccine of any of claims 49-51 for use for treatment of or immunization against infection with a pathogen or against a tumor, wherein the bacterium comprises or encodes an antigen, protein, or epitope thereof from the pathogen or tumor.

55. The bacterium or vaccine of claim 54, wherein the bacterium encodes the antigen, protein, or epitope thereof under control of a promoter recognized by the bacterium; and the bacterium comprises a genome modification(s), whereby it does not replicate *in vivo*.

56. Use of the bacterium of any of claims 1-48 and 53 in the manufacture of a medicament for the treatment of cancer or for immunization against or for treatment of a pathogen.

57. The bacterium of any of claims 1-48 and 53-56, or the vaccine of any of claims 49-51, wherein an encoded therapeutic product is a cytokine.

58. The bacterium or vaccine of claim 57, wherein the cytokine is IL-15/IL-15R alpha chain complex.

59. The bacterium of any of claims 1-48 and 53 for use in therapy.