CLAIMS:

1. An immunostimulatory bacterium, comprising a plasmid encoding an immunostimulatory protein that, in unmodified form, is part of a cytosolic DNA/RNA sensor pathway that leads to expression of type I interferon (IFN), wherein:

the immunostimulatory protein is modified to have increased activity or to constitutively induce type I interferon;

modifications are selected from among amino acid insertions, deletions, and replacements;

the genome of the bacterium is modified to reduce or eliminate infection of epithelial cells; and

the nucleic acid encoding the immunostimulatory protein is operatively linked to regulatory sequences recognized by a eukaryotic host.

2. The immunostimulatory bacterium of claim 1, wherein:

the immunostimulatory protein is selected from among STING, MDA5, IRF-3, IRF-7, and RIG-I; and

the immunostimulatory protein comprises a modification(s) that is a gain-of-function (GOF) mutation(s) that renders the STING, MDA5, IRF-3, IRF-7, or RIG-I constitutively active, whereby expression of type I IFN is constitutive.

3. The immunostimulatory bacterium of claim 1 or claim 2, wherein the modifications, which are amino acid replacements, are selected as follows:

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

b) in MDA5, with reference to SEQ ID NO:310, one or more selected from among: 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;

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

e) in IRF-7, with reference to SEQ ID NO:313, one or more of: S477D/S479D, S475D/S477D/S479D, and S475D/S476D/S477D/S479D/S483D/S487D; and

f) conservative amino acids replacements of any of a)-e) that render type I interferon expression constitutive.

4. The immunostimulatory bacterium of any of claims 1-3, wherein the immunostimulatory protein is STING.

5. The immunostimulatory bacterium of claim 4, wherein the immunostimulatory protein is a modified STING protein selected from among:

a) a modified non-human STING protein that has lower NF-κB signaling activity compared to the NF-κB signaling activity of human STING, wherein:

i) the non-human STING protein is modified to include a mutation or mutations so that it has increased type I interferon (IFN) pathway signaling activity or acts constitutively to induce type I IFN;

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

iii) the STING protein optionally has a deletion of the TRAF6 binding site;

b) the modified non-human STING protein of a) that is modified to constitutively induce type I IFN;

c) a chimeric STING protein that comprises a human STING and replacement of the C-terminal tail (CTT) of the human STING protein with the CTT from a non-human STING protein that has reduced NF-κB signaling activity compared to the NF-κB signaling activity of the human STING protein; and

d) a modified chimeric STING protein of c) that is modified to include a mutation or mutations so that it has increased type I interferon (IFN) pathway signaling activity or acts constitutively in the absence of cytosolic nucleic acids, wherein the mutations are insertions, deletions, and/or replacements of amino acids.

6. The immunostimulatory bacterium of any of claims 1-5, wherein:

the immunostimulatory protein is a modified STING protein;

the modified STING protein comprises one or more modification(s) associated with gain-of-function (GOF) that result(s) in the constitutive activation of the encoded STING protein and/or enhanced sensitivity, or increased affinity for binding to endogenous ligands;

the modification is one or more of an insertion, deletion, and replacement of an amino acid or amino acids;

the modification corresponds, by reference to and alignment with human STING, to a mutation that occurs in STING in a human interferonopathy; and

full-length human STING has the sequence set forth in any of SEQ ID NOs:305-309.

7. The immunostimulatory bacterium of any of claims 1-6, wherein:

the immunostimulatory protein is a modified STING protein;

the modification(s) that confer(s) increased activity or constitutive activity is one or more amino acid replacements that correspond(s) to one or more of R284G, S102P, V147L, V147M, N154S, V155M, G166E, C206Y, G207E, S102P/F279L, F279L, R281Q, 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 one of SEQ ID NOs:305-309.

8. The immunostimulatory bacterium of any of claims 1-7, wherein the non-human STING is a STING protein from a species selected from among Tasmanian devil, marmoset, cattle, cat, ostrich, boar, bat, manatee, crested ibis, coelacanth, zebrafish, and ghost shark.

9. The immunostimulatory bacterium of claim 8, wherein the non-human STING protein is a Tasmanian devil STING protein of SEQ ID NO:331, or an allelic variant thereof having at least 98% sequence identity to the STING protein of SEQ ID NO:331 and having lower NF-κB signaling activity than human STING.

10. The immunostimulatory bacterium of any of claims 1-9, wherein:

the immunostimulatory protein is a STING protein that comprises a replacement corresponding to C206Y or R284G; and

corresponding residues are numbered by alignment to the sequence of human STING as set forth in any of SEQ ID NOs:305-309.

11. The immunostimulatory bacterium of claim 10, wherein the modified STING protein comprises the sequence of amino acids set forth in SEQ ID NO: 332 or 333 or a protein having at least 98% sequence identity thereto, and comprising the replacement corresponding to C206Y and R284G, respectively.

12. The immunostimulatory bacterium of any of claims 1-11, wherein the sequences of the non-human species STING proteins are those set forth in SEQ ID NOs: 331, 338 and 341-350, or the non-human STING proteins are allelic variants of any of the STING proteins set forth in SEQ ID NOs: 331, 338 and 341-350, having at least 98% sequence identity thereto.

13. The immunostimulatory bacterium of any of claims 1-12, wherein:

the immunostimulatory protein is a STING protein that is a chimeric protein that comprises human STING with replacement of the C-terminal tail (CTT) with the CTT from a second STING protein that has reduced NF-κB signaling activity compared to the NF-κB signaling activity of human STING; and

the chimeric STING protein comprises modifications, whereby the STING protein constitutively induces type I interferon.

14. The immunostimulatory bacterium of claim 13, wherein the TRAF6 binding site in the replacing CTT is deleted.

15. The immunostimulatory bacterium of claim 13, wherein the replacing CTT is from a Tasmanian devil, marmoset, cattle, cat, ostrich, boar, bat, manatee, crested ibis, coelacanth, zebrafish, or ghost shark STING protein, and it replaces the human STING CTT.

16. The immunostimulatory bacterium of any of claims 13-15, wherein the replacing CTT is selected from among the following species and has a sequence:

Tasmanian devil	RQEEFAIGPKRAMTVTTSSTLSQEPQLLISGMEQPLSLRTDGF	SEQ ID NO:353,
Marmoset	EEEEVTVGSLKTSEVPSTSTMSQEPELLISGMEKPLPLRSDLF	SEQ ID NO:354,
Cow	EREVTMGSTETSVMPGSSVLSQEPELLISGLEKPLPLRSDVF	SEQ ID NO:355,
Cat	EREVTVGSVGTSMVRNPSVLSQEPNLLISGMEQPLPLRTDVF	SEQ ID NO:356,
Ostrich	RQEEYTVCDGTLCSTDLSLQISESDLPQPLRSDCL	SEQ ID NO:357,
Boar	EREVTMGSAETSVVPTSSTLSQEPELLISGMEQPLPLRSDIF	SEQ ID NO:358,
Bat	EKEEVTVGTVGTYEAPGSSTLHQEPELLISGMDQPLPLRTDIF	SEQ ID NO:359,
Manatee	EREEVTVGSVGTSVVPSPSSPSTSSLSQEPKLLISGMEQPLPLR TDVF	SEQ ID NO:360,
Crested ibis	CHEEYTVYEGNQPHNPSTTLHSTELNLQISESDLPQPLRSDCF	SEQ ID NO:361,
Coelacanth (variant 1)	QKEEYFMSEQTQPNSSSTSCLSTEPQLMISDTDAPHTLKRQVC	SEQ ID NO:362,
Coelacanth (variant 2)	QKEEYFMSEQTQPNSSSTSCLSTEPQLMISDTDAPHTLKSGF	SEQ ID NO:363, or
Ghost shark	LTEYPVAEPSNANETDCMSSEPHLMISDDPKPLRSYCP	SEQ ID NO:365,

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

17. The immunostimulatory bacterium of any of claims 13-16, wherein the human STING CTT that is replaced comprises the sequence EKEEVTVGSLKTSAVPSTSTMSQEPELLISGMEKPLPLRTDFS (SEQ ID NO:352), or is an allelic variant having at least 98% sequence identity thereto.

18. The immunostimulatory bacterium of any of claims 1-17, wherein the immunostimulatory protein is a modified STING protein that constitutively induces type I IFN, and is a chimeric protein in which the human STING CTT is replaced with a CTT from Tasmanian devil STING.

19. The immunostimulatory bacterium of claim 18, wherein the C-terminal tail (CTT) from the Tasmanian devil STING comprises the sequence: RQEEFAIGPKRAMTVTTSSTLSQEPQLLISGMEQPLSLRTDGF (SEQ ID NO:353), or is an allelic variant having at least 98% sequence identity thereto.

20. A modified Stimulator of Interferon Genes (STING) protein that is from a non-human species, or that is a chimeric variant human STING protein, wherein:

the modified STING protein and variant of the chimeric STING protein comprise one or more mutations associated with gain-of-function (GOF) that result(s) in the constitutive activation of the encoded STING protein to result in constitutive induction of type I interferon;

the mutation(s) comprise one or more of an insertion, deletion, and replacement of an amino acid or amino acids;

the chimeric STING protein comprises a portion of a human STING protein and a portion of the non-human STING protein;

the non-human or chimeric STING protein constitutively induces type I interferon, and has attenuated nuclear factor kappa-light-chain-enhancer of activated B cell (NF-κB) signaling activity, compared to the NF-κB signaling activity of human STING;

the chimeric STING protein comprises replacement of a C-terminal tail (CTT) region in the human STING protein 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.

21. The modified STING protein or chimeric STING protein of claim 20, wherein the mutation or mutations is/are any that correspond to those associated with the human auto-inflammatory disease STING-associated vasculopathy with onset in infancy (SAVI).

22. The modified Stimulator of Interferon Genes (STING) protein of claim 20 or claim 21 that is a chimera, comprising replacement of the CTT (C-terminal tail) region in a STING protein from a human STING with the CTT of a STING protein from a second species, wherein:

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

the STING chimera is modified to include a mutation or mutations so that it has type I IFN signaling activity, and acts constitutively, in the absence of stimulation by ligands, cytosolic nucleic acids or STING ligands, to induce type I IFN signaling activity; and

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

23. The modified Stimulator of Interferon Genes (STING) protein of any of claims 20-22 that comprises the sequence of amino acids set forth in SEQ ID NO:336 or

sequence having at least 98% sequence identity thereto and comprising the replacement corresponding to R284G.

24. The modified STING protein of any of claims 20-22, wherein the non-human species is Tasmanian devil, marmoset, cattle, cat, ostrich, boar, bat, manatee, crested ibis, coelacanth, zebrafish, or ghost shark.

25. The modified STING protein of any of claims 20-24, wherein the full-length unmodified human non-chimeric STING protein comprises the sequence of amino acids 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.

26. A delivery vehicle, comprising a modified STING protein of any of claims 20-25.

27. An immunostimulatory bacterium, comprising a plasmid encoding a STING protein of any of claims 20-25.

28. The immunostimulatory bacterium of any of claims 1-19 and 27 that comprises, encoded on the plasmid, a combination of:

a) nucleic acid encoding one or more of a modified STING, RIG-I, MDA5, IRF3, or IRF7 protein, wherein the modified protein increases type I interferon expression or results in constitutive expression of type I interferon; and

b) nucleic acid encoding one or more of IL-2, IL-7, IL-12p70 (IL-12p40 + IL-12p35), IL-15, IL-15/IL-15R alpha chain complex, IL-2 that has attenuated binding to IL-2Ra, IL-2 modified so that it does not bind to IL-2Ra, IL-18, IL-36 gamma, CXCL9, CXCL10, CXCL11, CCL3, CCL4, CCL5, proteins that are involved in or that effect or potentiate recruitment/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, a TGF-beta polypeptide antagonist, and members of the tumor necrosis factor receptor (TNFR) superfamily.

29. The immunostimulatory bacterium of claim 28 that comprises nucleic acid encoding a STING from a) and two of the proteins in b).

30. The immunostimulatory bacterium of any of claims 1-19 and 27-29, wherein the genome of the immunostimulatory bacterium is modified whereby:

the bacterium lacks flagella; or

the bacterium is *pagP*$^-$; or

the bacterium lacks flagella and is *pagP*$^-$; or

the bacterium is *msbB*$^-$/*pagP*$^-$; or

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

the wild-type bacterium of the bacterium that lacks flagella is a species that has flagella.

31. The immunostimulatory bacterium of any of claims 1-19 and 27-30 that is auxotrophic for adenosine, or for adenosine and adenine.

32. The immunostimulatory bacterium of any of claims 1-19 and 27-31 that is auxotrophic for adenosine.

33. The immunostimulatory bacterium of any of claims 1-19 and 27-32, wherein the genome of the immunostimulatory bacterium is modified whereby the bacterium is *pagP*$^-$/*msbB*$^-$.

34. The immunostimulatory bacterium of any of claims 1-19 and 27-33 that is aspartate-semialdehyde dehydrogenase$^-$ (*asd*$^-$), wherein the bacterium is *asd*$^-$ by virtue of disruption or deletion of all or a portion of the endogenous gene encoding aspartate-semialdehyde dehydrogenase (*asd*), whereby endogenous *asd* is not expressed.

35. The immunostimulatory bacterium of claim 34 that encodes aspartate-semialdehyde dehydrogenase (*asd*) on the plasmid under control of a bacterial promoter.

36. The immunostimulatory bacterium of any of claims 1-19 and 27-35 that is *asd*$^-$, *purI*$^-$, *msbB*$^-$, lacks flagella, and is *pagP*$^-$.

37. The immunostimulatory bacterium of any of claims 1-19 and 27-36, wherein the nucleic acid encoding the immunostimulatory protein on the plasmid is operatively linked to nucleic acid encoding a secretory signal, whereby, upon expression in a host, the protein is secreted.

38. The immunostimulatory bacterium of any of claims 1-19 and 27-37, wherein one or more genes or operons involved in SPI-1-dependent invasion are deleted or inactivated, whereby the immunostimulatory bacterium does not invade or infect epithelial cells.

39. The immunostimulatory bacterium of any of claims 1-19 and 27-38 that is a Gram-negative bacterium.

40. The immunostimulatory bacterium of any of claims 1-19 and 27-39, 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*, *Erysipelothrix*, *Yersinia*, or *Rochalimaea quintana*, or an attenuated strain thereof, or a modified strain thereof of any of the preceding list of bacterial strains.

41. The immunostimulatory bacterium of any of claims 1-19 and 27-40 that is a strain of *Salmonella*.

42. The immunostimulatory bacterium any of claims 1-19 and 27-41 that is a *Salmonella typhimurium* strain.

43. The immunostimulatory bacterium of any of claims 1-19 and 27-42, wherein the unmodified strain of the immunostimulatory bacterium is an attenuated *Salmonella typhimurium* strain selected from among strains designated as AST-100, VNP20009, YS1646 (ATCC #202165), RE88, SL7207, χ 8429, χ 8431, and χ 8468, or is a wild-type bacterium that has all of the identifying characteristics of the strain deposited as ATCC Accession No. 14028, or is strain ATCC 14028.

44. A pharmaceutical composition, comprising the immunostimulatory bacterium of any of claims 1-19 and 27-43 or the delivery vehicle of claim 26 in a pharmaceutically acceptable vehicle.

45. The immunostimulatory bacterium of any of claims 1-19 and 27-43 for use for treatment of cancer.

46. Use of the immunostimulatory bacterium of any of claims 1-19 and 27-43 in the manufacture of a medicament for the treatment of cancer.

47. The delivery vehicle of claim 26 for use for treatment of cancer.

48. The immunostimulatory bacterium of claim 45, the use of claim 46, or the delivery vehicle of claim 47, wherein the cancer comprises a solid tumor.

49. The immunostimulatory bacterium, the use, or the delivery vehicle of any of claims 45-48, wherein the cancer is selected from among 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, gastric cancer, lymphoma, and leukemia.