CLAIMS

1. A nucleic acid construct, comprising nucleic acid encoding a plurality of anti-cancer products as a polycistronic sequence under control of a single promoter.

2. The construct of claim 1, wherein the polycistronic sequence comprises a 2A peptide between each open reading frame (ORF) encoding each product.

3. The construct of claim 1 or claim 2, wherein the anti-cancer products are proteins.

4. The construct of claim 2 or claim 3, wherein the 2A peptide is one or more of T2A, P2A, E2A, or F2A.

5. The construct of any of claims 1-4, wherein the encoded products comprise one or more immunostimulatory protein(s) that confer(s) or contributes to an anti-tumor immune response in a tumor microenvironment.

6. The construct of claim 5, wherein the one or more encoded immunostimulatory protein(s) comprises a cytokine.

7. The construct of claim 6, wherein the encoded products comprise a cytokine and a STING protein.

8. The construct of any of claims 5-7, wherein the modified STING protein is selected from among:

a) a modified non-human Stimulator of Interferon Genes (STING) polypeptide STING protein, wherein:

the non-human STING protein is one that has lower NF-κB signaling, and, optionally, higher type I interferon activation activity compared to the wild-type (WT) human STING protein; and

the non-human STING protein comprises a mutation, whereby the STING protein constitutively induces type I interferon (IFN);

b) a modified chimeric STING protein in which the C-terminal tail (CTT) region in a human STING protein is replaced with the CTT from a STING protein of another species that has lower NF-κB signaling activity signaling activity than human STING; and

c) a modified chimeric STING protein of b) further comprising a mutation whereby the chimeric STING protein constitutively induces type I IFN.

9. The construct of any of claims 5-8, wherein the encoded products comprise IL-15 or IL-15/IL-15R alpha chain complex and a modified STING protein that comprises a mutation(s) whereby the modified STING protein constitutively induces type I IFN.

10. The construct of any of claims 5-9, wherein an immunostimulatory protein that confers or contributes to an anti-tumor immune response in the tumor microenvironment is selected from among:

(a) 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-18, IL-21, IL-23, IL-36γ, IL-2 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 the recruitment and/or persistence of T-cells, CD40, CD40 ligand (CD40L), CD28, OX40, OX40 ligand (OX40L), 4-1BB, 4-1BB ligand (4-1BBL), 4-1BBL that has a cytoplasmic domain deletion or truncation to eliminate immunosuppressive reverse signaling, members of the B7-CD28 family, CD47 antagonists, an anti-IL6 antibody or IL-6 binding decoy receptor, TGF-beta polypeptide antagonists, bi-specific T-cell engager antibodies and members of the tumor necrosis factor receptor (TNFR) superfamily; and/or

(b) one or more of: IFN-α, IFN-β, GM-CSF, IL-2, IL-7, IL-12, IL-15, IL-18, IL-21, IL-23, IL-12p70 (IL-12p40 + IL-12p35), IL-15/IL-15R alpha chain complex, IL-36 gamma, IL-2 that has attenuated binding to IL-2Ra, IL-2 that is modified so that it does not bind to IL-2Ra, CXCL9, CXCL10 (IP-10), CXCL11, CCL3, CCL4, CCL5, molecules involved in the potential recruitment and/or persistence of T-cells, CD40, CD40 ligand (CD40L), OX40, OX40 ligand (OX40L), 4-1BB, 4-1BB ligand (4-1BBL), 4-1BBL with a deleted cytoplasmic domain (4-1BBLΔcyt) or with a partially deleted cytoplasmic domain, which the cytoplasmic domain is deleted or truncated to eliminate the immunosuppressive reverse signaling, members of the B7-CD28 family, and members of the tumor necrosis factor receptor (TNFR) superfamily.

11. The construct of any of claims 1-10, comprising:

(a) nucleic acid encoding 4-1BBL with a deleted, or partially deleted, cytoplasmic domain, or a partially deleted cytoplasmic domain and optionally including amino acid modifications, whereby the resulting 4-1BBL assumes the proper orientation when expressed in a cell; and/or

(b) nucleic acid encoding a 4-1BBL variant with a deleted or partially deleted cytoplasmic domain, or a modified 4-1BBL with a truncated and modified cytoplasmic domain, wherein the sequence of the 4-1BBL is set forth in SEQ ID NO:390, SEQ ID NO:391, and SEQ ID NO:392.

12. The construct of any of claims 1-5, 10 and 11, comprising nucleic acid encoding any of the following products and combinations of products:

one or more of IL-12, or IL-15, or IL12p70, or IL-15/IL-15R alpha chain complex;

a cytokine and a Stimulator of Interferon Genes (STING) pathway agonist;

a cytokine, a STING pathway agonist, and either a costimulatory receptor ligand or an immune checkpoint inhibitor;

a cytokine, a STING pathway agonist, and a TGF-beta polypeptide antagonist; and

a cytokine, a STING pathway agonist, a TGF-beta polypeptide antagonist, and either a co-stimulatory receptor ligand or an immune checkpoint inhibitor,

wherein a STING pathway agonist is any product that increases type I interferon expression via activation of the STING pathway.

13. The construct of any of claims 1-12, comprising nucleic acid encoding a Stimulator of Interferon Genes (STING) polypeptide.

14. The construct of any of claims 1-13, comprising nucleic acid encoding a combination of therapeutic products selected from among the following combinations:

an anti-CTLA-4 antibody and a STING polypeptide,

IL-15 and a STING polypeptide,

4-1BBL and a STING polypeptide,

~~a TGF-beta receptor decoy or antagonist polypeptide, and a STING polypeptide,~~

~~IL-12 and a STING polypeptide,~~

~~an anti-CTLA-4 antibody, IL-15, and a STING polypeptide,~~

~~4-1BBL, IL-15, and a STING polypeptide,~~

~~a TGF-beta receptor decoy or antagonist polypeptide, IL-15, and a STING polypeptide,~~

~~an anti-CTLA-4 antibody, IL-12, and a STING polypeptide,~~

~~4-1BBL, IL-12, and a STING polypeptide,~~

~~a TGF-beta receptor decoy or polypeptide antagonist, IL-12, and a STING polypeptide,~~

~~an anti-CTLA-4 antibody, IL-15, a TGF-beta receptor decoy or polypeptide antagonist, and a STING polypeptide,~~

~~4-1BBL, IL-15, a TGF-beta receptor decoy or polypeptide antagonist, and a STING polypeptide,~~

~~an anti-CTLA-4 antibody, IL-12, a TGF-beta receptor decoy or polypeptide antagonist, and a STING polypeptide,~~

~~4-1BBL, IL-12, a TGF-beta receptor decoy or polypeptide antagonist, and a STING polypeptide,~~

~~an anti-CTLA-4 antibody, IL-12, IL-15, and a STING polypeptide,~~

~~4-1BBL, IL-12, IL-15, and a STING polypeptide,~~

~~a TGF-beta receptor decoy or polypeptide antagonist, IL-12, IL-15, and a STING polypeptide,~~

~~a TGF-beta receptor decoy or polypeptide antagonist, IL-12, IL-15, and a STING polypeptide,~~

~~an anti-CTLA-4 antibody, IL-12, IL-15, a TGF-beta receptor decoy or polypeptide antagonist, and a STING polypeptide,~~

~~4-1BBL, IL-12, IL-21, a TGF-beta receptor decoy or polypeptide antagonist, and a STING polypeptide,~~

~~an anti-CTLA-4 antibody, IL-12, IL-15, and a TGF-beta receptor decoy or polypeptide antagonist,~~

~~4-1BBL, IL-12, IL-21, and a TGF-beta receptor decoy or polypeptide antagonist,~~

~~IL-12, IL-15, and a STING polypeptide,~~

~~IL-15, IL-21, and a STING polypeptide,~~

~~IL-12, IL-21, and a STING polypeptide,~~

~~an anti-CTLA-4 antibody, IL-15, IL-21, and a STING polypeptide,~~

~~an anti-CTLA-4 antibody, IL-12, IL-21, and a STING polypeptide,~~

~~4-1BBL, IL-15, IL-21, and a STING polypeptide,~~

~~4-1BBL, IL-12, IL-21, and a STING polypeptide,~~

an anti-CTLA-4 antibody, and IL-15,

an anti-CTLA-4 antibody, IL-15, and a TGF-beta receptor decoy or polypeptide antagonist,

4-1BBL and IL-15,

4-1BBL, IL-15, and a TGF-beta receptor decoy or polypeptide antagonist,

an anti-CTLA-4 antibody, and IL-12,

an anti-CTLA-4 antibody, IL-12, and a TGF-beta receptor decoy or polypeptide antagonist,

4-1BBL, and IL-12,

4-1BBL, IL-12, and a TGF-beta receptor decoy or polypeptide antagonist,

an anti-CTLA-4 antibody, and a TGF-beta receptor decoy or polypeptide antagonist,

4-1BBL, and a TGF-beta receptor decoy or polypeptide antagonist,

IL-15, and a TGF-beta receptor decoy or polypeptide antagonist,

IL-12, and a TGF-beta receptor decoy or polypeptide antagonist,

IL-12, IL-15, and a TGF-beta receptor decoy or polypeptide antagonist, and

IL-15, IL-21, and a TGF-beta receptor decoy or polypeptide antagonist, wherein:

4-1BBL is 4-1BBL with a deleted cytoplasmic domain, 4-1BBL with a modified cytoplasmic domain, 4-1BBL with a truncated cytoplasmic domain, or 4-1BBL with a truncated and modified cytoplasmic domain;

an anti-CTLA-4 antibody is an scFv or an scFv-Fc; and

a STING polypeptide is a wild-type STING, or a variant STING polypeptide, or a chimeric STING polypeptide, or a chimeric STING polypeptide with amino acid replacements.

15. The construct of any of claims 1-14 that encodes a combination of therapeutic products selected from among:

IL-2 and IL-12p70;

IL-2 and IL-21;

IL-2, IL-12p70, and a STING gain-of-function (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 or a TGF-β polypeptide antagonist, IL-2, and IL-12p70;~~

~~a TGF-β decoy receptor or a TGF-β polypeptide antagonist, IL-2, and IL-21;~~

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

~~a TGF-β decoy receptor or a TGF-β polypeptide antagonist, IL-2, IL-21, and a STING GOF variant;~~

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

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

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

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

~~a TGF-β decoy receptor or a TGF-β polypeptide antagonist, IL-15/IL-15Rα, and IL-12p70;~~

~~a TGF-β decoy receptor or a TGF-β polypeptide antagonist, IL-15/IL-15Rα, and IL-21;~~

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

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

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

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

~~a TGF-β decoy receptor or a TGF-β polypeptide antagonist, IL-12p70, and IL-21;~~

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

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

~~a TGF-β decoy receptor or a TGF-β polypeptide antagonist, and IL-12p70;~~

~~a TGF-β decoy receptor or a TGF-β polypeptide antagonist, IL-12p70, and a STING GOF variant;~~

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

~~a TGF-β decoy receptor or a TGF-β polypeptide antagonist, IL-12p70, and IL-18;~~

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

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

~~a TGF-β decoy receptor or a TGF-β polypeptide antagonist, 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); and~~

~~a CD40 agonist and a STING GOF variant, wherein:~~

~~4-1BBL is 4-1BBL with a deleted cytoplasmic domain (4-1BBLΔcyt), 4-1BBL with a modified cytoplasmic domain, 4-1BBL with a truncated cytoplasmic domain, or 4-1BBL with a truncated and modified cytoplasmic domain; and~~

~~an anti-CTLA-4 antibody is an scFv or an scFv-Fc.~~

~~16. The construct of any of claims 1-15, wherein:~~

~~the STING polypeptide is modified to result in increased or constitutive expression of a type I interferon (IFN), or is a chimeric polypeptide comprising a human STING polypeptide with a C-terminal tail (CTT) from a different species that has lower NF-κB signaling activity than the NF-κB signaling activity of human STING, and wherein:~~

~~the TRAF6 binding site in the CTT optionally is deleted; and~~

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

~~17. The construct of any of claims 1-16, wherein the encoded therapeutic proteins comprise IL-12p70, and a chimeric human STING polypeptide with a CTT from Tasmanian devil and an amino acid replacement that results in increased or constitutive expression of type I interferon, or is a STING polypeptide with an amino acid replacement that results in increased or constitutive expression of type I interferon, where a mutation that results in increased or constitutive expression of type I interferon is a gain-of-function (GOF) mutation.~~

~~18. The construct of any of claims 5-17, wherein the amino replacement in the STING polypeptide corresponds to R284G with reference, for alignment, to any of SEQ ID NOs: 305-309.~~

~~19. The construct of any of claims 5-18, wherein the STING polypeptide comprises the replacement N154S.~~

~~20. The construct of any of claims 1-19, comprising:~~

~~(a) nucleic acid encoding IL-36γ; and/or~~

~~(b) nucleic acid encoding an immune checkpoint inhibitor antibody, or an antigen-binding portion thereof; and/or~~

~~(c) nucleic acid encoding a product that is an antibody that is scFv, or that is an scFv-Fc two-chain polypeptide.~~

~~21. The construct of claim 20, wherein:~~

~~the nucleic acid encodes an immune checkpoint inhibitor antibody, or an antigen-binding portion thereof; and~~

~~the immune checkpoint is CTLA-4, or PD-1, or PD-L1.~~

~~22. A plasmid, comprising the construct of any of claims 1-21.~~

~~23. The plasmid of claim 22 that is a bacterial plasmid, wherein the construct is operatively linked to eukaryotic transcriptional regulatory sequences.~~

~~24. The plasmid of claim 23, wherein the transcriptional regulatory sequences comprise a eukaryotic promoter.~~

~~25. A composition, comprising the mixture of anti-cancer protein products encoded by the construct or plasmid of any of claims 1-24.~~

26. An immunostimulatory bacterium, comprising the construct or plasmid of any of claims 1-24.

27. The immunostimulatory bacterium of claim 26, wherein the genome of the bacterium is modified so that the resulting bacterium is *msbB*$^-$/*purI*$^-$.

28. The immunostimulatory bacterium of claim 26 or claim 27, wherein the bacterium is *msbB*$^-$ and *purI*$^-$, whereby the full length of at least the coding portion of the *msbB*$^-$ and *purI*$^-$ genes is deleted.

29. The immunostimulatory bacterium of any of claims 26-28, wherein the genome of the bacterium is modified, whereby the bacterium lacks flagella.

30. The immunostimulatory bacterium of any of claims 26-29 that comprises genome modifications, whereby the bacterium is *msbB*$^-$/*pagP*$^-$.

31. The immunostimulatory bacterium of any of claims 26-30 that comprises genome modifications, whereby the bacterium does not express L-asparaginase II, so that the bacterium is *ansB*$^-$.

32. An immunostimulatory bacterium, comprising the construct or plasmid of any of claims 1-24, wherein:

the immunostimulatory bacterium comprises genome modifications, whereby the resulting strain is attenuated for bacterial inflammation by modification of lipid A to reduce TLR2/4 signaling, and has deletion of expression of the flagellin subunits to reduce TLR5 recognition and inflammasome induction; and optionally

the immunostimulatory bacterium is a *Salmonella* species.

33. An immunostimulatory bacterium, comprising a plasmid encoding a plurality of therapeutic products, wherein the genome of the bacterium is modified so that the bacterium is *msbB*$^-$ and *purI*$^-$, whereby the full length of at least the coding portion of the *msbB* and *purI* genes is deleted.

34. An immunostimulatory bacterium, comprising a plasmid encoding a therapeutic product under control of a eukaryotic promoter, 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 does not activate the synthesis of secreted asparaginase, for example, wherein the asparaginase is L-asparaginase II, encoded by the gene *ansB*.

35. The immunostimulatory bacterium of claim 34 that has genome modifications, whereby the bacterium lacks flagella, and is *pagP*$^-$, *ansB*$^-$, and *csgD*$^-$.

36. The immunostimulatory bacterium of claim 35 that is Δ*asd*/ΔFLG/Δ*pagP*/Δ*ansB*/Δ*csgD*.

37. The immunostimulatory bacterium of any of claims 33-36 that has genome modifications, whereby the bacterium is *msbB*$^-$.

38. The immunostimulatory bacterium of any of claims claim 33-37 that has genome modifications, whereby the bacterium is an adenosine auxotroph, or is an adenosine and adenine auxotroph.

39. The immunostimulatory bacterium of any of claims claim 33-38 that has genome modifications, whereby the bacterium is *purI*$^-$.

40. The immunostimulatory bacterium of any of claims 33-39, wherein the plasmid encodes aspartate-semialdehyde dehydrogenase (*asd*).

41. The immunostimulatory bacterium of any of claims 33-40 that is *purI*-.

42. An immunostimulatory bacterium, comprising a plasmid encoding a plurality of therapeutic products under control of a eukaryotic promoter, 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 penta-acylated lipopolysaccharide (LPS);

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

the plasmid encodes a plurality of complementary anti-cancer therapeutic products under control of a single promoter, wherein each of the complementary therapeutic products treats a different aspect of a cancer, or acts via a different mechanism, so that the combined effect is at least additive of the effect of each product separately.

43. An immunostimulatory bacterium, comprising a plasmid encoding a therapeutic product under control of a eukaryotic promoter, 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, TLR4, and TLR5; and

the plasmid encodes a plurality of complementary therapeutic products under control of a single promoter.

44. An immunostimulatory bacterium, comprising a plasmid encoding a therapeutic product under control of a eukaryotic promoter, 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 does not activate the synthesis of curli fimbriae and/or cellulose; and

the plasmid encodes a plurality of complementary therapeutic products under control of a single promoter.

45. An immunostimulatory bacterium, comprising a plasmid encoding a therapeutic product under control of a eukaryotic promoter, 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 is auxotrophic for purines, adenosine, or ATP, and is modified by deletion or disruption of all or of a sufficient portion of a gene or genes, whereby the bacterium lacks flagella; and

the plasmid encodes a plurality of therapeutic products under control of a single eukaryotic promoter.

46. An immunostimulatory bacterium, comprising a plasmid encoding a therapeutic product under control of a eukaryotic promoter, 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; and

the plasmid encodes a plurality of therapeutic products under control of a single promoter.

47. An immunostimulatory bacterium, comprising a plasmid encoding a therapeutic product under control of a eukaryotic promoter, 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 specifically infect tumor-resident myeloid cells; and~~

~~the plasmid encodes a plurality of therapeutic products under control of a single promoter.~~

~~48. An immunostimulatory bacterium, comprising a plasmid encoding a therapeutic product under control of a eukaryotic promoter, 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 specifically infect tumor-resident myeloid cells, and is unable to replicate in tumor-resident myeloid cells.~~

~~49. An immunostimulatory bacterium, comprising a plasmid encoding a therapeutic product under control of a eukaryotic promoter, wherein the genome of the immunostimulatory bacterium comprises two or more modifications selected from among:~~

~~a) deletion or disruption of all or of a sufficient portion of a gene or genes, whereby the bacterium has been modified to generate penta-acylated lipopolysaccharide, 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 penta-acylated lipopolysaccharide; and~~

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

~~b) deletion or disruption of all or of a sufficient portion of a gene or genes, whereby the bacterium has attenuated recognition by one or more of TLR2, TLR4, and TLR5;~~

~~c) deletion or disruption of all or of a sufficient portion of a gene or genes, whereby the bacterium does not activate the synthesis of curli fimbriae and/or cellulose;~~

~~d) deletion or disruption of all or of a sufficient portion of a gene or genes, whereby the bacterium does not activate the synthesis of secreted asparaginase;~~

~~e) deletion or disruption of all or of a sufficient portion of a gene or genes, whereby the bacterium is auxotrophic for purines, adenosine, or ATP;~~

~~f) deletion or disruption of all or of a sufficient portion of a gene or genes, whereby the bacterium lacks flagella;~~

~~g) deletion or disruption of all or of a sufficient portion of a gene or genes, whereby the bacterium has been modified to specifically infect tumor-resident myeloid cells;~~

~~h) deletion or disruption of all or of a sufficient portion of a gene or genes, whereby the bacterium has been modified to specifically infect tumor-resident myeloid cells, and is unable to replicate in tumor-resident myeloid cells; and~~

~~i) deletion or disruption of either or both of *lppA* and *lppB* to decrease or eliminate lipoprotein expression in the membrane, whereby expression of an encoded therapeutic protein is increased in the tumor microenvironment and/or in tumor-resident immune cells.~~

~~50. The immunostimulatory bacterium of claim 49 comprising modifications a), d) and f), or comprising modifications c) and d).~~

~~51. The immunostimulatory bacterium of claim 49, comprising modifications a), c), d), e) and f).~~

52. The immunostimulatory bacterium of claim 49, comprising modifications a), c), d), e), f) and i), or comprising modifications a), d) f), and i), or comprising modifications c), d) and i), or comprising modifications f) and i), or comprising modifications a) i).

53. The immunostimulatory bacterium of claim 49, comprising modifications a), b), d) and f), or comprising modifications a), b), c) and d).

54. The immunostimulatory bacterium of any of claims 26-53, wherein *lpp.1* and *lppB* are deleted.

55. The immunostimulatory bacterium of any of claims 26-54 that lacks flagella and is *msbB*$^-$/*pagP*$^-$, wherein the plasmid encodes a combination of two or more therapeutic proteins selected from among a co-stimulatory molecule, a cytokine, a STING pathway agonist, and an immune checkpoint inhibitor antibody.

56. 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 phenotype macrophage.

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

the immunostimulatory bacterium comprises modifications in its genome, whereby the bacterium infects tumor-resident macrophages, and does not infect epithelial cells; and

expression of the therapeutic product in a macrophage converts human M2 macrophages to an M1 or M1-like phenotype.

58. The immunostimulatory bacterium of any of claims 26-57, comprising a plasmid encoding a therapeutic product, where expression of the therapeutic product in a macrophage converts human M2 macrophages to an M1 or M1-like phenotype.

59. The immunostimulatory bacterium of any of claims 26-58 wherein the therapeutic product is part of a cytosolic DNA/RNA sensor pathway that leads to expression of type I interferon (IFN).

60. The immunostimulatory bacterium of claim 59, wherein the expression of the type I IFN is constitutive.

61. The immunostimulatory bacterium of claim 59 or claim 60, 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 GOF variant product does not require cytosolic nucleic acids, nucleotides, dinucleotides, or cyclic dinucleotides to result in expression of type I IFN.

62. The immunostimulatory bacterium of any of claims 26-61, wherein the therapeutic product is a variant STING protein.

63. The immunostimulatory bacterium of any of claims 26-62, wherein infection by the bacterium converts human M2 macrophages into M1-like, type I IFN producing cells.

64. The immunostimulatory bacterium of any of claims 26-63 that lacks flagella, wherein the wild-type bacterium has flagella, and the immunostimulatory bacterium is *pagP*$^-$/*msbB*$^-$.

65. The immunostimulatory bacterium of any of claims 26-64, wherein the immunostimulatory bacterium contains genome modifications, whereby the bacterium lacks flagella and does not produce L-asparaginase II (*ansB*).

66. The immunostimulatory bacterium of claim 65, wherein the immunostimulatory bacterium also has genome modifications whereby the bacterium is *msbB*$^-$ and *pagP*$^-$.

67. The immunostimulatory bacterium of any of claims 26-66, wherein the immunostimulatory bacterium has modifications of the genome, whereby the bacterial phenotype conferred by the genome is Δ*asd*/ΔFLG/Δ*pagP*/Δ*ansB*/Δ*csgD* or Δ*asd*/ΔFLG/Δ*pagP*/Δ*ansB*/Δ*csgD*/Δ*msbB*/Δ*purI*, wherein the plasmid optionally encodes aspartate-semialdehyde dehydrogenase (*asd*).

68. The immunostimulatory bacterium of any of claims 26-67, comprising a plasmid that encodes a STING polypeptide.

69. The immunostimulatory bacterium of claim 68, wherein the STING polypeptide is a variant STING polypeptide that results in increased or constitutive expression of type I interferon.

70. The immunostimulatory bacterium of claim 69, wherein the STING polypeptide is a human chimeric STING polypeptide that comprises a C-terminal tail (CTT) from Tasmanian devil STING.

71. The immunostimulatory bacterium of claim 69 or claim 70, wherein the STING polypeptide comprises the replacement corresponding to R284G, with reference, for alignment, to any of SEQ ID NOs:305-309.

72. The immunostimulatory bacterium of claim 71, further comprising a replacement corresponding to N154S, with reference to any of SEQ ID NOs:305-309.

73. The immunostimulatory bacterium of any of claims 26-72, comprising a plasmid encoding one or more of IL-12, IL-15, and IL-21.

74. The immunostimulatory bacterium of any of claims 26-73 that is a *Salmonella* strain.

75. The immunostimulatory bacterium of any of claims 26-74, wherein the therapeutic product is an anti-cancer therapeutic.

76. The immunostimulatory bacterium of any of claims 26-75, wherein the bacterium encodes a therapeutic product that is an immunostimulatory protein.

77. The immunostimulatory bacterium of claim 76, 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.

78. The immunostimulatory bacterium of any of claims 26-77, wherein the bacterium comprises a genomic modification whereby it lacks flagella.

79. The immunostimulatory bacterium of any of claims 26-78, wherein the bacterium comprises a genomic modification whereby it is *pagP*$^-$ or *msbB*$^-$/*pagP*$^-$.

80. The immunostimulatory bacterium of any of claims 26-79, wherein:

the bacterium comprises genomic modifications 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.

81. An immunostimulatory bacterium, comprising a plasmid encoding a therapeutic product under control of a eukaryotic promoter, wherein the genome of the immunostimulatory bacterium is modified by deletion or disruption of all or of a sufficient portion of *csgD*, whereby the bacterium is *csgD*$^-$, and does not activate the synthesis of curli fimbriae.

82. An immunostimulatory bacterium, comprising a plasmid encoding a therapeutic product under control of a eukaryotic promoter, 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.

83. An immunostimulatory bacterium, comprising a plasmid encoding a therapeutic product under control of a eukaryotic promoter, 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.

84. The immunostimulatory bacterium of any of claims 26-83, further comprising deletion of or disruption of all or of a sufficient portion of the genes encoding the flagella, whereby the bacterium is flagellin$^-$ (*fliC*$^-$/*fljB*$^-$) and does not produce flagella, wherein the wild-type bacterium has flagella.

85. An immunostimulatory bacterium, comprising a plasmid encoding a therapeutic product under control of a eukaryotic promoter, wherein the genome of the immunostimulatory bacterium is modified by deletion of or disruption of all or of a sufficient portion of the genes *lppA* and *lppB*, encoding the bacterial lipoprotein, whereby the lipoprotein is not produced, and wherein the therapeutic product encoded on the plasmid is an anti-cancer therapeutic.

86. The immunostimulatory bacterium of claim 85, 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.

87. The immunostimulatory bacterium of any of claims 82-86, 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*$^-$.

88. The immunostimulatory bacterium of any of claims 82, 83, and 85-87, wherein the bacterium comprises modifications of the genome, whereby the bacterium lacks flagella.

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

90. The immunostimulatory bacterium of any of claims 26-89, wherein the bacterium is auxotrophic for purines.

91. The immunostimulatory bacterium of any of claims 26-89, wherein the bacterium is auxotrophic for adenosine.

92. The immunostimulatory bacterium of any of claims 26-89 that is auxotrophic for adenosine, adenine, and ATP.

93. The immunostimulatory bacterium of any of claims 26-92, wherein the bacterium is *purI*$^-$.

94. The immunostimulatory bacterium of any of claims 26-93, wherein the bacterium is *pagP*$^-$.

95. The immunostimulatory bacterium of any of claims 26-94, wherein the bacterium is *asd*$^+$.

96. The immunostimulatory bacterium of any of claims 26-95 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.

97. The immunostimulatory bacterium of any of claims 26-96 that encodes aspartate-semialdehyde dehydrogenase (*asd*) on the plasmid under control of a bacterial promoter.

98. The immunostimulatory bacterium of any of claims 26-97, wherein the bacterium is *msbB*$^-$.

99. The immunostimulatory bacterium of any of claims 26-98 that comprises genome modifications, whereby the bacterium is *asd*$^+$, *purI*$^-$, *msbB*$^-$, flagellin$^-$, and *pagP*$^-$, wherein the wild-type bacterium has flagella.

100. The immunostimulatory bacterium of any of claims 26-98 that is *asd*$^+$, *csgD*$^-$, *purI*$^-$, *msbB*$^-$, flagellin$^-$ and *pagP*$^-$, wherein the wild-type bacterium has flagella.

101. The immunostimulatory bacterium of any of claims 26-98 that is *ansB*$^-$, *asd*$^+$, *csgD*$^-$, *purI*$^-$, *msbB*$^-$, flagellin$^-$ (*fliC*$^-$/*fljB*$^-$), and *pagP*$^-$, wherein the wild-type bacterium has flagella.

102. The immunostimulatory bacterium of any of claims 96-100, wherein the bacterium is flagellin$^-$ (*fliC*$^-$/*fljB*$^-$), wherein the wild-type bacterium has flagella.

103. The immunostimulatory bacterium of any of claims 26-102, wherein the genome of the bacterium is modified by deletion or disruption of all or of a sufficient portion of the gene *lppA* and/or *lppB*, whereby the bacterium is *lppA*$^-$ and/or *lppB*$^-$, whereby expression in the tumor microenvironment and/or tumor-resident macrophages of the therapeutic protein encoded on the plasmid is increased, compared to the same immunostimulatory bacterium except with intact *lppA* and/or *lppB*.

104. An immunostimulatory bacterium, comprising a plasmid encoding a therapeutic product under control of a eukaryotic promoter, 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 is *ansB*$^-$, *asd*$^+$, *csgD*$^-$, *purI*$^-$, *msbB*$^-$, flagellin$^-$, and *pagP*$^-$, wherein the wild-type bacterium has flagella.

105. An immunostimulatory bacterium, comprising a plasmid encoding a therapeutic product under control of a eukaryotic promoter, 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 is *ansB*$^-$, *asd*$^+$, *csgD*$^-$, *purI*$^-$, *msbB*$^-$, flagellin$^-$, wherein the wild-type bacterium has flagella, and *pagP*$^-$.

106. The immunostimulatory bacterium of claim 104 or claim 105, wherein the bacterium is flagellin$^-$ (*fliC*$^-$/*fljB*$^-$).

107. The immunostimulatory bacterium of claim 105 or 106, wherein the bacterial genome comprises further modifications, whereby the bacterium is *ansB*$^-$, *asd*$^-$, *csgD*$^-$, *purI*$^-$, *msbB*$^-$, flagellin$^-$ (*fliC*$^-$/*fljB*$^-$), *pagP*$^-$, *lpxA*$^-$, and *lppB*$^-$.

108. The immunostimulatory bacterium of any of claims 26-107, wherein the therapeutic product is an anti-cancer therapeutic.

109. The immunostimulatory bacterium of any of claims 26-108, 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.

110. The immunostimulatory bacterium of any of claims 26-109, wherein one or more genes or operons involved in SPI-1 invasion are deleted or inactivated, whereby the immunostimulatory bacterium does not invade or infect epithelial cells.

111. The immunostimulatory bacterium of claim 110, wherein one or more of *avrA*, *hilA*, *hilD*, *invA*, *invB*, *invC*, *invE*, *invF*, *invG*, *invH*, *invI*, *invJ*, *iacP*, *iagB*, *spaO*, *spaQ*, *spaR*, *spaS*, *orgA*, *orgB*, *orgC*, *prgH*, *prgI*, *prgJ*, *prgK*, *sicA*, *sicP*, *sipA*, *sipB*, *sipC*, *sipD*, *sirC*, *sopB*, *sopD*, *sopE*, *sopE2*, *sprB*, and *sptP* is deleted or inactivated.

112. The immunostimulatory bacterium of any of claims 26-111, wherein the plasmid is present in low copy number, or in medium copy number.

113. The immunostimulatory bacterium of any of claims 26-111, wherein the plasmid comprises a medium-to-low copy number origin of replication.

114. The immunostimulatory bacterium of any of claims 26-111, wherein the plasmid comprises a low copy number origin of replication.

115. The immunostimulatory bacterium of any of claims 26-111 and 114, wherein the plasmid is present in low copy number.

116. The immunostimulatory bacterium of any of claims 26-111, wherein the plasmid is present in a copy number of 150 or less.

117. The immunostimulatory bacterium of any of claims 26-111, where in the plasmid is present in a copy number greater than 150.

118. The immunostimulatory bacterium of any of claims 26-111, wherein the plasmid is present in high copy number.

119. The immunostimulatory bacterium of any of claims 26-111, wherein the plasmid is present in medium copy number, which is between 20 and 150, inclusive, is less than 150 or less than about 150 and more than 20 or about 20, or is between 20 and 150 copies.

120. The immunostimulatory bacterium of any of claims 26-111, wherein the number of copies of the plasmid is greater than 150.

121. The immunostimulatory bacterium of claim 116, wherein the number of copies of the plasmid is 150 copies or fewer, or is less than or equal to 150.

122. The immunostimulatory bacterium of any of claims 26-115, 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.

123. The immunostimulatory bacterium of any of claims 26-122, wherein the therapeutic product is a nucleic acid or a protein.

~~124. The immunostimulatory bacterium of claim 123, wherein the therapeutic product is a protein.~~

~~125. The immunostimulatory bacterium of any of claims 26-124, wherein the plasmid encodes two or more therapeutic products.~~

~~126. The immunostimulatory bacterium of any of claims 26-125, wherein the encoded therapeutic product(s) on the plasmid is/are anti-cancer treatment(s).~~

~~127. The immunostimulatory bacterium of any of claims 26-126, 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.~~

~~128. The immunostimulatory bacterium of claim 127, wherein the co-stimulatory molecule lacks a cytoplasmic domain, or has a modified truncated cytoplasmic domain to ensure that the encoded co-stimulatory molecule is expressed in the correct orientation in a cell, or has a truncated cytoplasmic domain whereby immunosuppressive reverse signaling is eliminated or reduced.~~

~~129. The immunostimulatory bacterium of any of claims 26-128, 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 or the plasmid.~~

~~130. The immunostimulatory bacterium of any of claims 26-129, wherein the nucleic acid encoding the product on the plasmid is operatively linked to regulatory sequences recognized by a eukaryotic host.~~

~~131. The immunostimulatory bacterium of any of claims 26-130, 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.~~

~~132. The immunostimulatory bacterium of claim 131, 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.~~

~~133. The immunostimulatory bacterium of any of claims 26-132, wherein the eukaryotic promoter is an RNA polymerase II promoter, or an RNA polymerase III promoter.~~

~~134. The immunostimulatory bacterium of claim 133, wherein the promoter is an RNA polymerase II promoter that is a viral promoter or a mammalian RNA polymerase II promoter.~~

~~135. The immunostimulatory bacterium of claim 134, 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.~~

~~136. The immunostimulatory bacterium of any of claims 26-134, 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.~~

~~137. The immunostimulatory bacterium of any of claims 26-134, 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.

138. The immunostimulatory bacterium of any of claims 26-134, 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.

139. The immunostimulatory bacterium of any of claims 26-138, wherein the plasmid comprises regulatory sequences that comprise a terminator and/or promoters selected from among SV40, hGH, BGH, MND, chicken beta-globulin, and rbGlob (rabbit globulin) genes, to control expression of the therapeutic product(s).

140. The immunostimulatory bacterium of any of claims 26-139, wherein the encoded therapeutic product(s) is/are operatively linked to a signal sequence for secretion from a cell containing the plasmid.

141. The immunostimulatory bacterium of any of claims 26-140, 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.

142. The immunostimulatory bacterium of any of claims 26-141, 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.

143. The immunostimulatory bacterium of any of claims 26-142, 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, and a polyA tail.

144. The immunostimulatory bacterium of any of claims 26-143, wherein the plasmid comprises a construct that includes a bacterial terminator positioned to decrease read-through from a bacterial promoter on the plasmid.

145. The immunostimulatory bacterium of any of claims 26-144, wherein the eukaryotic promoter on the plasmid is oriented in the opposite direction from a bacterial promoter on the plasmid.

146. The immunostimulatory bacterium of claim 145, wherein the bacterial promoter controls expression of the *asd* gene.

147. The immunostimulatory bacterium of any of claims 26-146 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).

148. The immunostimulatory bacterium of any of claims 26-147, 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 is a variant thereof.

149. The immunostimulatory bacterium of claim 148, 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.

~~150. The immunostimulatory bacterium of claim 148, wherein the therapeutic product is a variant that, when expressed in a subject, leads to constitutive expression of type I IFN.~~

~~151. The immunostimulatory bacterium of claim 148, 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.~~

~~152. The immunostimulatory bacterium of any of claims 26-151, wherein the therapeutic product is selected from among STING, RIG-I, MDA-5, IRF-3, IRF-7, TRIM56, RIP1, Sec5, TRAF3, TRAF2, TRAF6, STAT1, LGP2, DDX3, DHX9, DDX1, DDX9, DDX21, DHX15, DHX33, DHX36, DDX60, and SNRNP200, and variants thereof that increase activity or increase activity so that type I interferon activity is increased or constitutive.~~

~~153. The immunostimulatory bacterium of any of claims 26-152, 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, and variants thereof that increase activity or increase activity so that type I interferon activity is increased or constitutive.~~

~~154. The immunostimulatory bacterium of any of claims 26-153, wherein the therapeutic product is a variant protein that has increased activity that results in increased expression of type I interferon (IFN), or results in constitutive expression of type I IFN.~~

~~155. The immunostimulatory bacterium of any of claims 26-154, wherein the plasmid encodes a gain-of-function, constitutively active variant of a protein that, in humans, promotes or causes interferonopathies.~~

~~156. The immunostimulatory bacterium of any of claims 62-80 and 148-155, wherein the therapeutic product is a variant that comprises a mutation that eliminates a phosphorylation site in a STING protein to thereby reduce nuclear factor kappa-light-chain-enhancer of activated B-cell (NF-κB) signaling.~~

~~157. The immunostimulatory bacterium of any of claims 148-156, wherein the therapeutic product that induces type I IFN is STING, RIG-I, IRF-3, or MDA5, or a variant thereof.~~

~~158. The immunostimulatory bacterium of any of claims 148-157, 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, or MDA5, or a variant thereof.~~

~~159. The immunostimulatory bacterium of any of claims 148-158, wherein the therapeutic product is a variant of STING, RIG-I, IRF-3, or MDA5 that comprises a gain-of-function mutation resulting in increased expression of type I IFN.~~

~~160. The immunostimulatory bacterium of any of claims 148-159, wherein the therapeutic product is a variant of STING, RIG-I, IRF-3, 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.~~

~~161. The immunostimulatory bacterium of any of claims 148-160, 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, for alignment to SEQ ID NO:312; and

the residues are replaced with aspartic acid residues.

162. The immunostimulatory bacterium of claim 161, wherein IRF-3 comprises the replacement S396D with reference, for alignment, to SEQ ID NO:312.

163. The immunostimulatory bacterium of claim 161, wherein IRF-3 comprises the replacements S396D/S398D/S402D/T404D/S405D with reference, for alignment, to SEQ ID NO:312.

164. The immunostimulatory bacterium of any of claims 148-163, wherein the therapeutic product is selected from among STING, RIG-I, MDA-5, IRF-3, IRF-7, TRIM56, RIP1, Sec5, TRAF3, TRAF2, TRAF6, STAT1, LGP2, DDX3, DHX9, DDX1, DDX9, DDX21, DHX15, DHX33, DHX36, DDX60, and SNRNP200, and variants thereof that increase activity or increase activity so that type I interferon activity is increased or constitutive.

165. The immunostimulatory bacterium of any of claims 148-164, 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.

166. The immunostimulatory bacterium of any of claims 148-165, 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, or RIG-I constitutively active, whereby expression of type I IFN is constitutive.

167. The immunostimulatory bacterium of claim 165 or claim 166, wherein the mutations are selected as follows:

a) in STING, with reference, for alignment, 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, for alignment, 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, for alignment, to SEQ ID NO:311, one or both of E373A and C268F; and

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

168. The immunostimulatory bacterium of any of claims 148-167, wherein the therapeutic product is a variant STING that contains one or more amino replacement(s) selected, with reference, for alignment, to any of 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, S324A/S326A, and N154S/R284G, and conservative replacements thereof.

169. The immunostimulatory bacterium of any of claims 26-168, wherein:

the therapeutic protein increases or induces expression of a type I IFN; and

the type I IFN is an interferon-α or interferon-β.

170. The immunostimulatory bacterium of any of claims 26-169, wherein one or more genes or operons involved in SPI-1 invasion or SPI-1 independent invasion are deleted, disrupted, or inactivated, whereby the immunostimulatory bacterium does not invade or infect epithelial cells, or has a reduced ability to invade or infect epithelial cells.

171. The immunostimulatory bacterium of claim 170, wherein one or more of *avrA*, *hilA*, *hilD*, *invA*, *invB*, *invC*, *invE*, *invF*, *invG*, *invH*, *invI*, *invJ*, *iacP*, *iagB*, *spaO*, *spaP*, *spaQ*, *spaR*, *spaS*, *orgA*, *orgB*, *orgC*, *prgH*, *prgI*, *prgJ*, *prgK*, *sicA*, *sicP*, *sipA*, *sipB*, *sipC*, *sipD*, *sirC*, *sopB*, *sopD*, *sopE*, *sopE2*, *sprB*, and *sptP* is deleted, disrupted, or inactivated.

172. The immunostimulatory bacterium of claim 171, wherein the one or more genes is/are selected from among *pagN*, *hlyE*, *pefI*, *srgD*, *srgA*, *srgB*, and *srgC*.

173. The immunostimulatory bacterium of any of claims 26-172 that has a deletion or disruption of a gene encoding a protein in the SPI-2 complex.

174. The immunostimulatory bacterium of any of claims 26-173, wherein the plasmid encodes an immunostimulatory protein that confers or contributes to an anti-tumor immune response in the tumor microenvironment.

175. The immunostimulatory bacterium of claim 174, wherein the immunostimulatory protein that confers or contributes to an anti-tumor immune response in the tumor microenvironment 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-18, IL-21, IL-23, IL-36γ, IL-2 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 the recruitment and/or persistence of T-cells, CD40, CD40 ligand (CD40L), CD28, OX40, OX40 ligand (OX40L), 4-1BB, 4-1BB ligand (4-1BBL), 4-1BBl that has a deleted or truncated or otherwise modified cytoplasmic domain to eliminate the immunosuppressive reverse signaling, members of the B7-CD28 family, CD47 antagonists, an anti-IL6 antibody or IL-6 binding decoy receptor, TGF-beta polypeptide antagonists, and members of the tumor necrosis factor receptor (TNFR) superfamily.

176. The immunostimulatory bacterium of claim 174 or claim 175, wherein the plasmid encodes a modified 4-1BBL, whose sequence is set forth in SEQ ID NO:390, SEQ ID NO:391, or SEQ ID NO:392.

177. The immunostimulatory bacterium of claim 175 or claim 176, further comprising a tag linked to the co-stimulatory protein to facilitate purification or expression thereof.

178. The immunostimulatory bacterium of claim 177, wherein the tag is a c-myc tag comprising the sequence EQKLISEEDL, set forth as residues 2-11 of SEQ ID NO:392.

179. The immunostimulatory bacterium of any of claims 174-178, wherein the plasmid encodes a 4-1BBL polypeptide and at least one additional therapeutic protein.

180. The immunostimulatory bacterium of claim 179, wherein the additional therapeutic protein(s) is/are IL-15Rα-IL-15sc, or IL-12, or IL-15Rα-IL-15sc and IL-12.

181. The immunostimulatory bacterium of any of claims 174-180, comprising a 1-4BBL polypeptide and one or more additional therapeutic polypeptides encoded in a polycistronic nucleic acid under control of a single promoter, wherein the 1-4BBL polypeptide is the first polypeptide in the polycistron.

182. The immunostimulatory bacterium of any of claims 174-181, 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 in the cytoplasmic domain or that lacks a cytoplasmic domain, for expression on an antigen-presenting cell (APC), to eliminate the immunosuppressive reverse signaling; 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 the truncated or deleted cytoplasmic domain.

183. The immunostimulatory bacterium of any of claims 26-182, wherein the encoded product comprises one or more of a STING protein, a modified STING protein, a chimeric STING protein, an anti-CTLA-4 antibody, IL-15, 4-1BBL and modified or truncated forms thereof, a TGF-beta receptor decoy or polypeptide antagonist, IL-12, and IL-21, and/or any of the following:

one or more of IL-12, or IL-15, or IL12p70, or IL-15/IL-15R alpha chain complex;

a cytokine, and a STING pathway agonist;

a cytokine, a STING pathway agonist, and either a co-stimulatory molecule or an immune checkpoint inhibitor;

a cytokine, a STING pathway agonist, and a TGF-beta receptor decoy or polypeptide antagonist; and/or

a cytokine, a STING pathway agonist, a TGF-beta receptor decoy or polypeptide antagonist, and either a co-stimulatory molecule or an immune checkpoint inhibitor.

184. The immunostimulatory bacterium of any of claims 26-183, wherein the plasmid includes nucleic acid encoding a product that induces tumor cell apoptosis or is cytotoxic to tumor cells.

185. The immunostimulatory bacterium of claim 184, wherein:

the product is a nucleic acid; and

the nucleic acid encoding the product includes nucleic acid encoding a secretion signal whereby the product is secreted.

186. The immunostimulatory bacterium of claim 183 or claim 184, wherein the product induces apoptosis.

187. The immunostimulatory bacterium of claim 186, wherein the product that induces apoptosis is azurin.

188. The immunostimulatory bacterium of any of claims 174-187, wherein the plasmid encodes an immunostimulatory protein that confers or contributes to an anti-tumor immune response in the tumor microenvironment, and the immunostimulatory protein is a cytokine or a chemokine.

189. The immunostimulatory bacterium of any of claims 174-188, wherein the plasmid encodes an immunostimulatory protein that confers or contributes to an anti-tumor immune response in the tumor microenvironment that is a co-stimulatory molecule or cytoplasmic domain-deleted or truncated or otherwise modified form thereof.

190. The immunostimulatory bacterium of claim 189, 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, B7RP1, and OX40L, and cytoplasmic domain deleted or truncated or truncated and modified forms thereof, where the modifications promote correct orientation when the protein is expressed in a cell, and the cytoplasmic deletions, truncations and/or modifications eliminate or reduce immunosuppressive reverse signaling.

191. The immunostimulatory bacterium of any of claims 26-190, wherein the plasmid encodes a therapeutic product that is a TGF-beta polypeptide antagonist.

192. The immunostimulatory bacterium of claim 191, wherein the TGF-beta polypeptide antagonist is selected from among an anti-TGF-beta antibody or a fragment thereof, an anti-TGF-beta receptor antibody or a fragment thereof, a soluble TGF-beta antagonist polypeptide, and a TGF-beta binding decoy receptor.

193. The immunostimulatory bacterium of claim 191 or claim 192, wherein nucleic acid encoding the TGF-beta polypeptide antagonist comprises nucleic acid encoding a signal sequence for secretion of the encoded polypeptide.

194. The immunostimulatory bacterium of any of claims 26-193, wherein the therapeutic product is an antibody or antigen-binding fragment thereof.

195. The immunostimulatory bacterium of claim 194, 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, a single-chain antibody, and an scFv-Fc two-chain antibody.

196. The immunostimulatory bacterium of claim 195, wherein the antibody is an scFV.

197. The immunostimulatory bacterium of claim 195 or claim 196, wherein the antibody comprises an Fc, whereby the resulting antibody comprises two chains.

198. The immunostimulatory bacterium of any of claims 195-197, wherein the antibody is encoded by nucleic acid comprising nucleic acid encoding the variable light chain, a linker, the variable heavy chain, and an IgG Fc, whereby the encoded antibody is an scFv-Fc.

199. The immunostimulatory bacterium of any of claims 195-198, wherein the antibody is an anti-CTLA-4 antibody.

200. The immunostimulatory bacterium of any of claims 194-199, wherein the antibody or antigen-binding fragment thereof is humanized or is human.

201. The immunostimulatory bacterium of any of claims 194-200, wherein the antibody or antigen-binding fragment thereof is an antagonist of PD-1, PD-L1, CTLA-4, VEGF, VEGFR2, or IL-6.

202. The immunostimulatory bacterium of any of claims 26-201, 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.

203. The immunostimulatory bacterium of claim 202, 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).

204. 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.

205. The immunostimulatory bacterium of claim 204, 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).

206. The immunostimulatory bacterium of any of claims 26-205, 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.

207. The immunostimulatory bacterium of any of claims 26-206, 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 peptides, whereby, upon translation, each product is separately expressed.

208. The immunostimulatory bacterium of any of claims 202-207, 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).

209. The immunostimulatory bacterium of any of claims 26-208, wherein:

the therapeutic product is a co-stimulatory molecule with a cytoplasmic domain deletion or truncation or other modification 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, truncation or other modification.

210. The immunostimulatory bacterium of claim 209, wherein the co-stimulatory molecule with the deleted, truncated or otherwise modified cytoplasmic domain is 4-1BBL, CD80, CD86, CD27L, B7RP1, or OX40L, and variants that increase correct orientation of the protein when expressed in a cells.

211. The immunostimulatory bacterium of any of claims 26-210 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-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/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, TRIM56, RIP1, Sec5, TRAF3, TRAF2, TRAF6, STAT1, LGP2, DDX3, DHX9, DDX1, DDX9, DDX21, DHX15, DHX33, DHX36, DDX60, or SNRNP200.

212. The immunostimulatory bacterium of any of claims 26-211 that encodes or further encodes one or more of a TGF-beta inhibitory antibody or antigen-binding fragment thereof, a TGF-beta binding decoy receptor, an anti-IL6 antibody or antigen-binding fragment thereof, and an IL-6 binding decoy receptor.

213. The immunostimulatory bacterium of any of claims 26-212 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 gain-of-function (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 or polypeptide antagonist, IL-2, and IL-12p70;

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

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

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

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

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

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

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

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

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

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

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

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

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

~~a TGF-β decoy receptor or polypeptide antagonist, IL-12p70, and IL-21;~~

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

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

~~a TGF-β decoy receptor or polypeptide antagonist, and IL-12p70;~~

~~a TGF-β decoy receptor or polypeptide antagonist, IL-12p70, and a STING GOF variant;~~

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

~~a TGF-β decoy receptor or polypeptide antagonist, IL-12p70, and IL-18;~~

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

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

~~a TGF-β decoy receptor or polypeptide antagonist, 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); and~~

~~a CD40 agonist and a STING GOF variant, wherein:~~

~~4-1BBL is 4-1BBL with a deleted cytoplasmic domain, 4-1BBL with a modified cytoplasmic domain, 4-1BBL with a truncated cytoplasmic domain, or 4-1BBL with a truncated and modified cytoplasmic domain; and~~

~~an anti-CTLA-4 antibody is an scFv or an scFv-Fc.~~

~~214. The immunostimulatory bacterium of any of claims 26-213, that comprises nucleic acid encoding a combination of therapeutic products selected from among the following combinations:~~

~~an anti-CTLA-4 antibody and STING,~~

~~IL-15 and STING,~~

~~4-1BBL and STING,~~

~~TGF-beta decoy receptor or polypeptide antagonist, and STING,~~

~~IL-12 and STING,~~

~~an anti-CTLA-4 antibody, IL-15, and STING,~~

~~4-1BBL, IL-15, and STING,~~

~~TGF-beta decoy receptor or polypeptide antagonist, IL-15, and STING,~~

~~an anti-CTLA-4 antibody, IL-12, and STING,~~

~~4-1BBL, IL-12, and STING,~~

~~TGF-beta decoy receptor or antagonist polypeptide, IL-12, and STING,~~

~~an anti-CTLA-4 antibody, IL-15, a TGF-beta decoy receptor or polypeptide antagonist, and STING,~~

~~4-1BBL, and IL-15, a TGF-beta decoy receptor or polypeptide antagonist, and STING,~~

~~an anti-CTLA-4 antibody, and IL-12, and a TGF-beta decoy receptor or polypeptide antagonist, and STING,~~

~~4-1BBL, and IL-12, a TGF-beta decoy receptor or polypeptide antagonist, and STING,~~

~~an anti-CTLA-4 antibody, IL-12, IL-15, and STING,~~

~~4-1BBL, IL-12, IL-15, and STING,~~

a TGF-beta decoy receptor or polypeptide antagonist, IL-12, IL-15, and STING,

a TGF-beta decoy receptor or polypeptide antagonist, IL-12, IL-15, and STING,

an anti-CTLA-4 antibody, IL-12, IL-15, a TGF-beta decoy receptor or polypeptide antagonist, and STING,

4-1BBL, IL-12, IL-21, a TGF-beta decoy receptor or polypeptide antagonist, and STING,

an anti-CTLA-4 antibody, IL-12, IL-15, and a TGF-beta decoy receptor or polypeptide antagonist,

4-1BBL, IL-12, IL-21, and a TGF-beta decoy receptor or polypeptide antagonist,

IL-12, IL-15, and STING,

IL-15, IL-21, and STING,

IL-12, IL-21, and STING,

an anti-CTLA-4 antibody, IL-15, IL-21, and STING,

an anti-CTLA-4 antibody, IL-12, IL-21, and STING,

4-1BBL, IL-15, IL-21, and STING,

4-1BBL, IL-12, IL-21, and STING,

an anti-CTLA-4 antibody, and IL-15,

an anti-CTLA-4 antibody, IL-15, and a TGF-beta decoy receptor or polypeptide antagonist,

4-1BBL and IL-15,

4-1BBL, IL-15, and TGF-beta decoy receptor or polypeptide antagonist,

an anti-CTLA-4 antibody and IL-12,

an anti-CTLA-4 antibody, and IL-12, and a TGF-beta decoy receptor or polypeptide antagonist,

4-1BBL and IL-12,

4-1BBL, IL-12, and a TGF-beta decoy receptor or polypeptide antagonist,

an anti-CTLA-4 antibody, and a TGF-beta decoy receptor or polypeptide antagonist,

4-1BBL and a TGF-beta decoy receptor or polypeptide antagonist,

IL-15 and a TGF-beta decoy receptor or polypeptide antagonist,

IL-12 and a TGF-beta decoy receptor or polypeptide antagonist,

IL-12, IL-15, and a TGF-beta decoy receptor or polypeptide antagonist, and IL-15, and IL-21, and a TGF-beta decoy receptor or polypeptide antagonist, wherein:

IL-15 is IL-15 or IL-15/IL-15R alpha chain complex;

STING is a STING polypeptide, or a variant STING polypeptide, or a chimeric STING polypeptide, or a chimeric STING with amino acid replacements;

TGF-beta is a soluble TGF-beta decoy or TGF-beta antagonist;

4-1BBL is 4-1BBL with a deleted cytoplasmic domain, 4-1BBL with a modified cytoplasmic domain, 4-1BBL with a truncated cytoplasmic domain, or 4-1BBL with a truncated and modified cytoplasmic domain; and

an anti-CTLA-4 antibody is an scFv or an scFv-Fc.

215. The immunostimulatory bacterium of claim 214, wherein the TGF-beta decoy comprises an Fc fusion or is an anti-TGF antibody or an antigen-binding fragment thereof.

216. The immunostimulatory bacterium of claim 214 or claim 215, wherein the 4-1BBL is full-length, or is full-length with amino acid replacements at Ser5, and/or Ser8, whereby immunosuppressive reverse signaling is reduced or eliminated, or is 1-4BBL with a deleted cytoplasmic domain, or a truncated cytoplasmic domain that eliminates or reduces immunosuppressive reverse signaling, or is 4-1BBL that has amino acid replacements in the truncated cytoplasmic domain, whereby the 4-1BBL is in the correct orientation when expressed in a cell.

217. The immunostimulatory bacterium of any of claims 214-216, wherein the STING polypeptide comprises the replacement R284G, or comprises the replacements N154S/R284G, or is a chimeric STING polypeptide that is a chimeric human STING polypeptide with a CTT from Tasmanian Devil, or is a chimeric human STING polypeptide with a CTT from Tasmanian Devil and the replacement corresponding to R284G or the replacements corresponding to N154S/R284G, all with reference, for alignment, to SEQ ID NOs:305-309.

218. The immunostimulatory bacterium of any of claims 213-215, wherein the STING gain-of-function (GOF) variant is/are selected from among any set forth in claim 167 or claim 168.

219. 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); and~~

~~a CD40 agonist and a STING GOF variant.~~

~~220. The immunostimulatory bacterium or cell of claim 219, wherein the STING GOF variant is selected from among any set forth in claim 167 or claim 168.~~

~~221. The immunostimulatory bacterium any of claims 26-220, wherein an encoded therapeutic product comprises an Fc domain.~~

~~222. The immunostimulatory bacterium of any of claims 26-221, wherein an encoded therapeutic product comprises the B7 protein transmembrane domain.~~

~~223. The immunostimulatory bacterium of any of claims 26-222, wherein an encoded therapeutic product is GPI-anchored.~~

224. The immunostimulatory bacterium of any of claims 26-223, wherein an encoded therapeutic product comprises human serum albumin or its derivatives thereof that increase serum half-life of the encoded product.

225. The immunostimulatory bacterium of any of clams 26-224, wherein an encoded therapeutic product comprises a fusion to collagen.

226. The immunostimulatory bacterium of any of claims 26-225, wherein the bacterium is a Gram-negative bacterium.

227. The immunostimulatory bacterium of any of claims 26-226,

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 an attenuated strain thereof or a modified strain thereof of any of the preceding list of bacterial strains.

228. The immunostimulatory bacterium of any of claims 26-226, 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*, *Legionella pneumophila*, *Rhodococcus equi*, *Pseudomonas aeruginosa*, *Helicobacter mustelae*, *Vibrio cholerae*, *Bacillus subtilis*, *Erysipelothrix rhusiopathiae*, *Yersinia enterocolitica*, *Rochalimaea quintana*, or *Agrobacterium tumerfacium*.

229. The immunostimulatory bacterium of any of claims 26-228 that is an attenuated bacterium or is a Gram-negative bacterium.

230. The immunostimulatory bacterium of any of claims 26-229 that is a strain of *Salmonella*.

231. The immunostimulatory bacterium of claim 230 that is a *Salmonella typhimurium* strain.

232. The immunostimulatory bacterium of claim 230 or claim 231, wherein the unmodified *Salmonella* is a wild-type strain.

233. The immunostimulatory bacterium of claim 230 or claim 231, wherein the unmodified *Salmonella* strain is attenuated.

234. The immunostimulatory bacterium of any of claims 26-233, wherein the immunostimulatory bacterium is derived from strain AST-100 (VNP20009 or YS1646), or strain ATCC 14028, or a strain having all of the identifying characteristics of strain ATCC 14028.

235. The immunostimulatory bacterium of any of claims 227-233 that is *ansB*$^-$, *asd*$^-$, *csgD*$^-$, *purI*$^-$, *msbB*$^-$, flagellin$^-$ (*fliC*$^-$/*fljB*$^-$), and *pagP*$^-$.

236. The immunostimulatory bacterium of any of claims 26-235, wherein the bacterium encodes and expresses the gene resistance to complement killing (*rck*).

237. The immunostimulatory bacterium of claim 236, wherein the *rck* gene is a *Salmonella rck* gene.

238. The immunostimulatory bacterium of any of claims 26-237 that, when intravenously administered at a therapeutic dose, induces less than 150 pg/ml of each of serum IL-6, serum TNF-alpha, and serum IL-10, when measured at 7 days post-treatment.

239. An immunostimulatory bacterium that, when intravenously administered at a therapeutic dose, induces less than 150 pg/ml of each of serum IL-6, serum TNF-alpha, and serum IL-10, when measured at 7 days post treatment.

240. The immunostimulatory bacterium of claim 238 or claim 239, wherein the dose is $1x10^8$ CFUs (colony forming units).

241. The immunostimulatory bacterium of claim 238 or claim 239, wherein the dose is $1x10^8$ CFUs – $1x10^9$ CFUs.

242. An immunostimulatory bacterium, comprising a plasmid that encodes a therapeutic product, and that is modified to encode and express the gene resistance to complement killing (*rck*), wherein the wild-type bacterium does not encode *rck*.

243. The immunostimulatory bacterium of claim 242 that is an *E. coli* strain.

244. A delivery vehicle encoding a truncated co-stimulatory molecule with a full or partial cytoplasmic domain deletion, for expression on an antigen-presenting cell (APC), wherein 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 deleted cytoplasmic domain.

245. The delivery vehicle of claim 244, wherein the co-stimulatory molecule is 4-1BBL, CD80, CD86, CD27L, B7RP1, or OX40L, or a variant thereof with a deleted or truncated cytoplasmic domain and/or mutations that confer proper orientation of the protein when expressed in a cell.

246. The delivery vehicle of claim 244 or claim 245 that is an immunostimulatory bacterium, an exosome, a nanoparticle, an oncolytic virus, or a cell.

247. The delivery vehicle of any of claims 244-246 that is a cell.

248. The delivery vehicle of claim 247, wherein the cell is a stem cell.

249. The delivery vehicle of claim 248, wherein the stem cell is a mesenchymal stem cell (MSC).

250. The delivery vehicle of claim 249, wherein the MSC is genetically modified to express a combination of immunomodulatory cytokines.

251. The delivery vehicle of claim 250, wherein the cytokines are Interleukin 12 (IL-12) and Interleukin 21 (IL-21).

252. An isolated cell, comprising the delivery vehicle of any of claims 244-251.

253. An isolated cell, comprising the immunostimulatory bacterium of any of claims 26-243.

254. The cell of claim 252 or claim 253 that is an immune cell, a stem cell, a tumor cell, or a primary cell line.

255. The cell of claim 254 that is a hematopoietic cell.

256. The cell of claim 255 that is a T-cell.

257. The cell of any of claims 252-256 that is produced *ex vivo* by infecting the cell with the delivery vehicle or immunostimulatory bacterium.

258. The cell of any of claims 252-254 that is a stem cell that is not of embryonic origin.

259. The cell of any of claims 252-254, wherein the cell is a stem cell.

260. The cell of claim 259, wherein the stem cell is a mesenchymal stem cell (MSC).

261. The cell of claim 260, wherein the MSC is genetically modified to express a combination of immunomodulatory cytokines.

262. The cell of claim 261, wherein the cytokines are Interleukin 12 (IL-12) and Interleukin 21 (IL-21).

263. A pharmaceutical composition, comprising the immunostimulatory bacterium of any of claims 26-243, or the delivery vehicle of any of claims 244-251, or the cell of any of claims 252-262, in a pharmaceutically acceptable vehicle.

264. A pharmaceutical composition, comprising the immunostimulatory bacterium of claim 84 in a pharmaceutically acceptable vehicle.

265. The pharmaceutical composition of claim 263 or claim 264 that is formulated for administration without dilution.

266. The pharmaceutical composition of any of claims 263-265 that is formulated for systemic administration.

267. The pharmaceutical composition of any of claims 263-266 that is formulated for parenteral administration.

268. The pharmaceutical composition of claim 267 that is formulated for intravenous administration.

269. The pharmaceutical composition of claim 267 that is formulated for intratumoral administration.

270. The pharmaceutical composition of claim 267 that is formulated for intraperitoneal administration.

271. The pharmaceutical composition of claim 266 that is formulated for oral administration.

272. A method of treatment of cancer that comprises a solid tumor or a hematological malignancy in a subject, comprising administering the immunostimulatory bacterium of any of claims 26-243, or the delivery vehicle of any of claims 244-251, or the cell of any of claims 252-262, or the pharmaceutical composition of any of claims 263-271.

273. Use of the immunostimulatory bacterium of any of claims 26-244, or the delivery vehicle of any of claims 244-251, or the cell of any of claims 252-262, or the pharmaceutical composition of any of claims 263-271, for the treatment of a cancer that comprises a solid tumor or a hematological malignancy in a subject.

274. The immunostimulatory bacterium of any of claims 26-244, or the delivery vehicle of any of claims 244-251, or the cell of any of claims 252-262, or the pharmaceutical composition of any of claims 263-271, for use for the treatment of a cancer that comprises a solid tumor or a hematological malignancy in a subject.

~~275. The method, use, immunostimulatory bacterium, delivery vehicle, cell, or pharmaceutical composition of any of claims 272-274, wherein the subject is a human.~~

~~276. The method, use, immunostimulatory bacterium, delivery vehicle, cell, or pharmaceutical composition of any of claims 272-275, wherein the cancer comprises a solid tumor.~~

~~277. The method, use, immunostimulatory bacterium, delivery vehicle, cell, or pharmaceutical composition of any of claims 272-275, wherein the cancer comprises a hematological malignancy.~~

~~278. The method, use, immunostimulatory bacterium, delivery vehicle, cell, or pharmaceutical composition of any of claims 272-277, wherein the treatment comprises combination therapy in which a second anti-cancer agent or treatment is administered.~~

~~279. The method, use, immunostimulatory bacterium, delivery vehicle, cell, or pharmaceutical composition of claim 278, wherein the second anti-cancer agent or treatment is administered before, concomitantly with, after, or intermittently with, the immunostimulatory bacterium, delivery vehicle, cell, or pharmaceutical composition.~~

~~280. The method, use, immunostimulatory bacterium, delivery vehicle, cell, or pharmaceutical composition of claim 278 or claim 279, wherein the second anti-cancer agent or treatment is an immunotherapy.~~

~~281. The method, use, immunostimulatory bacterium, delivery vehicle, cell, or pharmaceutical composition of any of claims 272-280, wherein administration of the immunostimulatory bacterium, delivery vehicle, cell, or pharmaceutical composition is parenteral.~~

~~282. The method, use, immunostimulatory bacterium, delivery vehicle, cell, or pharmaceutical composition of any of claims 272-280, wherein administration of the immunostimulatory bacterium, delivery vehicle, cell, or pharmaceutical composition is oral, or rectal, or by aerosol into the lung, or intratumoral.~~

~~283. The method, use, immunostimulatory bacterium, delivery vehicle, cell, or pharmaceutical composition of any of claims 272-280, wherein administration of the immunostimulatory bacterium, delivery vehicle, cell, or pharmaceutical composition is intravenously, intramuscularly, or subcutaneously.~~

~~284. The method, use, immunostimulatory bacterium, delivery vehicle, cell, or pharmaceutical composition of any of claims 272-283, 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.~~

~~285. The method, use, immunostimulatory bacterium, delivery vehicle, cell, or pharmaceutical composition of claim 280, wherein the immunotherapy comprises administration of an anti-PD-1, or anti-PD-L1, or anti-CTLA-4 antibody, or antigen-binding portions or forms thereof.~~

~~286. The method, use, immunostimulatory bacterium, delivery vehicle, cell, or pharmaceutical composition of any of claims 272-285, wherein the immunostimulatory bacterium is a *Salmonella*, *Shigella*, *Listeria*, or *E. coli* species.~~

~~287. The method, use, immunostimulatory bacterium, delivery vehicle, cell, or pharmaceutical composition of any of claims 272-286, wherein the immunostimulatory bacterium is a *Salmonella* species.~~

288. The method, use, immunostimulatory bacterium, delivery vehicle, cell, or pharmaceutical composition of any of claims 272-287, wherein the immunostimulatory bacterium is a *Salmonella typhimurium* strain.

289. The method, use, immunostimulatory bacterium, delivery vehicle, cell, or pharmaceutical composition of any of claims 272-288, wherein administration of the immunostimulatory bacterium is by intraperitoneal or intratumoral administration.

290. The method, use, immunostimulatory bacterium, delivery vehicle, cell, or pharmaceutical composition of any of claims 272-289, wherein the subject has metastatic cancer.

291. The method, use, immunostimulatory bacterium, delivery vehicle, cell, or pharmaceutical composition of any of claims 272-290, 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, or antigen-binding portions or forms thereof.

292. The method, use, immunostimulatory bacterium, delivery vehicle, cell, or pharmaceutical composition of any of claims 272-291, 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.

293. The method, use, immunostimulatory bacterium, delivery vehicle, cell, or pharmaceutical composition of any of claims 272-292, wherein the immunostimulatory bacterium is *ansB*$^-$, *asd*$^-$, *csgD*$^-$, *purI*$^-$, *msbB*$^-$, flagellin$^-$ (*fliC*$^-$/*fljB*$^-$), and *pagP*$^-$.

294. A method of selecting a subject for treatment with the immunostimulatory bacterium of any of claims 26-243, or the delivery vehicle of any of claims 244-251, or the cell of any of claims 252-262, or the pharmaceutical composition of any of claims 263-271, comprising:

obtaining a biological sample from the subject; and

detecting one or more biomarkers that indicate an immune-excluded or immune-desert tumor phenotype.

295. The method of claim 294, wherein the biomarker is selected from among:

a test indicative of T-cell or tumor-infiltrating lymphocyte (TIL) infiltration into the tumor microenvironment;

a biomarker that measures the restriction of T-cells or TILs to the invasive margin of the tumor and tumor core;

the level of TILs;

an adenosine signature (Nanostring) indicative of CXCL1, CXCL2, CXCL3, CXCL5, CXCL8, THBS1, IL-6, CSF-3, IL-1beta, CCL2, CCL3, or CCL7;

a myeloid signature (Nanostring) indicative of CXCL1, CXCL2, CXCL3, CXCL8, IL-6, or PTGS2; and

levels of one or more of CD3, CD8, CD73, CD39, TNAP (tissue-nonspecific alkaline phosphatase), CD38, CD45, CD68, PD-L1, and FoxP3.

296. A method of monitoring therapy with the immunostimulatory bacterium of any of claims 26-243, or the delivery vehicle of any of claims 244-251, or the cell of any of claims 252-262, or the pharmaceutical composition of any of claims 263-271, comprising:

obtaining a biological sample from a subject, and detecting a change in the level of a biomarker, wherein:

an increase in a biomarker indicative of an anti-cancer phenotype indicates that treatment is effective; and

the biomarkers are any that indicate a cytokine response, activation of Type I Interferon, or activation of Type II Interferon.

297. The method of claim 296, wherein:

the biomarker is selected from among the level of one or more of CXCL10/IP-10, CXCL9, Interferon-alpha, Interferon-beta, the pro-inflammatory serum cytokines IL-6, TNF-α, MCP-1, or CCL2, and IL-18 binding protein; and

an increase in the level of one or more of the biomarkers indicates that treatment is effective.

298. The method of any of claims 294-297, wherein the biological sample is a tumor biopsy, or a sample of a body fluid.

299. The method of any of claims 294-298, further comprising administering the immunostimulatory bacterium of any of claims 26-243, or the delivery vehicle of any of claims 244-251, or the cell of any of claims 252-262, or the pharmaceutical composition of any of claims 263-271.

300. 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.

301. 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.

302. The modified STING protein of claim 300 or claim 301, 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.

303. The modified STING protein of any of claims 300-302, 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.

304. The modified STING protein of any of claims 300-303, wherein the mutation or mutations is/are any that correspond to those associated with the auto-inflammatory disease STING-associated vasculopathy (SAVI).

305. 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.

306. The modified STING protein of any of claims 303-305, 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.

307. The modified STING protein of any of claims 303-306, 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.

308. The modified STING protein of any of claims 300-307, wherein the type I IFN signaling activity is at least or at least about 30% that of a wild type human STING protein.

309. The modified STING protein of any of claims 300-308, 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.

310. The modified STING protein of any of claims 300-309, 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.

311. The modified STING protein of any of claims 300-310, 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.

312. The modified STING protein of any of claims 300-311 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.

313. The modified STING protein of claim 312, 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.

314. The modified STING protein of claim 312, 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.

315. The modified STING protein of claim 313 or claim 314, 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.

316. The modified STING protein of claim 314 or claim 315, wherein the human CTT comprises the sequence EKEEVTVGSLKTSAVPSTSTMSQEPELLISGMEKPLPLRTDFS (SEQ ID NO:370), or is an allelic variant having at least 98% sequence identity thereto.

317. The modified STING protein of any of claims 305-316, wherein the modified STING protein is a chimera in which the human STING CTT is replaced with a CTT from the Tasmanian devil STING.

318. The modified STING protein of claim 317, 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.

319. The modified STING protein of any of claims 300-318, comprising a deletion or disruption of the TRAF6 binding site.

320. The modified STING protein of claim 319, wherein the STING protein is a human STING protein, and the TRAF6 binding site comprises the amino acid residues DFS at the C-terminus.

321. The modified STING protein of any of claims 300-320, comprising a modification that increases type I interferon signaling activity, or that renders the activity constitutive in the absence of cytosolic nucleic acids.

322. The modified STING protein of claim 321, 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.

323. The modified STING protein of any of claims 300-322, 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, for alignment, to the sequence of human STING, as set forth in any of SEQ ID NOs:305-309.

324. The modified STING protein of claim 323 that comprises a replacement corresponding to C206Y or R284G, with reference, for alignment, to the sequence of human STING, as set forth in any of SEQ ID NOs:305-309.

325. The modified STING protein of claim 324 that comprises replacements corresponding to N154S/R284G.

326. The modified STING protein of claim 300 that is a Tasmanian devil, marmoset, cattle, cat, ostrich, boar, bat, manatee, crested ibis, coelacanth, mouse, or ghost shark STING protein.

327. A delivery vehicle, comprising nucleic acids encoding the modified STING protein of any of claims 300-326.

328. A delivery vehicle, comprising nucleic acids encoding a STING protein from a non-human species, wherein the STING protein has type I IFN signaling activity, and attenuated NF-κB signaling activity compared to the NF-κB signaling activity of human STING.

329. The delivery vehicle of claim 328, 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.

330. The delivery vehicle of claim 328 or claim 329, wherein the type I IFN signaling activity is at least or at least about 30% of the type I IFN signaling activity of wild-type human STING.

331. The delivery vehicle of any of claims 327-330, wherein the NF-κB signaling activity of the non-human STING protein is less than 30%, less than 20%, less than 15%, less than 10%, or less than 5% of the NF-κB signaling activity of human STING.

332. The delivery vehicle of any of claims 327-331, wherein the non-human species is Tasmanian devil, marmoset, cattle, cat, ostrich, boar, bat, manatee, crested ibis, coelacanth, mouse, or ghost shark.

333. The delivery vehicle of any of claims 327-332 that is a cell, an exosome, an oncolytic virus or viral vector, a liposome or other lipid-based vehicle, or an immunostimulatory bacterium.

334. The delivery vehicle of claim 333, wherein the delivery vehicle is a cell that is a stem cell or an immune cell.

335. The delivery vehicle of claim 333, wherein the delivery vehicle is the immunostimulatory bacterium of any of claims 26-243.

336. The delivery vehicle of claim 335, wherein the immunostimulatory bacterium is *ansB*$^-$, *asd*$^-$, *csgD*$^-$, *purI*$^-$, *msbB*$^-$, flagellin$^-$ (*fliC*$^-$/*fljB*$^-$), and *pagP*$^-$.

337. The delivery vehicle of claim 335, wherein the immunostimulatory bacterium is *ansB*$^-$, *asd*$^-$, *csgD*$^-$, *purI*$^-$, *msbB*$^-$, flagellin$^-$ (*fliC*$^-$/*fljB*$^-$), *pagP*$^-$, *lppA*$^-$ and *lppB*$^-$.

338. An immunostimulatory bacterium, comprising a plasmid encoding the modified STING protein of any of claims 300-326, or encoding a STING protein from a non-human species, wherein the encoded STING protein has type I IFN signaling activity, and attenuated NF-κB signaling activity compared to the NF-κB signaling activity of human STING.

339. The immunostimulatory bacterium of claim 338, that is *ansB*$^-$, *asd*$^-$, *csgD*$^-$, *purI*$^-$, *msbB*$^-$, flagellin$^-$, wherein the wild-type bacterium has flagella, and *pagP*$^-$.

340. The immunostimulatory bacterium of claim 338, that is *ansB*$^-$, *asd*$^-$, *csgD*$^-$, *purI*$^-$, *msbB*$^-$, flagellin$^-$ (*fliC*$^-$/*fljB*$^-$), wherein the wild-type bacterium has flagella, *pagP*$^-$, *lppA*$^-$, and *lppB*$^-$.

341. The immunostimulatory bacterium of any of claims 338-340, wherein the non-human species is selected from among Tasmanian devil, marmoset, cattle, cat, ostrich, boar, bat, manatee, crested ibis, coelacanth, mouse, and ghost shark.

342. The immunostimulatory bacterium of any of claims 338-341, or the delivery vehicle of any of claims 327-337, wherein the immunostimulatory bacterium is a Gram-negative bacterium.

343. The immunostimulatory bacterium of any of claims 338-342, or the delivery vehicle of any of claims 327-337, wherein the immunostimulatory 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 an attenuated strain thereof, or a modified strain thereof of any of the preceding list of bacterial strains.

344. The immunostimulatory bacterium of any of claims 338-342, or the delivery vehicle of any of claims 327-337, wherein the immunostimulatory 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*, *Legionella pneumophila*, *Rhodococcus equi*, *Pseudomonas aeruginosa*, *Helicobacter mustelae*, *Vibrio cholerae*, *Bacillus subtilis*, *Erysipelothrix rhusiopathiae*, *Yersinia enterocolitica*, *Rochalimaea quintana*, or *Agrobacterium tumerfacium*, or an attenuated strain thereof, or a modified strain thereof of any of the preceding list of bacterial strains.

345. The immunostimulatory bacterium of any of claims 338-342, or the delivery vehicle of any of claims 327-337, wherein the immunostimulatory bacterium is an attenuated bacterium.

346. The immunostimulatory bacterium of any of claims 338-342, or the delivery vehicle of any of claims 327-337, wherein the bacterium is a strain of *Salmonella*.

347. The immunostimulatory bacterium or delivery vehicle of claim 346, wherein the bacterium is a *Salmonella typhimurium* strain.

348. The immunostimulatory bacterium or delivery vehicle of claim 346 or claim 347, wherein the unmodified *Salmonella* is a wild-type strain.

349. The immunostimulatory bacterium or delivery vehicle of claim 346 or claim 347, wherein the unmodified *Salmonella* strain is attenuated.

350. The immunostimulatory bacterium or delivery vehicle of any of claims 327-349, wherein the immunostimulatory bacterium is derived from strain AST-100 (VNP20009 or YS1646), or strain ATCC 14028, or a strain having all of the identifying characteristics of strain ATCC 14028.

351. A pharmaceutical composition, comprising the modified STING protein of any of claims 300-326, or the delivery vehicle of any of claims 327-337, or the immunostimulatory bacterium of any of claims 338-350, in a pharmaceutically acceptable vehicle.

352. An isolated cell, comprising the modified STING protein of any of claims 300-326, or the delivery vehicle of any of claims 327-337, or the immunostimulatory bacterium of any of claims 338-350, wherein the cell is not a zygote of a fertilized human egg.

353. The cell of claim 352 that is an immune cell, a stem cell, a tumor cell, or a primary cell line.

354. An isolated cell or cultured cells, comprising the immunostimulatory bacterium of any of claims 338-350.

355. The cell of claim 353 or claim 354 that is a hematopoietic cell.

356. The cell of claim 355 that is a T-cell.

357. The cell of any of claims 352-356 that is produced *ex vivo* by infecting the cell with the immunostimulatory bacterium or delivery vehicle.

~~358. The cell of claim 357 that is a T-cell, or a hematopoietic cell.~~

~~359. A method of treatment of cancer, comprising administering the modified STING protein of any of claims 300-326, or the delivery vehicle of any of claims 327-337, or the immunostimulatory bacterium of any of claims 338-350, or the pharmaceutical composition of claim 351, or the cell of any of claims 352-358, to a subject with a cancer that comprises a solid tumor or is a hematological malignancy.~~

~~360. The method of claim 359, wherein the cancer comprises a solid tumor.~~

~~361. The method of claim 359 or claim 360, wherein the cancer is metastatic.~~

~~362. The method of any of claims 359-361, wherein the cancer is selected from among lymphoma; leukemia; 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.~~

~~363. Use of the modified STING protein of any of claims 300-326, or the delivery vehicle of any of claims 327-337, or the immunostimulatory bacterium of any of claims 338-350, or the pharmaceutical composition of claim 351, or the cell of any of claims 352-358, for the treatment of cancer.~~

~~364. The use of claim 363, wherein the cancer comprises a solid tumor or a hematological malignancy.~~

~~365. The use of claim 363 or claim 364, wherein the cancer is metastatic.~~

~~366. The use of any of claims 363-365, wherein the cancer is selected from among lymphoma; leukemia; 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.~~

~~367. The modified STING protein, delivery vehicle, immunostimulatory bacterium, pharmaceutical composition, cell, method, or use of any of claims 300-366, wherein the non-human STING protein has the sequence of amino acids set forth in any of SEQ ID NOs: 349, 356, or 359-369, or is an allelic variant of the STING protein of each species, having at least 98% sequence identity to the sequence of amino acids set forth in any of SEQ ID NOs: 349, 356, or 359-369.~~

~~368. The modified STING protein, delivery vehicle, immunostimulatory bacterium, pharmaceutical composition, cell, method, or use of any of claims 300-366, wherein the non-human STING protein or chimera has the sequence of amino acids set forth in any of SEQ ID NOs: 350-355, 357, or 358.~~

~~369. A method of converting an M2 macrophage to an M1 or M1-like phenotype, comprising administering the immunostimulatory bacterium of any of claims 26-243 and 338-350 to a subject with a condition, disease, or disorder treated by enhancing an anti-tumor immune response.~~

~~370. Use of an immunostimulatory bacterium of any of claims 26-243 and 338-350 or the immunostimulatory bacterium of any of claims 25-343 and 338-350 for use to convert an M2 macrophage to an M1 or M1-like phenotype macrophage in a subject with cancer, whereby an anti-tumor immune response is induced or enhanced.~~

~~371. The method of claim 369 or use or bacterium of claim 370, wherein the disease, disorder, or condition is a cancer that comprises a solid tumor.~~

~~372. An isolated cell that comprises an immunostimulatory bacterium of any of claims 26-243 and 338-350.~~

~~373. The cell of claim 372 that is an immune cell or a stem cell.~~

~~374. The cell of claim 373, wherein the cell is a stem cell that is not an embryonic stem cell.~~

~~375. The cell of claim 373 that is a T-cell.~~

~~376. The cell of claim 375 that is a CAR-T cell.~~

~~377. A method of treatment of cancer, comprising administering the cell of any of claims 372-376.~~

~~378. The cell of any of claims 372-376 for use for the treatment of cancer.~~

~~379. Use of the cell of any of claims 372-376 for the treatment of cancer.~~

WHAT IS CLAIMED:

1. A nucleic acid construct, comprising nucleic acid encoding a plurality of anti-cancer products as a polycistronic sequence under control of a single promoter, wherein:

the encoded products comprise at least two proteins;

one protein is part of a cytosolic DNA/RNA sensor pathway that leads to expression of type I interferon (IFN), comprising one or more modifications, whereby activity of the protein constitutively induces expression of type I interferon (IFN); and

the second protein is different from the first and is a protein(s) that confer(s) or contributes to an anti-tumor immune response in a tumor microenvironment.

2. The construct of claim 1, wherein the polycistronic sequence comprises a 2A peptide between each open reading frame (ORF) encoding each product.

3. The construct of claim 2, wherein the 2A peptide is one or more of T2A, P2A, E2A, or F2A.

4. The construct of any of claims 1-3, wherein the protein that is part of a cytosolic DNA/RNA sensor pathway is Stimulator of Interferon Genes (STING), RIG-I, MDA-5, IRF-3, or IRF-7.

5. The nucleic acid construct of any of claims 1-4, comprising nucleic acid encoding a plurality of anti-cancer products as a polycistronic sequence under control of a single promoter, wherein:

one product is a modified STING protein; and

the modified STING protein has constitutive activity to induce expression of type I interferon, and lower NF-κB signaling activity compared to unmodified human STING.

6. The construct of claim 5, wherein the modified STING protein is selected from among:

a) a modified non-human STING protein, wherein:

the non-human STING protein is one that has lower NF-κB signaling, and, optionally, higher type I interferon activation activity compared to the wild-type (WT) human STING protein; and

the non-human STING protein comprises a mutation, whereby the STING protein constitutively induces type I interferon (IFN); and

b) a modified chimeric STING protein in which the C-terminal tail (CTT) region in a human STING protein is replaced with the CTT from a STING protein of another species that has lower NF-κB signaling activity than human STING; and the modified chimeric STING protein further comprises a mutation whereby the chimeric STING protein constitutively induces type I IFN.

7. The construct of any of claims 1-6, wherein a second product encoded in the polycistronic sequence is a cytokine.

8. The construct of any of claims 1-7, wherein a second product encoded in the polycistronic sequence is a protein selected from among:

(a) 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-18, IL-21, IL-23, IL-36γ, IL-2 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 the recruitment and/or persistence of T-cells, CD40, CD40 ligand (CD40L), CD28, OX40, OX40 ligand (OX40L), 4-1BB, 4-1BB ligand (4-1BBL), 4-1BBL that has a cytoplasmic domain deletion or truncation to eliminate immunosuppressive reverse signaling, members of the B7-CD28 family, CD47 antagonists, an anti-IL6 antibody or IL-6 binding decoy receptor, TGF-beta polypeptide antagonists, bi-specific T-cell engager antibodies, and members of the tumor necrosis factor receptor (TNFR) superfamily; and/or

(b) one or more of: IFN-α, IFN-β, GM-CSF, IL-2, IL-7, IL-12, IL-15, IL-18, IL-21, IL-23, IL-12p70 (IL-12p40 + IL-12p35), IL-15/IL-15R alpha chain complex, IL-36 gamma, IL-2 that has attenuated binding to IL-2Ra, IL-2 that is modified so that it does not bind to IL-2Ra, CXCL9, CXCL10 (IP-10), CXCL11, CCL3, CCL4, CCL5, molecules involved in the potential recruitment and/or persistence of T-cells, CD40, CD40 ligand (CD40L), OX40, OX40 ligand (OX40L), 4-1BB, 4-1BB ligand (4-1BBL), 4-1BBL with a deleted cytoplasmic domain (4-1BBLΔcyt) or with a partially deleted cytoplasmic domain, which the cytoplasmic domain is deleted or truncated to eliminate the immunosuppressive reverse signaling, members of the B7-CD28 family, and members of the tumor necrosis factor receptor (TNFR) superfamily.

9. The construct of any of claims 1-8, comprising:

(a) nucleic acid encoding 4-1BBL with a deleted, or partially deleted, cytoplasmic domain, or a partially deleted cytoplasmic domain and optionally including amino acid modifications, whereby the resulting 4-1BBL assumes the proper orientation when expressed in a cell; and/or

(b) nucleic acid encoding a 4-1BBL variant with a deleted or partially deleted cytoplasmic domain, or a modified 4-1BBL with a truncated and modified cytoplasmic domain, wherein the sequence of the 4-1BBL is set forth in SEQ ID NO:390, SEQ ID NO:391, and SEQ ID NO:392.

10. The construct of any of claims 1-9, wherein the encoded polycistronic products comprise a modified STING and IL-15 or IL-15/IL-15R alpha chain complex.

11. The construct of any of claims 1-10, wherein:

the first protein is a modified STING;

the TRAF6 binding site in the CTT of the STING protein optionally is deleted; and

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

12. The construct of any of claims 1-11, wherein the encoded polycistronic products comprise modified STING and IL-12p70.

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

the protein that is part of a cytosolic DNA/RNA sensor pathway is STING;

the construct comprises a modified STING;

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.

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

the protein that is part of a cytosolic DNA/RNA sensor pathway is STING;

the modified STING is a modified chimeric protein comprising a STING from a first species and the CTT from a second species that has lower NF-κB signaling activity than human STING replacing the CTT from the first species;

the first species is human; and

the replacing CTT is from a Tasmanian devil, marmoset, cattle, cat, ostrich, boar, bat, manatee, crested ibis, coelacanth, or ghost shark STING protein.

15. The construct of any of claims 1-14, wherein:

the protein that is part of a cytosolic DNA/RNA sensor pathway is STING;

the modified STING is a modified chimeric STING; and

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, and

Ghost shark LTEYPVAEPSNANETDCMSSEPHLMISDDPKPLRSYCP SEQ ID NO:383,

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

16. The construct of any of claims 1-15, wherein:

the protein that is part of a cytosolic DNA/RNA sensor pathway is STING; and

the modification that renders the STING activity constitutive is:

a) one or more amino acid replacements that correspond(s) 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, for alignment, to the sequence of human STING, as set forth in any of SEQ ID NOs:305-309; or

b) a replacement corresponding to C206Y or R284G, with reference, for alignment, to the sequence of human STING, as set forth in any of SEQ ID NOs:305-309; or

c) the replacements corresponding to N154S/R284G with reference, for alignment, to the sequence of human STING, as set forth in any of SEQ ID NOs:305-309.

17. The construct of any of claims 1-16, wherein:

the protein that is part of a cytosolic DNA/RNA sensor pathway is STING;

the chimeric STING comprises a human STING polypeptide with a CTT from Tasmanian devil and an amino acid replacement that results in constitutive expression of type I interferon; optionally

the chimeric STING has the sequence of amino acids set forth in SEQ ID NO: 354 or 397, or a sequence having at least 95% sequence identity therewith and including the replacement that renders the STING constitutively active and having lower NF-κB signaling activity compared to unmodified human STING.

18. A plasmid, comprising the construct of any of claims 1-17.

19. The plasmid of claim 18 that is a bacterial plasmid, wherein the construct is operatively linked to eukaryotic on or more transcriptional regulatory sequences.

20. The plasmid of claim 19, wherein the transcriptional regulatory sequences comprise a promoter.

21. The plasmid of claim 20, wherein the promoter is a eukaryotic promoter.

22. The plasmid of any of claims 18-21, wherein the construct includes an enhancer, a eukaryotic promoter, an IRES, a localization sequence, the open reading frame encoding the therapeutic products, and a polyA tail; and/or

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 a 2A peptide, whereby, upon translation, each product is separately expressed; and optionally

the construct includes a bacterial terminator positioned to decrease read-through from a bacterial promoter on the plasmid; and/or optionally

the eukaryotic promoter on the plasmid is oriented in the opposite direction from a bacterial promoter on the plasmid.

23. A delivery vehicle, comprising the construct of any of claims 1-17, or the plasmid of any of claims 18-22.

24. An immunostimulatory bacterium, comprising the construct of any of claims 1-17, or the plasmid of any of claims 18-22.

25. The immunostimulatory bacterium of claim 24, wherein the genome of the bacterium is modified, whereby:

the bacterium lacks flagella, wherein the wild-type bacterium has flagella; or

the bacterium comprises genome modifications, whereby the bacterium is *msbB*$^{-}$/*pagP*$^{-}$; or

the bacterium lacks flagella, and is *pagP*$^{-}$, *ansB*$^{-}$, and *csgD*$^{-}$, wherein the wild-type bacterium has flagella; and/or

the bacterium lacks flagella, and is *msbB*$^{-}$, *pagP*$^{-}$, *ansB*$^{-}$, and *csgD*$^{-}$, wherein the wild-type bacterium has flagella; or

the bacterium is *asd*$^{-}$, *csgD*$^{-}$, *purI*$^{-}$, *msbB*$^{-}$, flagellin^{-} and *pagP*$^{-}$, wherein the wild-type bacterium has flagella; or

the bacterium is *csgD*$^{-}$, *purI*$^{-}$, *msbB*$^{-}$, flagellin^{-} and *pagP*$^{-}$, wherein the wild-type bacterium has flagella.

26 The immunostimulatory bacterium of claim 24, wherein the bacterium comprises genome modifications whereby the bacterium lacks flagella and is *msbB*$^{-}$/*pagP*$^{-}$.

27. An immunostimulatory bacterium, comprising a plasmid encoding a therapeutic product under control of a eukaryotic promoter, 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 does not activate the synthesis of secreted asparaginase.

28. The immunostimulatory bacterium of any of claims 24-27 that comprises genome modifications, whereby the bacterium does not express L-asparaginase II, so that the bacterium is *ansB*$^{-}$.

29. The immunostimulatory bacterium of any of claims 24-28, wherein the genome of the bacterium is modified to be *asd*$^{-}$; and

the plasmid encodes aspartate-semialdehyde dehydrogenase (*asd*).

30. The immunostimulatory bacterium of any of claims 24-29 that auxtrophic for adenosine.

31. The immunostimulatory bacterium of any of claims 24-30, wherein:

the bacterium is a Gram-negative bacterium; or

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 an attenuated strain thereof or a modified strain thereof of any of the preceding list of bacterial strains; or

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*, *Legionella pneumophila*, *Rhodococcus equi*, *Pseudomonas aeruginosa*, *Helicobacter mustelae*, *Vibrio cholerae*, *Bacillus subtilis*, *Erysipelothrix rhusiopathiae*, *Yersinia enterocolitica*, *Rochalimaea quintana*, or *Agrobacterium tumerfacium*, or an attenuated strain thereof or a modified strain thereof.

32. The immunostimulatory bacterium of any of claims 24-31, wherein the bacterium is a strain of *Salmonella* or an attenuated strain thereof or a modified strain thereof.

33. The immunostimulatory bacterium of claim 32, wherein the bacterium is a *Salmonella typhimurium* strain, or an attenuated strain thereof or a modified strain thereof,

34. The immunostimulatory bacterium of claim 32 or claim 33, wherein the bacterium is derived from strain AST-100 (VNP20009 or YS1646), or strain ATCC 14028, or a strain having all of the identifying characteristics of strain ATCC 14028.

35. The delivery vehicle of claim 23 that is an immunostimulatory bacterium, an exosome, a nanoparticle, an oncolytic virus, or a cell.

36. Use of the immunostimulatory bacterium of any of claims 24-34, or the delivery vehicle of claim 23, in the manufacture of a pharmaceutical composition for treating cancer.

37. The use of claim 36, wherein the cancer comprises a solid tumor or a hematological malignancy.

38. The use of claim 36 or claim 37, 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.

39. An isolated cell, comprising the construct of any of claims 1-17, the plasmid of any of claims 18-22, the delivery vehicle of claim 23 or 35, or the immunostimulatory bacterium of any of claims 24-34, wherein the cell is not a zygote of a fertilized human egg or an embryonic stem cell.

40. The cell of claim 39, wherein:

the cell is an immune cell or a stem cell; optionally

the immune cell is a T-cell that optionally is a CAR-T cell.

41. Use of the cell of claim 39 or claim 40 in the manufacture of a medicament for the treatment of cancer.