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.