CLAIMS

What is claimed is:

1. Use of a pharmaceutical composition in manufacture of a medicament for treating a cancer, an autoimmune condition, or an inflammatory disorder, wherein the pharmaceutical composition comprises an isolated polynucleotide encoding a chimeric protein having a general structure of:

N terminus – (a) – (b) – (c) – C terminus,

wherein:

(A)

(a) is a first domain comprising an extracellular domain of T cell immunoreceptor with Ig and ITIM domains (TIGIT), or a variant or a fragment thereof that is capable of binding a TIGIT ligand,

(c) is a second domain comprising an extracellular domain of LIGHT (homologous to lymphotoxin, exhibits inducible expression and competes with HSV glycoprotein D for binding to herpesvirus entry mediator, a receptor expressed on T lymphocytes), or a variant or a fragment thereof that is capable of binding a LIGHT receptor, or glucocorticoid-induced TNFR-related protein ligand (GITRL), or a variant or a fragment thereof that is capable of binding a GITRL receptor, and

(b) is a linker adjoining the first and second domains, wherein the linker comprises at least one cysteine residue capable of forming a disulfide bond and/or comprises a hinge-CH2-CH3 Fc domain;

(B)

(a) is a first domain comprising an extracellular domain of programmed death-1 (PD-1), or a variant or a fragment thereof that capable of binding a PD-1 ligand,

(c) is a second domain comprising an extracellular domain of OX40 ligand (OX40L), or a variant or a fragment thereof that capable of binding an OX40L receptor, or 4-1BB Ligand (4-1BBL), or a variant or a fragment thereof that capable of binding a 4-1BBL receptor,

(b) is a linker adjoining the first and second domains, wherein the linker comprises at least one cysteine residue capable of forming a disulfide bond and/or comprises a hinge-CH2-CH3 Fc domain;

(C)

(a) is a first domain comprising an extracellular domain of T-cell immunoglobulin mucin receptor 3 (TIM3), or a variant or a fragment thereof that capable of binding a TIM3 ligand,

(c) is a second domain comprising an extracellular domain of CD40 ligand (CD40L), or a variant or a fragment thereof that capable of binding a CD40L receptor, and

(b) is a linker adjoining the first and second domains, wherein the linker comprises at least one cysteine residue capable of forming a disulfide bond and/or comprises a hinge-CH2-CH3 Fc domain;

(D)

(a) is a first domain comprising an extracellular domain of V-set and immunoglobulin domain-containing protein 8 (VSIG8), or a variant or a fragment thereof that capable of binding a VSIG8 ligand,

(c) is a second domain comprising an extracellular domain of 4-1BB Ligand (4-1BBL), or a variant or a fragment thereof that capable of binding a 4-1BBL receptor,

(b) is a linker adjoining the first and second domains, wherein the linker comprises at least one cysteine residue capable of forming a disulfide bond and/or comprises a hinge-CH2-CH3 Fc domain; or

(E)

(a) is a first domain comprising an extracellular domain of signal regulatory protein α (SIRPα), or a variant or a fragment thereof that is capable of binding a SIRPα ligand,

(c) is a second domain comprising an extracellular domain of CD40 ligand (CD40L), or a variant or a fragment thereof that is capable of binding a CD40L receptor, and

(b) is a linker adjoining the first and second domains, wherein the linker comprises at least one cysteine residue capable of forming a disulfide bond and/or comprises a hinge-CH2-CH3 Fc domain.

2. The use of claim 1, wherein:

the TIGIT ligand is selected from CD155/PVR, Nectin-2, Nectin-3 and Nectin-4;

the LIGHT receptor is TNFRSF3/LTBR;

the GITRL receptor is glucocorticoid-induced TNFR-related protein (GITR);

the PD-1 ligand is PD-L1 or PD-L2;

the OX40L receptor is OX40;

the 4-1BBL receptor is 4-1BB;

the TIM3 ligand is selected from galectin 9, phosphatidylserine (PtdSer), CEACAM1 and high mobility group protein B1 (HMGB1);

the CD40L receptor is CD40; and/or

the SIRPα ligand is CD47.

3. The use of claim 1 or claim 2, wherein:

the hinge-CH2-CH3 Fc domain is derived from IgG1 or IgG4, optionally human IgG1 or human IgG4, optionally wherein the hinge-CH2-CH3 Fc domain comprises an amino acid sequence that is at least about 95% identical to the amino acid sequence of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, or SEQ ID NO: 5; and/or

the linker further comprises wherein the linker further comprises the linker comprises one or more joining linkers, such joining linkers independently selected from SEQ ID NOs: 6 to 52, optionally wherein the linker comprises two or more joining linkers each joining linker independently selected from SEQ ID NOs: 6 to 52; wherein one joining linker is N terminal to the hinge-CH2-CH3-Fc domain and another joining linker is C terminal to the hinge-CH2-CH3-Fc domain.

4. The use of any one of claims 1 to 3, wherein the polynucleotide is or comprises an mRNA or a modified mRNA (mmRNA), optionally wherein the polynucleotide is or comprises an mmRNA, optionally wherein

the mmRNA further comprises a 3' untranslated region (UTR), optionally wherein the 3' UTR comprises at least one microRNA-122 (miR-122) binding site, optionally wherein the miR-122 binding site is a miR-122-3p binding site or a miR-122-5-binding site, optionally wherein the mmRNA further comprises a spacer sequence between the open reading frame and the miRNA binding site, optionally wherein the spacer sequence comprises at least about 10 nucleotides, at least about 20 nucleotides, at least about 30 nucleotides, at least about 40 nucleotides, at least about 50 nucleotides, at least about 60 nucleotides, at least about 70 nucleotides, at least about 80 nucleotides, at least about 90 nucleotides, or at least about 100 nucleotides; and/or

the mmRNA further comprises a 5' UTR, optionally wherein the 5' UTR harbors a Kozak sequence and/or forms a secondary structure that stimulate elongation factor binding; and/or

the mmRNA further comprises a 5' terminal cap, optionally wherein the 5' terminal cap is a Cap0, Cap1, ARCA, inosine, N1-methyl-guanosine, 2'fluoro-guanosine, 7-deaza-guanosine, 8-oxo-guanosine, 2-amino-guanosine, LNA-guanosine, 2-azidoguanosine, Cap2, Cap4, 5' methylG cap, or an analog thereof.

5. The use of claim 4, wherein the mmRNA comprises one or more modifications; optionally wherein the modification comprises:

N1-methylpseudouridine (m1Ψ), pseudouridine (Ψ), 2-thiouridine (s2U), 4'-thiouridine, 5-methylcytosine, 2-thio-1-methyl-1-deaza-pseudouridine, 2-thio-1-methyl-pseudouridine, 2-thio-5-aza-uridine, 2-thio-dihydropseudouridine, 2-thio-dihydrouridine, 2-thio-pseudouridine, 4-methoxy-2-thio-pseudouridine, 4-methoxy-pseudouridine, 4-thio-1-methyl-pseudouridine, 4-thio-pseudouridine, 5-aza-uridine, dihydropseudouridine, 5-methyluridine, 5-methoxyuridine, 2'-O-methyl uridine, 1-methyl-pseudouridine (m1Ψ), 5-methoxy-uridine (mo5U), 5-methyl-cytidine (m5C), α-thio-guanosine, α-thio-adenosine, 5-cyano uridine, 4'-thio uridine 7-deaza-adenine, 1-methyl-adenosine (m1A), 2-methyl-adenine (m2A), N6-methyl-adenosine (m6A), and 2,6-Diaminopurine, (I), 1-methylinosine (m1I), wyosine (imG), methylwyosine (mimG), 7-deaza-guanosine, 7-cyano-7-deaza-guanosine (preQ0), 7-aminomethyl-7-deaza-guanosine (preQ1), 7-methyl-guanosine (m7G), 1-methyl-guanosine (m1G), 8-oxo-guanosine, 7-methyl-8-oxo-guanosine, and a combination of any two or more thereof; and/or

pyridin-4-one ribonucleoside, 5-aza-uridine, 2-thio-5-aza-uridine, 2-thiouridine, pseudouridine, 4-thio-pseudouridine, 2-thio-pseudouridine, 5-hydroxyuridine, 3-methyluridine, 5-carboxymethyl-uridine, 1-carboxymethyl-pseudouridine, 5-propynyl-uridine, 1-propynyl-pseudouridine, 5-taurinomethyluridine, 1-taurinomethyl-pseudouridine, 5-taurinomethyl-2-thio-uridine, 1-taurinomethyl-4-thio-uridine, 5-methyl-uridine, 1-methyl-pseudouridine, 4-thio-1-methyl-pseudouridine, 2-thio-1-methyl-pseudouridine, 1-methyl-1-deaza-pseudouridine, 2-thio-1-methyl-1-deaza-pseudouridine, dihydrouridine, dihydropseudouridine, 2-thio-dihydrouridine, 2-thio-dihydropseudouridine, 2-methoxyuridine, 2-methoxy-4-thio-uridine, 4-methoxy-pseudouridine, 4-methoxy-2-thio-pseudouridine, 5-aza-cytidine, pseudoisocytidine, 3-methyl-cytidine, N4-acetylcytidine, 5-formylcytidine, N4-methylcytidine, 5-hydroxymethylcytidine, 1-methyl-pseudoisocytidine,

pyrrolo-cytidine, pyrrolo-pseudoisocytidine, 2-thio-cytidine, 2-thio-5-methyl-cytidine, 4-thio-pseudoisocytidine, 4-thio-1-methyl-pseudoisocytidine, 4-thio-1-methyl-1-deaza-pseudoisocytidine, 1-methyl-1-deaza-pseudoisocytidine, zebularine, 5-aza-zebularine, 5-methyl-zebularine, 5-aza-2-thio-zebularine, 2-thio-zebularine, 2-methoxy-cytidine, 2-methoxy-5-methyl-cytidine, 4-methoxy-pseudoisocytidine, 4-methoxy-1-methyl-pseudoisocytidine, 2-aminopurine, 2, 6-diaminopurine, 7-deaza-adenine, 7-deaza-8-aza-adenine, 7-deaza-2-aminopurine, 7-deaza-8-aza-2-aminopurine, 7-deaza-2,6-diaminopurine, 7-deaza-8-aza-2,6-diaminopurine, 1-methyladenosine, N6-methyladenosine, N6-isopentenyladenosine, N6-(cis-hydroxyisopentenyl)adenosine, 2-methylthio-N6-(cis-hydroxyisopentenyl) adenosine, N6-glycinylcarbamoyladenosine, N6-threonylcarbamoyladenosine, 2-methylthio-N6-threonyl carbamoyladenosine, N6,N6-dimethyladenosine, 7-methyladenine, 2-methylthio-adenine, and 2-methoxy-adenine, inosine, 1-methyl-inosine, wyosine, wybutosine, 7-deaza-guanosine, 7-deaza-8-aza-guanosine, 6-thio-guanosine, 6-thio-7-deaza-guanosine, 6-thio-7-deaza-8-aza-guanosine, 7-methyl-guanosine, 6-thio-7-methyl-guanosine, 7-methylinosine, 6-methoxy-guanosine, 1-methylguanosine, N2-methylguanosine, N2,N2-dimethylguanosine, 8-oxo-guanosine, 7-methyl-8-oxo-guanosine, 1-methyl-6-thio-guanosine, N2-methyl-6-thio-guanosine, and N2,N2-dimethyl-6-thio-guanosine, and a combination of any two or more thereof; and/or

the modification is selected from N1-methylpseudouridine, pseudouridine,5-methylcytosine, 5-methoxyuridine, and a combination thereof; and/or

at least one N1-methylpseudouridine; and/or

optionally wherein the mmRNA is fully modified with chemically-modified uridines, optionally wherein the mmRNA is a fully modified with N1-methylpseudouridine; and/or

optionally wherein the modifications are selected from pyridin-4-one ribonucleoside, 5-aza-uridine, 2-thio-5-aza-uridine, 2-thiouridine, pseudouridine, 4-thio-pseudouridine, 2-thio-pseudouridine, 5-hydroxyuridine, 3-methyluridine, 5-carboxymethyl-uridine, 1-carboxymethyl-pseudouridine, 5-propynyl-uridine, 1-propynyl-pseudouridine, 5-taurinomethyluridine, 1-taurinomethyl-pseudouridine, 5-taurinomethyl-2-thio-uridine, 1-taurinomethyl-4-thio-uridine, 5-methyl-uridine, 1-methyl-pseudouridine, 4-thio-1-methyl-pseudouridine, 2-thio-1-methyl-pseudouridine, 1-methyl-1-deaza-pseudouridine, 2-thio-1-methyl-1-deaza-pseudouridine,

dihydrouridine, dihydropseudouridine, 2-thio-dihydrouridine, 2-thio-dihydropseudouridine, 2-methoxyuridine, 2-methoxy-4-thio-uridine, 4-methoxy-pseudouridine, and 4-methoxy-2-thio-pseudouridine or a combination of any two or more thereof; and/or

optionally the modifications are selected from 5-aza-cytidine, pseudoisocytidine, 3-methyl-cytidine, N4-acetylcytidine, 5-formylcytidine, N4-methylcytidine, 5-hydroxymethylcytidine, 1-methyl-pseudoisocytidine, pyrrolo-cytidine, pyrrolo-pseudoisocytidine, 2-thio-cytidine, 2-thio-5-methyl-cytidine, 4-thio-pseudoisocytidine, 4-thio-1-methyl-pseudoisocytidine, 4-thio-1-methyl-1-deaza-pseudoisocytidine, 1-methyl-1-deaza-pseudoisocytidine, zebularine, 5-aza-zebularine, 5-methyl-zebularine, 5-aza-2-thio-zebularine, 2-thio-zebularine, 2-methoxy-cytidine, 2-methoxy-5-methyl-cytidine, 4-methoxy-pseudoisocytidine, and 4-methoxy-1-methyl-pseudoisocytidine; and/or

optionally wherein the modifications are selected from 2-aminopurine, 2, 6-diaminopurine, 7-deaza-adenine, 7-deaza-8-aza-adenine, 7-deaza-2-aminopurine, 7-deaza-8-aza-2-aminopurine, 7-deaza-2,6-diaminopurine, 7-deaza-8-aza-2,6-diaminopurine, 1-methyladenosine, N6-methyladenosine, N6-isopentenyladenosine, N6-(cis-hydroxyisopentenyl)adenosine, 2-methylthio-N6-(cis-hydroxyisopentenyl) adenosine, N6-glycinylcarbamoyladenosine, N6-threonylcarbamoyladenosine, 2-methylthio-N6-threonyl carbamoyladenosine, N6,N6-dimethyladenosine, 7-methyladenine, 2-methylthio-adenine, and 2-methoxy-adenine; and/or

optionally the modifications are selected from inosine, 1-methyl-inosine, wyosine, wybutosine, 7-deaza-guanosine, 7-deaza-8-aza-guanosine, 6-thio-guanosine, 6-thio-7-deaza-guanosine, 6-thio-7-deaza-8-aza-guanosine, 7-methyl-guanosine, 6-thio-7-methyl-guanosine, 7-methylinosine, 6-methoxy-guanosine, 1-methylguanosine, N2-methylguanosine, N2,N2-dimethylguanosine, 8-oxo-guanosine, 7-methyl-8-oxo-guanosine, 1-methyl-6-thio-guanosine, N2-methyl-6-thio-guanosine, and N2,N2-dimethyl-6-thio-guanosine; and/or

optionally wherein the modifications are present on the major groove face, optionally wherein a hydrogen on C-5 of uracil is replaced with a methyl group or a halo group; and/or

the mmRNA further comprises one or more modifications selected from 5'-O-(1-Thiophosphate)-Adenosine, 5'-O-(1-Thiophosphate)-Cytidine, 5'-O-(1-Thiophosphate)-Guanosine, 5'-O-(1-Thiophosphate)-Uridine and 5'-O-(1-Thiophosphate)-Pseudouridine.

6. The use of any one of claims 1 to 5, wherein the pharmaceutical composition further comprises a lipidoid, a liposome, a lipoplex, a lipid nanoparticle, a polymeric nanoparticle, a peptide, a protein, a cell, a

nanoparticle mimic, a nanotube, or a conjugate, optionally wherein the pharmaceutical composition is formulated as a lipid nanoparticle (LNP), a lipoplex, or a liposome.

7. The use of claim 6, wherein the pharmaceutical composition is formulated as a lipid nanoparticle (LNP), optionally wherein:

the LNP comprises a molar ratio of about 20-60% ionizable amino lipid, about 5-25% phospholipid, about 25-55% structural lipid, and about 0.5-1.5% PEG lipid; or

the LNP comprises a molar ratio of about 50% ionizable amino lipid, about 8-12% phospholipid, about 37-40% structural lipid, and about 1-2% PEG lipid; or

the lipid nanoparticles comprise lipids selected from an ionizable lipid (*e.g.,* an ionizable cationic lipid selected from DLin-DMA, DLin-K-DMA, DLin-KC2-DMA, DLin-MC3-DMA, 98N12-5, and C12-200); a structural lipid (*e.g.,* distearoylphosphatidylcholine (DSPC)); cholesterol, and a polyethyleneglycol (PEG)-lipid (*e.g.,* a PEG-diacylglycerol (DAG), a PEG-dialkyloxypropyl (DAA), a PEG-phospholipid, a PEG-ceramide (Cer), or a mixture thereof, or a PEG-dilauryloxypropyl (C12, a PEG-dimyristyloxypropyl (C14), a PEG-dipalmityloxypropyl (C16), or a PEG-distearyloxypropyl (C18)); 1,2-dioleoyl-3-trimethylammoniumpropane (DOTAP); dioleoylphosphatidylethanolamine (DOPE) ; or

the lipid nanoparticles comprise (a) a cationic lipid comprising from 50 mol % to 85 mol % of the total lipid present in the particle; (b) a non-cationic lipid comprising from 13 mol % to 49.5 mol % of the total lipid present in the particle; and (c) a conjugated lipid that inhibits aggregation of particles comprising from 0.5 mol % to 2 mol % of the total lipid present in the particle,

optionally wherein the lipid nanoparticles comprise a lipid selected from SM-102, DLin-DMA, DLin-K-DMA, DLin-KC2-DMA, DLin-MC3-DMA, 98N12-5, and C12-200; a cholesterol; and a PEG-lipid.

8. The use of any one of claims 1 to 7, wherein the pharmaceutical composition is formulated for parenteral administration.

9. A pharmaceutical composition comprising an isolated modified mRNA (mmRNA) encoding a heterologous chimeric protein having an amino acid sequence that has at least about 95% sequence identity with an amino acid sequence selected from SEQ ID NOs: 81, 80, and 90-93.

10. The pharmaceutical composition of claim 9, wherein:

the mmRNA comprises a 3' untranslated region (UTR), wherein the 3' UTR comprises at least one microRNA-122 (miR-122) binding site, optionally wherein the miR-122 binding site is a miR-122-3p binding site or a miR-122-5-binding site; and/or

a spacer sequence between the open reading frame and the miRNA binding site, optionally wherein the spacer sequence comprises at least about 10 nucleotides, at least about 20 nucleotides, at least about 30 nucleotides, at least about 40 nucleotides, at least about 50 nucleotides, at least about 60 nucleotides, at least about 70 nucleotides, at least about 80 nucleotides, at least about 90 nucleotides, or at least about 100 nucleotides; and/or

a 5' UTR, optionally wherein the 5' UTR harbors a Kozak sequence and/or forms a secondary structure that stimulate elongation factor binding; and/or

a 5' terminal cap, optionally wherein the 5' terminal cap is a Cap0, Cap1, ARCA, inosine, N1-methyl-guanosine, 2'fluoro-guanosine, 7-deaza-guanosine, 8-oxo-guanosine, 2-amino-guanosine, LNA-guanosine, 2-azidoguanosine, Cap2, Cap4, 5' methylG cap, or an analog thereof.

11. The pharmaceutical composition of claim 9 or claim 10, wherein the mmRNA comprises one or more modifications, optionally wherein the modifications are selected from:

N1-methylpseudouridine (m1Ψ), pseudouridine (Ψ), 2-thiouridine (s2U), 4'-thiouridine, 5-methylcytosine, 2-thio-1-methyl-1-deaza-pseudouridine, 2-thio-1-methyl-pseudouridine, 2-thio-5-aza-uridine, 2-thio-dihydropseudouridine, 2-thio-dihydrouridine, 2-thio-pseudouridine, 4-methoxy-2-thio-pseudouridine, 4-methoxy-pseudouridine, 4-thio-1-methyl-pseudouridine, 4-thio-pseudouridine, 5-aza-uridine, dihydropseudouridine, 5-methyluridine, 5-methoxyuridine, 2'-O-methyl uridine, 1-methyl-pseudouridine (m1Ψ), 5-methoxy-uridine (mo5U), 5-methyl-cytidine (m5C), α-thio-guanosine, α-thio-adenosine, 5-cyano uridine, 4'-thio uridine 7-deaza-adenine, 1-methyl-adenosine (m1A), 2-methyl-adenine (m2A), N6-methyl-adenosine (m6A), and 2,6-Diaminopurine, (I), 1-methylinosine (m1I), wyosine (imG), methylwyosine (mimG), 7-deaza-guanosine, 7-cyano-7-deaza-guanosine (preQ0), 7-aminomethyl-7-deaza-guanosine (preQ1), 7-methyl-guanosine (m7G), 1-methyl-guanosine (m1G), 8-oxo-guanosine, 7-methyl-8-oxo-guanosine, and a combination of any two or more thereof; and/or

1-methyl-pseudouridine, pyridin-4-one ribonucleoside, 5-aza-uridine, 2-thio-5-aza-uridine, 2-thiouridine, pseudouridine, 4-thio-pseudouridine, 2-thio-pseudouridine, 5-hydroxyuridine, 3-methyluridine, 5-carboxymethyl-uridine, 1-carboxymethyl-pseudouridine, 5-propynyl-uridine, 1-

propynyl-pseudouridine, 5-taurinomethyluridine, 1-taurinomethyl-pseudouridine, 5-taurinomethyl-2-thio-uridine, 1-taurinomethyl-4-thio-uridine, 5-methyl-uridine, 4-thio-1-methyl-pseudouridine, 2-thio-1-methyl-pseudouridine, 1-methyl-1-deaza-pseudouridine, 2-thio-1-methyl-1-deaza-pseudouridine, dihydrouridine, dihydropseudouridine, 2-thio-dihydrouridine, 2-thio-dihydropseudouridine, 2-methoxyuridine, 2-methoxy-4-thio-uridine, 4-methoxy-pseudouridine, 4-methoxy-2-thio-pseudouridine, 5-aza-cytidine, pseudoisocytidine, 3-methyl-cytidine, N4-acetylcytidine, 5-formylcytidine, N4-methylcytidine, 5-hydroxymethylcytidine, 1-methyl-pseudoisocytidine, pyrrolo-cytidine, pyrrolo-pseudoisocytidine, 2-thio-cytidine, 2-thio-5-methyl-cytidine, 4-thio-pseudoisocytidine, 4-thio-1-methyl-pseudoisocytidine, 4-thio-1-methyl-1-deaza-pseudoisocytidine, 1-methyl-1-deaza-pseudoisocytidine, zebularine, 5-aza-zebularine, 5-methyl-zebularine, 5-aza-2-thio-zebularine, 2-thio-zebularine, 2-methoxy-cytidine, 2-methoxy-5-methyl-cytidine, 4-methoxy-pseudoisocytidine, 4-methoxy-1-methyl-pseudoisocytidine, 2-aminopurine, 2, 6-diaminopurine, 7-deaza-adenine, 7-deaza-8-aza-adenine, 7-deaza-2-aminopurine, 7-deaza-8-aza-2-aminopurine, 7-deaza-2,6-diaminopurine, 7-deaza-8-aza-2,6-diaminopurine, 1-methyladenosine, N6-methyladenosine, N6-isopentenyladenosine, N6-(cis-hydroxyisopentenyl)adenosine, 2-methylthio-N6-(cis-hydroxyisopentenyl) adenosine, N6-glycinylcarbamoyladenosine, N6-threonylcarbamoyladenosine, 2-methylthio-N6-threonyl carbamoyladenosine, N6,N6-dimethyladenosine, 7-methyladenine, 2-methylthio-adenine, and 2-methoxy-adenine, inosine, 1-methyl-inosine, wyosine, wybutosine, 7-deaza-guanosine, 7-deaza-8-aza-guanosine, 6-thio-guanosine, 6-thio-7-deaza-guanosine, 6-thio-7-deaza-8-aza-guanosine, 7-methyl-guanosine, 6-thio-7-methyl-guanosine, 7-methylinosine, 6-methoxy-guanosine, 1-methylguanosine, N2-methylguanosine, N2,N2-dimethylguanosine, 8-oxo-guanosine, 7-methyl-8-oxo-guanosine, 1-methyl-6-thio-guanosine, N2-methyl-6-thio-guanosine, and N2,N2-dimethyl-6-thio-guanosine, and a combination of any two or more thereof; or

N1-methylpseudouridine, pseudouridine, 5-methylcytosine, 5-methoxyuridine, and a combination thereof; or

at least one N1-methylpseudouridine.

12. The pharmaceutical composition of claim 11, wherein:

the mmRNA is fully modified with chemically-modified uridines, optionally, wherein the mmRNA is a fully modified with N1-methylpseudouridine; or

the modifications are selected from pyridin-4-one ribonucleoside, 5-aza-uridine, 2-thio-5-aza-uridine, 2-thiouridine, pseudouridine, 4-thio-pseudouridine, 2-thio-pseudouridine, 5-hydroxyuridine, 3-methyluridine, 5-carboxymethyl-uridine, 1-carboxymethyl-pseudouridine, 5-propynyl-uridine, 1-propynyl-pseudouridine, 5-taurinomethyluridine, 1-taurinomethyl-pseudouridine, 5-taurinomethyl-2-thio-uridine, 1-taurinomethyl-4-thio-uridine, 5-methyl-uridine, 1-methyl-pseudouridine, 4-thio-1-methyl-pseudouridine, 2-thio-1-methyl-pseudouridine, 1-methyl-1-deaza-pseudouridine, 2-thio-1-methyl-1-deaza-pseudouridine, dihydrouridine, dihydropseudouridine, 2-thio-dihydrouridine, 2-thio-dihydropseudouridine, 2-methoxyuridine, 2-methoxy-4-thio-uridine, 4-methoxy-pseudouridine, and 4-methoxy-2-thio-pseudouridine or a combination of any two or more thereof; or

the modifications are selected from 5-aza-cytidine, pseudoisocytidine, 3-methyl-cytidine, N4-acetylcytidine, 5-formylcytidine, N4-methylcytidine, 5-hydroxymethylcytidine, 1-methyl-pseudoisocytidine, pyrrolo-cytidine, pyrrolo-pseudoisocytidine, 2-thio-cytidine, 2-thio-5-methyl-cytidine, 4-thio-pseudoisocytidine, 4-thio-1-methyl-pseudoisocytidine, 4-thio-1-methyl-1-deaza-pseudoisocytidine, 1-methyl-1-deaza-pseudoisocytidine, zebularine, 5-aza-zebularine, 5-methyl-zebularine, 5-aza-2-thio-zebularine, 2-thio-zebularine, 2-methoxy-cytidine, 2-methoxy-5-methyl-cytidine, 4-methoxy-pseudoisocytidine, and 4-methoxy-1-methyl-pseudoisocytidine; or

the modifications are selected from 2-aminopurine, 2, 6-diaminopurine, 7-deaza-adenine, 7-deaza-8-aza-adenine, 7-deaza-2-aminopurine, 7-deaza-8-aza-2-aminopurine, 7-deaza-2,6-diaminopurine, 7-deaza-8-aza-2,6-diaminopurine, 1-methyladenosine, N6-methyladenosine, N6-isopentenyladenosine, N6-(cis-hydroxyisopentenyl)adenosine, 2-methylthio-N6-(cis-hydroxyisopentenyl) adenosine, N6-glycinylcarbamoyladenosine, N6-threonylcarbamoyladenosine, 2-methylthio-N6-threonyl carbamoyladenosine, N6,N6-dimethyladenosine, 7-methyladenine, 2-methylthio-adenine, and 2-methoxy-adenine; or

the modifications are selected from inosine, 1-methyl-inosine, wyosine, wybutosine, 7-deaza-guanosine, 7-deaza-8-aza-guanosine, 6-thio-guanosine, 6-thio-7-deaza-guanosine, 6-thio-7-deaza-8-aza-guanosine, 7-methyl-guanosine, 6-thio-7-methyl-guanosine, 7-methylinosine, 6-methoxy-guanosine, 1-methylguanosine, N2-methylguanosine, N2,N2-dimethylguanosine, 8-oxo-guanosine, 7-methyl-8-oxo-guanosine, 1-methyl-6-thio-guanosine, N2-methyl-6-thio-guanosine, and N2,N2-dimethyl-6-thio-guanosine; or

the modifications are present on the major groove face, optionally wherein a hydrogen on C-5 of uracil is replaced with a methyl group or a halo group; or

the mmRNA further comprises one or more modifications selected from 5'-O-(1-Thiophosphate)-Adenosine, 5'-O-(1-Thiophosphate)-Cytidine, 5'-O-(1-Thiophosphate)-Guanosine, 5'-O-(1-Thiophosphate)-Uridine and 5'-O-(1-Thiophosphate)-Pseudouridine.

13. The pharmaceutical composition of any one of claims 9 to 12, wherein the pharmaceutical composition further comprises a lipidoid, a liposome, a lipoplex, a lipid nanoparticle, a polymeric nanoparticle, a peptide, a protein, a cell, a nanoparticle mimic, a nanotube, or a conjugate.

14. The pharmaceutical composition of claim 13, wherein the pharmaceutical composition is formulated as a lipid nanoparticle (LNP), a lipoplex, or a liposome, optionally wherein the pharmaceutical composition is formulated as a lipid nanoparticle (LNP).

15. The pharmaceutical composition of claim 14, wherein the LNP comprises:

a molar ratio of about 20-60% ionizable amino lipid, about 5-25% phospholipid, about 25-55% structural lipid, and about 0.5-1.5% PEG lipid;

a molar ratio of about 50% ionizable amino lipid, about 8-12% phospholipid, about 37-40% structural lipid, and about 1-2% PEG lipid;

lipids selected from an ionizable lipid (*e.g.,* an ionizable cationic lipid selected from DLin-DMA, DLin-K-DMA, DLin-KC2-DMA, DLin-MC3-DMA, 98N12-5, and C12-200); a structural lipid (*e.g.,* distearoylphosphatidylcholine (DSPC)); cholesterol, and a polyethyleneglycol (PEG)-lipid (*e.g.,* a PEG-diacylglycerol (DAG), a PEG-dialkyloxypropyl (DAA), a PEG-phospholipid, a PEG-ceramide (Cer), or a mixture thereof, or a PEG-dilauryloxypropyl (C12, a PEG-dimyristyloxypropyl (C14), a PEG-dipalmityloxypropyl (C16), or a PEG-distearyloxypropyl (C18)); 1,2-dioleoyl-3-trimethylammoniumpropane (DOTAP); dioleoylphosphatidylethanolamine (DOPE);

(a) a cationic lipid comprising from 50 mol % to 85 mol % of the total lipid present in the particle; (b) a non-cationic lipid comprising from 13 mol % to 49.5 mol % of the total lipid present in the particle; and (c) a conjugated lipid that inhibits aggregation of particles comprising from 0.5 mol % to 2 mol % of the total lipid present in the particle; or

a lipid selected from SM-102, DLin-DMA, DLin-K-DMA, DLin-KC2-DMA, DLin-MC3-DMA, 98N12-5, and C12-200; a cholesterol; and a PEG-lipid.

16. The pharmaceutical composition of claim 14, wherein the heterologous chimeric protein has an amino acid sequence that has at least about 95%, or at least about 96%, or at least about 97%, or at least about 98%, or at least about 99% sequence identity with an amino acid sequence selected from SEQ ID NOs: 81, 80, and 90-93.

17. The pharmaceutical composition of any one of claims 9 to 16, wherein the heterologous chimeric protein comprises an amino acid sequence that has at least about 96%, or at least about 97%, or at least about 98%, or at least about 99% sequence identity with an amino acid sequence selected from SEQ ID NOs: 81, 80, and 90-93.

18. The pharmaceutical composition of any one of claims 9 to 17, wherein the pharmaceutical composition is formulated for parenteral administration.

19. Use of the pharmaceutical composition of any one of claims 9 to 18 in manufacture of a medicament for treating a cancer, an autoimmune condition, or an inflammatory disorder.