STING AGONISM FOR ANTIGEN SPECIFIC TOLERANCE

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority from U.S. Provisional Patent Application No. 63/566,663, filed March 18, 2024, hereby incorporated by reference in its entirety.

INCORPORATION BY REFERENCE OF SEQUENCE DISCLOSURE

[0002] The Sequence Listing, which is a part of the present disclosure, is submitted concurrently with the specification as a computer readable file. The name of the file containing the Sequence Listing is "70141_SeqListing.xml", which was created on March 13, 2025, and is 5,458,943 bytes in size. The subject matter of the Sequence Listing is incorporated herein in its entirety by reference.

FIELD OF THE DISCLOSURE

[0003] The present invention is directed, in general, to compositions comprising antigens and agents that activate the cGAS-STING pathway and methods of use to induce tolerogenic immune responses to an antigen.

BACKGROUND

[0004] The detection of foreign DNA is a basic mechanism by which the host perceives the presence of pathogens. In mammalian cells, this is largely done by the cyclic GMP–AMP synthase (cGAS)–stimulator of interferon genes (STING) pathway. STING is an endoplasmic reticulum adaptor protein that serves as a signaling hub, receiving input from several pattern recognition receptors, most of which sense ectopic DNA species in the cytosol. In short, cGAS binding to DNA leads to the production of 2′3′ cyclic GMP-AMP (cGAMP), which is a potent activator of STING. In particular, STING ensures the production of type I interferon (IFN) in response to invading DNA viruses, bacterial pathogens, as well as DNA leaking from mitochondria or the nucleus (e.g., in cells exposed to chemotherapy or radiotherapy).

[0005] Due to the production of IFN, the cGAS-STING pathway can provide protection or resistance against infections and cancer; however, improper or overactivation might cause severe inflammatory pathologies, including autoimmunity.

SUMMARY OF THE DISCLOSURE

[0006] The present disclosure demonstrates that activation of cGAS-STING pathway is useful to induce tolerance to specific antigens or allergens.

[0007] The present disclosure describes compositions and methods for inducing antigen specific tolerance comprising administration of agents that activate the cGAS-STING pathway and antigen. It is hypothesized herein that inclusion of an agent that activates the cGAS-STING pathway could lower the doses and/or frequency of administration of antigen-carrier particles required to induce tolerance.

[0008] The present invention provides compositions comprising: (i) one or more antigens, and (ii) one or more agents that activate the cGAS-STING pathway i.e., cGAS-STING activating agent. In various embodiments, the composition comprises the one or more antigen and cGAS-STING activating agent in the same composition. In various embodiments, the composition is an admixture comprising the one or more antigen and cGAS-STING activating agent in different compositions for use in combination. In various embodiments, the one or more antigens are coupled to cGAS-STING activating agents.

[0009] In some embodiments, the antigen is encapsulated in or coupled to apoptotic cells and the cGAS-STING activating agent is not encapsulated in or coupled to apoptotic cells, i.e., the cGAS-STING activating agent is "free" or "free in solution". In some embodiments, the antigen is not encapsulated in or coupled to apoptotic cells, i.e., the antigen is "free" or "free in solution, and the cGAS-STING activating agent is encapsulated in or coupled to apoptotic cells. In various embodiments, the antigens and cGAS-STING activating agent are encapsulated in or coupled to apoptotic cells. In some embodiments, the STING activating agent is encapsulated in apoptotic cells coupled to antigens. In some embodiments, the antigens are encapsulated in or coupled to a first population of apoptotic cells and the cGAS-STING activating agents are encapsulated in or coupled to a second population of apoptotic cells. In various embodiments, the composition comprises the apoptotic cells encapsulated or coupled to one or more antigen and cGAS-STING activating agent in the same composition. In various embodiments, the composition is an admixture comprising apoptotic cells encapsulated or coupled to one or more antigen and apoptotic cells encapsulating or coupled to cGAS-STING activating agent in different compositions for use in combination. In various embodiments, the apoptotic cells are coupled to or encapsulate one or more antigens coupled to cGAS-STING activating agents.

[0010] In some embodiments, the antigens are encapsulated in or coupled to carrier particles and the cGAS-STING activating agent is not encapsulated in or coupled to carrier particles, i.e., the cGAS-STING activating agent is "free" or "free in solution". In some embodiments, the antigens are "free" and the cGAS-STING activating agent is encapsulated in or coupled to carrier particles. In various embodiments, the antigens and cGAS-STING activating agent are

both encapsulated in or coupled to carrier particles. In some embodiments, the antigens are encapsulated in or coupled to a first population of carrier particles and the cGAS-STING activating agents are encapsulated in or coupled to a second population of carrier particles. In various embodiments, the composition comprises the carrier particles encapsulating or coupled to one or more antigen and cGAS-STING activating agent in the same composition. In various embodiments, the composition is an admixture comprising carrier particles encapsulating or coupled to one or more antigen and carrier particles encapsulating or coupled to cGAS-STING activating agent in different compositions for use in combination. In various embodiments, the carrier particles are coupled to or encapsulate one or more antigens coupled to cGAS-STING activating agents.

[0011] In various embodiments, the antigen comprises at least a portion of an autoimmune antigen, allergen, transplant antigen, enzyme replacement therapy, therapeutic protein, inhaled substance, injected substance, viral protein, vector for gene therapy, or transgene coded by the gene therapy. In various embodiments, the antigen is post-translationally modified.

[0012] In some embodiments, the antigen comprises at least a portion of myelin basic protein, acetylcholine receptor, endogenous antigen, myelin oligodendrocyte glycoprotein, pancreatic β-cell antigens, insulin, proinsulin, islet-specific glucose-6-phophatase catalytic subunit-related protein (IGRP), glutamic acid decarboxylase (GAD), zinc transporter 8 (ZnT8), collagen type 11, human cartilage gp39, gp130-RAPS, proteolipid protein, fibrillarin, small nucleolar protein, myelin associated glycoprotein, αβ-crystallin, RAS guanyl-releasing protein 2, GDP-l-fucose synthase (TSTA3), β-synuclein, 2',3'-cyclic nucleotide 3'-phosphodiesterase, myelin oligodendrocyte basic protein (MOBP), oligodendrocyte-specific protein (OSP), transaldolase H, S100 beta, contactin 2/TAG-1, KIR4.1, anoctamin 2, thyroid stimulating factor receptor, IGF-1R, thyroglobulin, thyroid peroxidase, sodium-iodide symporter, cytosolic 5'-nucleotidase 1A (cN1A), galactose-deficient IgA1 (Gd-IgA1), αMyHC, βMyHC, HSP60, synthetase Jo-1, proteinase 3 (PR3), 21-hydroxylase (21OH), Ro/SSA, La/SSB, 17-α-hydroxylase, cholesterol side-chain cleavage enzyme, cytochrome P450 2D6 (CYP2D6), phospholipase A2 receptor (PLA2R),GPIIb, GPIIIa, GABA-A receptor-associated protein (GABARAP), gephyrun, amphiphysin, ADAMTS13, myeloperoxidase, trichohyalin, tyrosinase-related protein 2, no-ncollagenous (NC1) domain of the a3 chain of type IV collagen (a3(IV)NC1), cardiolipin, β2 glycoprotein-I (β2GPI), C1-INH, actin, CYP11A1, laminin 332, β-4-integrin, connexin 26, cell density-enhanced protein tyrosine phosphatase-1 (DEP-1/CD148), and reovirus III major core protein lambda 1, cardiac myosin, GM1, GQ1b, Gd1a, collagen XVII,

extracellular matrix protein 1 (ECM1), peptidyl arginine deiminase-4, muscle specific kinase (MuSK), low-density lipoprotein receptor-related protein 4, heat shock proteins (Hsp 90, HSP 70, HSP60, HSP40), alpha-synuclein, parkin, PINK1, LRRK2, platelet derived growth factor receptor beta (PDGFRB), Smith antigen, alpha-fodrin, rhodopsin, gamma-enolase, glutathione-S-transferase, amyloid beta (Aβ), tau, and amyloid precursor protein (APP), dopamine, hydroxytryptamine, glutamate, S100b, glial fibrillary acidic protein (GFAP), rabaptin 5, receptor for advanced glycosylation end products (RAGE), angiotensin 2 type 1 receptor (AT1R), aldolase, ATP synthase, H+K+-ATPase, F-actin, formimidoyltransferase cyclodeaminase, hybrid insulin peptides, C-peptide, histones, glycoprotein gp70, vimentin, fibrinogen, collagen type II, α-enolase, clusterin, PAD2, PAD4, pyruvate dehydrogenase dehydrolipoamide acetyltransferase (PDC-E2), hair follicle antigen, aqua porin 4, Desmoglein 1, Desmoglein 3, BP180 (BPAG2), BP230, nicotinic acetylcholine receptor, orexin-1, orexin-2, protein O-mannosyltransferase 1 (POMT1), Tribbles homologue 2 (TRIB2), regulatory factor X4 (RFX4), hemagglutinin (HA), neuraminidase (NA), influenza RNA-dependent RNA polymerase subunit 1 (PB1), or influenza nucleoprotein (NP), tyrosinase, melan-A (MLANA), premelanosome protein (PMEL), α-elonase, tenascin, fibrinogen, aggrecan, vimentin, gliadin, α-gliadin, and human tropomyosin isoform 5, Bahia grass pollen (BaGP), peach allergen Pru p 3, alpha s 1-Casein Milk allergen, peanut allergen (Ara h 1, Ara h 2, Ara h 3, Ara h 4, Ara h 5, Ara h6, Ara h 7, Ara h 8, Ara h 9, Ara h 10, Ara h 11, Ara h 12, Ara h 13, Ara h 14, Ara h15, Ara h 16, Ara h 17, and Ara h 18), Apig1 celery allergen, Ber e1 Brazil nut allergen, β-Lactoglobulin Milk allergen, Bovine serum albumin, Cor a 1.04 Hazelnut allergen, Ovalbumin Egg allergen, Cor a 8, Cor a 14, Cor a 11, Cor a 9, Cor a 2, Cor a 12, Cor a 13, Cor a 15, Jug r 3, Jug r 8, Jug r 1, Jug r 2, Jug r 6, Jug r 4, Jug r 5, Jug r 7, Jug n 1, Jug n 2, Jug n 4, Car i 1, Car i 2, Car i 4, Ana o 3, Ana o 1, Ana o2, Pis v 1, Pis v 3, Pis v 2, Pis v 5Pru du 3, Pru du 6, Pru du 1, Pru du 4, Ber e 2, Coc n 1, Mac I 1, Mac I 2, Gly m 4, Gly m 7c, Gly m 8a,c, Gly m KTIc, Gly m BBIc, Gly m 2, Gly m 3, Gly m Bd 30k, Bet v 1, Japanese cedar pollen (Cry j 1, Cry j 2, Cry j 3, Cry j 4, Cry j IFR, Cry j Chitinase, Cry j Asp, Cry j LTP, and/or Cry j CPA9), Aldurazyme (laronidase), Cerezyme (imiglucerase), Elelyso (taliglucerase alfa), Vpriv (velaglucerase alfa), Fabrazyme (agalsidase beta), Replagal (agalsidase alfa), Myozyme/Lumizyme (alglucosidase alfa), Naglazyme (galsulfase), Elaprase (idursulfase), Brineura (cerliponase alfa), Kanuma (sebelipase alfa), Strensiq (asfotase alfa), Coagadex (coagulation factor X), Hemlibra (emicizumab), Advate, Eloctate, BeneFIX, Idelvion (albutrepenonacog alfa), Crysvita (burosumab), Nplate (romiplostim), Prolastin/Aralast/Glassia (alpha-1 antitrypsin), Thyrogen (thyrotropin alfa), Pegunigalsidase alfa (PRX-102), DNL310, ORYZON-ERT, Valoctocogene roxaparvovec (Roctavian), SPK-9001 (fidanacogene

elaparvovec), AVR-RD-01, AXO-AAV-GM1 and AXO-AAV-GM2, Val-1221, VEGF-B, M6P replacement therapy. In various embodiments, the antigens are selected from the peptides or proteins set out in Figure 5, Figure 6, Figure 7, Figure 8, or Figure 9.

[0013] In further embodiments, the antigen comprises an autoimmune antigen, an antigen expressed on a tissue to be transplanted into a subject, an enzyme, or an allergen. In non-limiting embodiments, the antigen comprises, for example, myelin basic protein, acetylcholine receptor, endogenous antigen, myelin oligodendrocyte glycoprotein, pancreatic beta-cell antigen, insulin, proinsulin, islet-specific glucose-6-phophatase catalytic subunit-related protein (IGRP), glutamic acid decarboxylase 65 (GAD65), collagen type 11, human cartilage gp39, gp130-RAPS, proteolipid protein, fibrillarin, small nucleolar protein, IGF-1R, thyroid stimulating factor receptor, thyroglobulin, thyroid peroxidase, sodium-iodide symporter, cytosolic 5'-nucleotidase 1A (cN1A), galactose-deficient IgA1 (Gd-IgA1), αMyHC, βMyHC, HSP60, synthetase Jo-1, proteinase 3 (PR3), 21-hydroxylase (21OH), Ro/SSA, La/SSB, 17-α-hydroxylase, cholesterol side-chain cleavage enzyme, cytochrome P450 2D6 (CYP2D6), phospholipase A2 receptor (PLA2R),GPIIb, GPIIIa, GABA-A receptor-associated protein (GABARAP), gephyrun, amphiphysin, ADAMTS13, myeloperoxidase, trichohyalin, tyrosinase-related protein 2, no-ncollagenous (NC1) domain of the a3 chain of type IV collagen (a3(IV)NC1), cardiolipin, β2 glycoprotein-I (β2GPI), C1-INH, actin, CYP11A1, laminin 332, β-4-integrin, connexin 26, cell density-enhanced protein tyrosine phosphatase-1 (DEP-1/CD148), and reovirus III major core protein lambda 1, cardiac myosin, GM1, GQ1b, Gd1a, collagen XVII, extracellular matrix protein 1 (ECM1), peptidyl arginine deiminase-4, muscle specific kinase (MuSK), low-density lipoprotein receptor-related protein 4, heat shock proteins (Hsp 90, HSP 70, HSP60, HSP40), alpha-synuclein, parkin, PINK1, LRRK2, platelet derived growth factor receptor beta (PDGFRB), Smith antigen, alpha-fodrin, rhodopsin, gamma-enolase, glutathione-S-transferase, amyloid beta (Aβ), tau, amyloid precursor protein (APP), dopamine, hydroxytryptamine, glutamate, S100b, glial fibrillary acidic protein (GFAP), rabaptin 5, receptor for advanced glycosylation end products (RAGE), angiotensin 2 type 1 receptor (AT1R), aldolase, ATP synthase, TAR DNA-binding protein 43 (TDP-43), H+K+-ATPase, formimidoyltransferase cyclodeaminase, hybrid insulin peptides, C-peptide, histones, vimentin, fibrinogen, collagen type II, clusterin, PAD2, PAD4, glycoprotein gp70, pyruvate dehydrogenase dehydrolipoamide acetyltransferase (PDC-E2), hair follicle antigen, aqua porin 4, Desmoglein 1, Desmoglein 3, BP180, BP230, nicotinic acetylcholine receptor, orexin-1 (also known as hypocretin (HCRT), orexin-2, protein O-mannosyltransferase 1 (POMT1), Tribbles homologue 2

(TRIB2), regulatory factor X4 (RFX4), hemagglutinin (HA), neuraminidase (NA), influenza RNA-dependent RNA polymerase subunit 1 (PB1), or influenza nucleoprotein (NP), tyrosinase, melan-A (MLANA), premelanosome protein (PMEL), α-elonase, tenascin, fibrinogen, aggrecan, vimentin, gliadin, α-gliadin, and human tropomyosin isoform 5, Bahia grass pollen (BaGP), peach allergen Pru p 3, alpha s 1-Casein Milk allergen, peanut allergen (Ara h 1, Ara h 2, Ara h 3, Ara h 4, Ara h 5, Ara h6, Ara h 7, Ara h 8, Ara h 9, Ara h 10, Ara h 11, Ara h 12, Ara h 13, Ara h 14, Ara h15, Ara h 16, Ara h 17, and Ara h 18), Apig1 celery allergen, Bere1 Brazil nut allergen, B-Lactoglobulin Milk allergen, Bovine serum albumin, Cor a 1.04 Hazelnut allergen, Ovalbumin Egg allergen, Cor a 8, Cor a 14, Cor a 11, Cor a 9, Cor a 2, Cor a 12, Cor a 13, Cor a 15, Jug r 3, Jug r 8, Jug r 1, Jug r 2, Jug r 6, Jug r 4, Jug r 5, Jug r 7, Jug n 1, Jug n 2, Jug n 4, Car i 1, Car i 2, Car i 4, Ana o 3, Ana o 1, Ana o2, Pis v 1, Pis v 3, Pis v 2, Pis v 5Pru du 3, Pru du 6, Pru du 1, Pru du 4, Ber e 2, Coc n 1, Mac I 1, Mac I 2, Gly m 4, Gly m 7c, Gly m 8a,c, Gly m KTIc, Gly m BBIc, Gly m 2, Gly m 3, Gly m Bd 30k, Bet v 1, Japanese cedar pollen (Cry j 1, Cry j 2, Cry j 3, Cry j 4, Cry j IFR, Cry j Chitinase, Cry j Asp, Cry j LTP, and/or Cry j CPA9).

[0014] In a further embodiment, the antigen comprises proteinaceous therapies used in enzyme or coagulation factor replacement such as Aldurazyme® (laronidase), Cerezyme® (imiglucerase), Elelyso® (taliglucerase alfa), Vpriv® (velaglucerase alfa), Fabrazyme® (agalsidase beta), Replagal® (agalsidase alfa), Myozyme®/Lumizyme® (alglucosidase alfa), Naglazyme® (galsulfase), Elaprase® (idursulfase), Brineura® (cerliponase alfa), Kanuma® (sebelipase alfa), Strensiq (asfotase alfa), Coagadex® (coagulation factor X), Hemlibra® (emicizumab), Advate®, Eloctate®, BeneFIX,® Idelvion® (albutrepenonacog alfa), Crysvita® (burosumab), Nplate® (romiplostim), Prolastin®/Aralast®/Glassia® (alpha-1 antitrypsin), Thyrogen® (thyrotropin alfa), Pegunigalsidase alfa (PRX-102), DNL310, ORYZON-ERT, Valoctocogene roxaparvovec (Roctavian®), SPK-9001 (fidanacogene elaparvovec), AVR-RD-01, AXO-AAV-GM1 and AXO-AAV-GM2, Val-1221, VEGF-B, or M6P Replacement Therapy.

[0015] In a further embodiment, the antigen comprises vectors for gene therapy selected from the group comprising adenovirus, AAV-1, AAV-2, AAV-3, AAV-4, AAV-5, AAV-6, AAV-7, AAV-8, AAV-9, AAV-10, AAV-12, AAV capsid protein (VP-1, VP-2, or VP-3), Anc80, herpes simplex virus, hepatitis B virus, lentivirus, retrovirus, alphavirus, flavivirus, rhabdovirus, measles virus, Newcastle disease virus, Coxsackievirus, transfusion transmitted viruses, anellovirus, human papilloma virus, poxvirus, vaccinia virus, modified Ankara virus, vesicular stomatitis virus, picornavirus, tobacco mosaic virus, cowpea mosaic virus, cowpea chlorotic mottle virus, physalis mosaic virus, Red clover necrotic mosaic virus, potato virus x, comovirus, chicken

anemia virus or cucumber mosaic virus. In various embodiments, the virus is an oncolytic virus. In various embodiments the virus is a chimeric virus, a synthetic virus, a mosaic virus, or a pseudotyped virus.

[0016] In further embodiments, the antigen comprises one or more antigenic epitopes. In a further embodiment, the antigen or epitope is associated with an allergy, an autoimmune disease, disease requiring gene therapy, protein replacement therapy, or enzyme replacement therapy, lysosomal storage disease, or an inflammatory disease or disorder. In some embodiments, the antigen is associated with achalasia, Addison's disease, adult Still's disease, agammaglobulinemia, alopecia areata, Alzheimer's disease, amyloidosis, amyotrophic lateral sclerosis, ankylosing spondylitis, anti-GBM/anti-TBM nephritis, antiphospholipid syndrome, autoimmune angioedema, autoimmune dysautonomia, autoimmune encephalomyelitis, autoimmune hepatitis, autoimmune inner ear disease (AIED), autoimmune myocarditis, autoimmune oophoritis, autoimmune orchitis, autoimmune pancreatitis, autoimmune retinopathy, autoimmune urticaria, axonal & neuronal neuropathy (AMAN), Baló disease, Behcet's disease, benign mucosal pemphigoid, bullous pemphigoid, Castleman disease (CD), celiac disease, Chagas disease, chronic inflammatory demyelinating polyneuropathy (CIDP), chronic recurrent multifocal osteomyelitis (CRMO), Churg-Strauss syndrome (CSS), eosinophilic granulomatosis (EGPA), cicatricial pemphigoid, Cogan's syndrome, cold agglutinin disease, congenital heart block, Coxsackie myocarditis, CREST syndrome, Crohn's disease, dermatitis herpetiformis, dermatomyositis, Devic's disease (neuromyelitis optica), discoid lupus, Dressler's syndrome, endometriosis, eosinophilic esophagitis (EoE), eosinophilic fasciitis, epilepsy, erythema nodosum, essential mixed cryoglobulinemia, Evans syndrome, fibromyalgia, fibrosing alveolitis, giant cell arteritis (temporal arteritis), giant cell myocarditis, glaucoma, glomerulonephritis, Goodpasture's syndrome, granulomatosis with polyangiitis, Graves' disease, Guillain-Barre syndrome, Hashimoto's thyroiditis, hemolytic anemia, Henoch-Schonlein purpura (HSP), herpes gestationis, pemphigoid gestationis (PG), hidradenitis suppurativa (HS) (acne inversa), hypogammalglobulinemia, IgA nephropathy, idiopathic thrombocytopenic purpura (ITP), inclusion body myositis (IBM), anti-melanoma differentiation-associated gene 5 (MDA5 myositis), inflammatory bowel disease, interstitial cystitis (IC), juvenile arthritis, juvenile diabetes (type 1 diabetes), juvenile myositis (JM), Kawasaki disease, latent autoimmune diabetes od adults (LADA), Lambert-Eaton syndrome, leukocytoclastic vasculitis, lichen planus, lichen sclerosus, ligneous conjunctivitis, linear IgA disease (LAD), lupus/systemic lupus, Lyme disease chronic, membranous nephropathy, Meniere's disease, microscopic polyangiitis (MPA), mixed connective tissue disease (MCTD), myelin oligodendrocyte glycoprotein associated disease

(MOGAD), Mooren's ulcer, Mucha-Habermann disease or PLEVA, multifocal motor neuropathy (MMN) or MMNCB, multiple sclerosis, myasthenia gravis, myositis, narcolepsy, neonatal lupus, neutropenia, ocular cicatricial pemphigoid, palindromic rheumatism (PR), pediatric acute liver failure (PALF), PANDAS, paraneoplastic cerebellar degeneration (PCD), Parkinson's disease, paroxysmal nocturnal hemoglobinuria (PNH), Parry Romberg syndrome, pars planitis (peripheral uveitis), parsonage-turner syndrome, pemphigus foliaceous, pemphigus vulgaris, peripheral neuropathy, perivenous encephalomyelitis, pernicious anemia (PA), POEMS syndrome, polyarteritis nodosa, polyglandular syndromes type I, II, III, polymyalgia rheumatica, polymyositis, post-myocardial infarction syndrome, post-pericardiotomy syndrome, primary biliary cholangitis, primary sclerosing cholangitis, progesterone dermatitis, psoriasis, psoriatic arthritis, pure red cell aplasia (PRCA), pyoderma gangrenosum, Raynaud's phenomenon, reactive arthritis, reflex sympathetic dystrophy, relapsing polychondritis, restless legs syndrome (RLS), retroperitoneal fibrosis, rheumatic fever, rheumatoid arthritis, sarcoidosis, Schmidt syndrome, scleritis, scleroderma, Sjögren's syndrome, sperm & testicular autoimmunity, stiff person syndrome (SPS), sub-acute bacterial endocarditis (SBE), Susac's syndrome, sympathetic ophthalmia (SO), Takayasu's arteritis, temporal arteritis/giant cell arteritis, thrombotic thrombocytopenic purpura (TTP), thyroid eye disease (TED), Tolosa-Hunt syndrome (THS), transverse myelitis, ulcerative colitis, undifferentiated connective tissue disease (UCTD), uveitis, vasculitis, vitiligo, PALF/ALF, Rasmussen's encephalitis, Lewy body dementia, encephalitis, Vogt-Koyanagi-Harada disease, a mucopolysaccharide storage disorder, gangliosidosis, alkaline hypophosphatasia, cholesterol ester storage disease, hyperuricemia, growth hormone deficiency, renal anemia, Gaucher's disease, Fabry's disease, Hurler's disease, Hunter's disease, Maroteaux-Lamy disease, hemophilia A, hemophilia B, von Willebrand disease, venous thrombosis, purpura fulminans, Mucopolysaccaridosis VI, Pompe disease, inherited retinal diseases (e.g., Leber congenital amaurosis, RPE65 mutation-associated retinal dystrophy), spinal muscular atrophy (SMA), inherited blood disorders, sickle cell disease, β-thalassemia, severe combined immunodeficiency (SCID), ADA-SCID (adenosine deaminase deficiency SCID), lipoprotein lipase deficiency, neurodegenerative diseases, Genetic Disorders, cystic fibrosis, Duchenne Muscular Dystrophy (DMD), Cardiomyopathies, Hunter Syndrome (MPS II), Mucopolysaccharidosis, Metabolic Disorders, Phenylketonuria (PKU), Crigler-Najjar syndrome type 1, methylmalonic acidemia, propionic acidemia, ornithine transcarbamylase deficiency, or glycogen storage disease type 1a, pediatric autoimmune neuropsychiatric disorders.

[0017] In various embodiments, the cGAS-STING activating agent triggers activation of one or more steps of the cGAS-STING pathway. In various embodiments, the cGAS-STING agent triggers cGAS catalytic activity, STING protein activation (e.g., confirmational changes, STING protein oligomerization, liberation from anchoring factors (such as STIM1), interaction with trafficking factors (for example, SEC24/23, STEEP) incorporation into coatomer protein complex II (COPII) vesicles, recruitment of TANK-binding kinase 1 (TBK1), TBK1 autophosphorylation, STING phosphorylation, recruitment of interferon regulatory factor 3 (IRF3), phosphorylation of IRF3, dimerization and translocation of IRF3 to the nucleus, expression of type 1 interferons (interferon alpha, interferon beta), interferon-stimulated genes (ISGs). In various embodiments, the cGAS-STING agent triggers LC3 associated phagocytosis, mitochondrial dysfunction, inhibition of transcription factor A mitochondrial (TFAM) inhibitor, mitochondrial DNA release (i.e. through BAX/BAF micropores, via voltage- dependent anion channel (VDAC) pores, or via mitochondrial permeability transition pore (MPTP)), depression of retroelements, DNA damage or replication stress, DNA leakage from mitochondria or nucleus, chromatin herniations, accumulation of cytoplasmic chromatin fragments (CCFs), or triggers genomic instability causing nuclear DNA to be encapsulated in micronuclei after mitosis, or rupture of the aberrant micro- organelle membrane.

[0018] In various embodiments, the cGAS-STING activating agent antagonizes STING pathway inhibitors. In various embodiments, STING pathway inhibitors include COPI vesicles, STING-SURF4 interactions, TREX, BAX/BAK, TFAM, VDAC1/VDAC3, 1ENPP1.

[0019] In various embodiments, the cGAS-STING activating agent can be natural or synthetic. In various embodiments, the cGAS-STING activating agent includes, cyclic dinucleotides, mitochondrial or nuclear DNA, agents inducing ER stress conditions, bacterial or viral components, or therapies that activate STING (e.g., ionizing radiation, chemotherapeutic drugs like cisplatin or etoposide, hypomethylating agents like decitabine). In various embodiments, the cGAS-STING activating agent includes, but is not limited to ectonucleotide pyrophosphatase/phosphodiesterase 1ENPP1 inhibitors (e.g., MV-626, SR-8314, SR-8291), bacterial vectors (e.g.,SYNB1891, STACT-TREX-1), cyclic dinucleotide monophosphates (CDN) (e.g. 2'3'-cGAMP, 3'3'cGAMP, c-di-AMP, c-di-GMP), CDN derivatives or analogs (e.g., 3'3'-cyclic AIMP, ML RR-CDA, 3'3'-cCAMP, ADU-S100 (2'3'-c-di-AM(PS)2 (Rp,Rp)), BI-STING, BMS-986301, GSK532, JNJ-4412, MK-1454, SB11285), non-CDN small molecules (ALG-031048, E7766, JNJ-6196, MK-2118, MSA-1, MSA-2, SNX281, SR-717, TAK676, TT1-10001), flavonoids and xanthones (flavone acetic acid (FAA), 5,6-dimethylxanthenone-4-acetic acid

(DMXAA), 10-carboxymethyl-9-acridanone (CMA), α-mangostin), other STING pathway activators (G10, dispiro diketopiperzine (DSDP), C11, diamidobenzimidazole (ABMZI), benzamide 20 BNBC), antibody-drug conjugates (XMT-2056, CRD-5500), GSK3745417, or exoSTING.

[0020] In some embodiments, the carrier particles comprise a liposome, lipid nanoparticle, polymersomes, micelles, polymeric nanoparticles, manganese ($Mn2^+$) based nanoparticles, acid-ionizable iron nanoadjuvant (INOP), mesoporus silica, metal-organic frameworks (MOFs), lipid nanodiscs, supramolecular nanoparticles, extracellular vesicles, or sono-driven nanoparticles. In a further embodiment, the carrier particles encapsulating or coupled to one or more antigens comprise a liposome, lipid nanoparticle, polymersomes, micelles, polymeric nanoparticles, manganese ($Mn2^+$) based nanoparticles, acid-ionizable iron nanoadjuvant (INOP), mesoporus silica, metal-organic frameworks (MOFs), lipid nanodiscs, supramolecular nanoparticles, extracellular vesicles, sono-driven nanoparticles.In a further embodiment, the carrier particles encapsulating or coupled to cGAS-STING activating agents comprise a liposome, lipid nanoparticle, polymersomes, micelles, polymeric nanoparticles, manganese ($Mn2^+$) based nanoparticles, acid-ionizable iron nanoadjuvant (INOP), mesoporus silica, metal-organic frameworks (MOFs), lipid nanodiscs, supramolecular nanoparticles, extracellular vesicles, sono-driven nanoparticles.

[0021] In some embodiments, the carrier particles comprise a lipid nanoparticle (LNP). In some embodiments, the lipids comprised within the LNP are selected from the group consisting of an anionic or cationic ionizable lipid, helper lipid, cholesterol, and PEG-lipids. In some embodiments, the lipids are selected from the group consisting of 1,2-di-O-octadecenyl-3-trimethylammonium-propane (DOTMA), 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE), 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP), dimethyldioctadecylammonium bromide (DDAB), 2,3-dioleyloxy-N-[2-(sperminecarboxamido)ethyl]-N,N-dimethyl-1-propanaminium trifluoroacetate (DOSPA), 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate (DLin-MC3-DMA; MC3), (2S)-2,5-bis(3-aminopropylamino)-N-[2-(dioctadecylamino)acetyl]pentanamide (DOGS; Transfectam), N1-[2-((1S)-1-[(3-aminopropyl)amino]-4-[di(3-aminopropyl)amino]butylcarboxamido)ethyl]-3,4-di[oleyloxy]-benzamide (MVL5), 3β-[N-(N′,N′-dimethylaminoethane)-carbamoyl]cholesterol (DC-Cholesterol), N4-cholesteryl-spermine (GL67), Di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), Heptadecan-9-yl 8-((2-

hydroxyethyl)(8-(nonyloxy)-8-oxooctyl)amino)octanoate (Lipid 5), Heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate (Lipid H (SM-102)), ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315), 1,1′-((2-(4-(2-((2-(bis(2-hydroxydodecyl)amino)ethyl)(2-hydroxydodecyl)amino)ethyl) piperazin-1-yl)ethyl)azanediyl) bis(dodecan-2-ol) (C12-200), Tetrakis (8-methylnonyl) 3,3′,3″,3‴-(((methylazanediyl)bis(propane-3,1 diyl))bis(azanetriyl)) tetrapropionate (306Oi10), 3,6-bis(4-(bis(2-hydroxydodecyl)amino)butyl) piperazine-2,5-dione (cKK-E12), (((3,6-dioxopiperazine-2,5-diyl)bis(butane-4,1-diyl))bis(azanetriyl))tetrakis(ethane-2,1-diyl) (9Z,9′Z,9″Z,9‴Z,12Z,12′Z,12″Z,12‴Z)- tetrakis(octadeca-9,12-dienoate) (OF-Deg-Lin), Ethylphosphatidylcholine (ePC), 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), Cholesterol, β-sitosterol, 1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 (PEG2000-DMG), 1,2-distearoyl-rac-glycero-3-methoxypolyethylene glycol-2000 (PEG2000-DSG), DODAP (1,2-dioleoyl-3-dimethylammonium-propane), DODMA (1,2-dioleoyl-3-dimethylammonium-propane), 1,2-dioleoyl-sn-glycero-3-phosphate (18PA), 1,2-dioleoyl-sn-glycero-3-phospho-l-serine (DOPS), Phosphatidic Acid (PA) derivatives, Cardiolipin, 1,2-Dioleoyl-sn-glycero-3-phosphate (DOPA), PEG2000-DSPE (1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000]), PEG2000-DOPE (1,2-dioleoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000]). In some embodiments, lipids comprising the LNP are apoptosis inducing and selected from the group consisting of phosphatidylserine, lysophosphatidylcholine, ceramide, oxidized phospholipids, prostaglandins. In various embodiments, the LNP encapsulates or is complexed to RNA, mRNA, circular RNA, or DNA encoding one or more antigens. In some embodiments, the carrier particles comprise a lipid nanoparticle (LNP) encapsulating or complexed to (i) RNA encoding one or more antigens and (ii) one or more cGAS-STING activating agents. In some embodiments, the lipid nanoparticles further comprise one or more immunomodulatory agents. In some embodiments, the immunomodulatory agent is selected from the group consisting of immunosuppressive agents, cytokines, chemokines, immunostimulants, or immune cell function modulators. In some embodiments, the immunomodulatory agent is selected from the group consisting of mTOR inhibitors, glucocorticoids, vitamins and vitamin derivatives, calcineurin inhibitors, nuclear factor kappa B inhibitors, kynurenine, aryl hydrocarbon receptor agonists, glycan and glycan binding proteins, apoptotic signaling pathway agonists, TLR agonists, inhibitory receptor activating agents, T-cell modulators, immunological synapse modulators, or Janus kinase inhibitors. In various embodiments, the immunomodulatory agents are selected from the group consisting of dexamethasone, rapamycin, cyclosporine A, FK506, ITE,

andrographolide, tofacitinib, rosiglitazone, iloprost, IL-10, PD-1, PD-L1/L2, IL-2, TGF-β, TGF-β-signaling agonist, GM-CSF, IFN-β, IL-35, IL-27, IL-4, hepatocyte growth factor, Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) agonist, vitamin D, retinoic acid. In some embodiments, the immunomodulators are encoded by mRNA.

[0022] In a further embodiment, the carrier particles have a positive zeta potential. In various embodiments, the zeta potential of the particles is from about +100 mV to about 0 mV, from about +100 mV to about +25 mV, from about +100 to about +30 mV, from about +80 mV to about +30 mV, from about +75 mV to about +30 mV, from about +70 mV to about +30 mV, from about +75 to about +35 mV, from about +70 to about +25 mV, from about +60 mV to about +30 mV, from about +60 mV to about +35 mV, or from about +50 mV to about +30 mV. In various embodiments, the zeta potential is about +25 mV, +30 mV, +35 mV, +40 mV, +45 mV, +50 mV, +55 mV, +60 mV, +65 mV, +70 mV, +75 mV, +80 mV, +85 mV, +90 mV, +95 mV or +100 mV, including all values and ranges therein. In various embodiments, the carrier particles have a zeta potential of between +30 mV to +80 mV. In various embodiments, the carrier particles have a zeta potential of between +30 mV to +60 mV.

[0023] In some embodiments, the carrier particles comprise a polymer selected from the group consisting of polyglycolic acid (PGA), polylactic acid (PLA), polysebacic acid (PSA), poly(lactic-co-glycolic) (PLGA), poly(lactic-co-sebacic) acid (PLSA), poly(glycolic-co-sebacic) acid (PGSA), polypropylene sulfide, poly(caprolactone), chitosan, a polysaccharide, or a lipid, polystyrene, diamond, a liposome, PEG, cyclodextran, a lipid or a metal such as iron (Fe), zinc (Zn), cadmium (Cd), gold (Au), silver (Ag), or combinations thereof.

[0024] In various embodiments, the polymer is a co-polymer. In various embodiments, the co-polymer has varying molar ratios of constituent polymers. In various embodiments, the molar ratio is 25:75, 30:70, 35:65, 40:60, 45:55, 50:50, 55:45, 60:40, 65:35, 70:30, 75:25, 80:20, 81:19, 82:18, 83:17, 84:16, 85:15, 86:14, 87:13, 88:12, 89:11, 90:10, 91:9, 92:8, 93:7, 94:6, 95:5, 96:4, 97:3, 98:2, 99:1, or 100:0, including all values and ranges that lie between these values.

[0025] In various embodiments, the carrier particles comprise poly (lactic-co-glycolic acid) (PLGA). In various embodiments, the particle comprises about 50:50, about 80:20 to about 100:0 polylactic acid: polyglycolic acid or from about 50:50, about 80:20 to about 100:0 polyglycolic acid: polylactic acid. In various embodiments, the particle comprises 50:50 polylactic acid: polyglycolic acid. In various embodiments, the particle comprises polylactic acid: polyglycolic acid from about 25:75, 30:70, 35:65, 40:60, 45:55, 50:50, 55:45, 60:40, 65:35,

70:30, 75:25, 80:20, 81:19, 82:18, 83:17, 84:16, 85:15, 86:14, 87:13, 88:12, 89:11, 90:10, 91:9, 92:8, 93:7, 94:6, 95:5, 96:4, 97:3, 98:2, 99:1, or 100:0, including all values and ranges that lie in between these values.

[0026] In various embodiments, the carrier particles have a negative zeta potential. In various embodiments, the zeta potential of the particles is from about -100 mV to about 0 mV, from about -100 mV to about -25 mV, from about -100 to about -30 mV, from about -80 mV to about -30 mV, from about -75 mV to about -30 mV, from about -70 mV to about -30 mV, from about -75 to about -35 mV, from about -70 to about -25 mV, from about -60 mV to about -30 mV, from about -60 mV to about -35 mV, or from about -50 mV to about -30 mV. In various embodiments, the zeta potential is about -1 mV, -5 mV, -10 mV, -15 mV, -25 mV, -30 mV, -35 mV, -40 mV, -45 mV, -50 mV, -55 mV, -60 mV, -65 mV, -70 mV, -75 mV, -80 mV, -85 mV, -90 mV, -95 mV or -100 mV, including all values and ranges therein. In various embodiments, the carrier particles have a negative zeta potential of between -30 mV to -80 mV. In various embodiments, the carrier particles have a negative zeta potential of between -30 mV to -60 mV. In various embodiments, the carrier particles have a negative zeta potential of between -40 mV to -90 mV. In various embodiments, the negative zeta potential is achieved by surface functionalization of the carrier particle. In various embodiments, the surface functionalization is carboxylation.

[0027] In various embodiments, the size, or diameter, of carrier particles is between 0.05 µm to about 10 µm. In various embodiments, the diameter of carrier particles is between 0.1 µm to about 10 µm. In various embodiments, the diameter of carrier particles is between 0.1 µm to about 5 µm. In various embodiments, the diameter of carrier particles is between 0.1 µm to about 3 µm. In various embodiments, the diameter of carrier particles is between 0.3 µm to about 5 µm. In various embodiments, the diameter of carrier particles is about 0.3 µm to about 3 µm. In various embodiments, the diameter of carrier particles is between about 0.3 µm to about 1 µm. In various embodiments, the diameter of carrier particles is between about 0.4 µm to about 1 µm. In various embodiments, the carrier particles have a diameter of about 100 to 10000 nm, about 100 to 5000 nm, about 100 to 3000 nm, about 100 to 2000 nm, about 100 to 1500 nm, about 300 to 5000 nm, about 300 to 3000 nm, about 300 to 1000 nm, about 300 to 800 nm, about 400 to 800 nm, or about 200 to 700 nm. In various embodiments, the carrier particles have a diameter of about 50 nm, 100 nm, 200 nm, 300 nm, 400 nm, 500 nm, 600 nm, 700 nm, 800 nm, 900 nm, 1000 nm, 1100 nm, 1200 nm, 1300 nm, 1400 nm, 1500 nm, or 2000 nm, including all values and ranges therein. In various embodiments, the diameter of the carrier

particle is between 400 nm to 800 nm. In various embodiments, the diameter of the carrier particle is between 350 nm to 800 nm.

[0028] In various embodiments, the carrier particles have a homogenous size distribution. In various embodiments, the carrier particles have a homogenous size distribution wherein at least 90% of the particles have a diameter of between 0.05 μm and about 10 μm, between 0.1 μm and about 10 μm, 0.1 μm and about 5 μm, 0.1 μm and about 3 μm, 0.3 μm and about 5 μm, 0.3 μm to about 3 μm including all values and ranges therein. In various embodiments, the carrier particles have a homogenous size distribution wherein at least 90% of the particles have a diameter of about 100 to 10000 nm, about 100 to 5000 nm, about 100 to 3000 nm, about 100 to 2000nm, about 300 to 5000 nm, about 300 to 3000 nm, about 300 to 1000 nm, about 300 to 800 nm, about 400 to 800 nm, or about 200 to 700 nm including all values and ranges therein. In various embodiments, the carrier particles have a diameter of about 50 nm, 100 nm, 200 nm, 300 nm, 400 nm, 500 nm, 600 nm, 700 nm, 800 nm, 900 nm, 1000 nm, 1100 nm, 1200 nm, 1300 nm, 1400 nm, 1500 nm, or 2000 nm including all values and ranges therein. In various embodiments, the carrier particles have a homogenous size distribution wherein at least 50% of the particles have a diameter of between about 0.05 μm and about 10 μm, about 0.1 μm and about 10 μm, about 0.1 μm and about 5 μm, about 0.1 μm and about 3 μm, about 0.3 μm and about 5 μm, and about 0.3 μm and about 3 μm including all values and ranges therein. In various embodiments, the particles have a homogenous size distribution wherein at least 50% of the particles have a diameter of about 100 to 10000 nm, about 100 to 5000 nm, about 100 to 3000 nm, about 100 to 2000nm, about 300 to 5000 nm, about 300 to 3000 nm, about 300 to 1000 nm, about 300 to 800 nm, about 400 to 800 nm, or about 200 to 700 nm including all values and ranges therein. In various embodiments, the carrier particles have a diameter of about 50 nm, 100 nm, 200 nm, 300 nm, 400 nm, 500 nm, 600 nm, 700 nm, 800 nm, 900 nm, 1000 nm, 1100 nm, 1200 nm, 1300 nm, 1400 nm, 1500 nm, or 2000 nm including all values and ranges therein. In various embodiments, the carrier particles have a homogenous size distribution wherein at least 10% of the particles have a diameter of between about 0.05 μm and about 10 μm, about 0.1 μm and about 10 μm, about 0.1 μm and about 5 μm, about 0.1 μm and about 3 μm, about 0.3 μm and about 5 μm, and about 0.3 μm and about 3 μm including all values and ranges therein. In various embodiments, the carrier particles have a homogenous size distribution wherein at least 10% of the particles have a diameter of about 100 to 10000 nm, about 100 to 5000 nm, about 100 to 3000 nm, about 100 to 2000nm, about 300 to 5000 nm, about 300 to 3000 nm, about 300 to 1000 nm, about 300 to 800 nm, about 400 to 800 nm, or about 200 to 700 nm including all values and ranges therein. In various embodiments, the

carrier particles have a diameter of about 50 nm, 100 nm, 200 nm, 300 nm, 400 nm, 500 nm, 600 nm, 700 nm, 800 nm, 900 nm, 1000 nm, 1100 nm, 1200 nm, 1300 nm, 1400 nm, 1500 nm, or 2000 nm including all values and ranges therein.

[0029] In various embodiments, the carrier particles have a negative zeta potential of between -100 mV and 0 mV, and wherein the particle is between 100 and 1000 nm in diameter. In various embodiments, the size of the carrier particles is between 400 and 800 nm and the particles have a negative zeta potential between -30 mV and -80 mV.

[0030] In various embodiments, the carrier particles comprise PLGA, encapsulate one or more antigens, are coupled to cGAS-STING activating agent, have a diameter between 100 nm to 1000 nm, and zeta potential between -30 mV and -90 mV. In various embodiments, the carrier particles comprise PLGA, encapsulate one or more antigens and cGAS-STING activating agent, have a diameter between 100 nm to 1000 nm, and zeta potential between -30 mV and -90 mV. In some embodiments, carrier particles comprise PLGA, are coupled to one or more antigens, encapsulate cGAS-STING activating agent, have a diameter between 100 nm to 1000 nm, and zeta potential between -30 mV and -90 mV.

[0031] In various embodiments, the carrier particles comprise PLGA, encapsulate one or more antigens, are coupled to cGAS-STING activating agent, have a diameter between 400 nm to 800 nm, and zeta potential between -30 mV and -90 mV. In various embodiments, the carrier particles comprise PLGA, encapsulate one or more antigens and cGAS-STING activating agent, have a diameter between 400 nm to 800 nm, and zeta potential between -30 mV and -90 mV. In some embodiments, carrier particles comprise PLGA, are coupled to one or more antigens, encapsulate cGAS-STING activating agent, have a diameter between 400 nm to 800 nm, and zeta potential between -30 mV and -90 mV.

[0032] In various embodiments, the carrier particles encapsulate one or more antigens, portions thereof, or combinations thereof. In various embodiments, the antigen comprises one or more proteins, peptides, antigenic epitopes, or combinations thereof.

[0033] In some embodiments, the antigen and/or the cGAS-STING activating agent is coupled to the outside surface of a carrier particle. In some embodiments, the antigen and/or the cGAS-STING activating agent is coupled to the inside surface of a carrier particle. In some embodiments, the antigen and/or the cGAS-STING activating agent is coupled to the inside and the outside surface of a carrier particle. In various embodiments, the antigen and/or cGAS-STING pathway activating agent are coupled to the same carrier particle or a different carrier

particle. In some embodiments, the antigens and/or the cGAS-STING activating agent are encapsulated in a carrier particle. In various embodiments, the antigen and/or cGAS-STING activating agent are encapsulated in the same carrier particle or a different carrier particle. In some embodiments, the carrier particle is surface functionalized. In some embodiments, the carrier particle is carboxylate surface functionalized. In some embodiments, the antigens are coupled to cGAS-STING activating agents.

[0034] In some embodiments, the disclosure provides methods of inducing antigen-specific tolerance in a subject, comprising: administering to said subject an effective amount of a composition comprising (i) one or more antigens, and (ii) one or more agents that activate the cGAS-STING pathway, and wherein the composition induces tolerance of said antigen in said subject.

[0035] In various embodiments, the disclosure provides a method of inducing antigen specific tolerance in a subject comprising; administering to said subject, a combination of (i) one or more antigens; and (ii) one or more cGAS-STING activating agents. In various embodiments, the one or more antigens and the one or more cGAS-STING activating agent are in the same composition or in a different composition.

[0036] In various embodiments, the antigen is encapsulated in or coupled to apoptotic cells and the cGAS-STING activating agent is not encapsulated in or coupled to apoptotic cells, i.e., the cGAS-STING activating agent is “free” or “free in solution”. In some embodiments, the antigen is not encapsulated in or coupled to apoptotic cells, i.e., the antigen is “free” or “free in solution, and the cGAS-STING activating agent is encapsulated in or coupled to apoptotic cells. In various embodiments, the antigens and cGAS-STING activating agent are both encapsulated in or coupled to apoptotic cells. In some embodiments, the antigens are encapsulated in or coupled to a first population of apoptotic cells and the cGAS-STING activating agents are encapsulated in or coupled to a second population of apoptotic cells. In various embodiments, the composition comprises the apoptotic cells encapsulating or coupled to one or more antigen and cGAS-STING activating agent in the same composition. In various embodiments, the composition is an admixture comprising apoptotic cells encapsulating or coupled to one or more antigen and apoptotic cells encapsulating or coupled to cGAS-STING activating agent in different compositions for use in combination. In various embodiments, the apoptotic cells are coupled to or encapsulate one or more antigens coupled to cGAS-STING activating agents.

[0037] In some embodiments, the antigens are encapsulated in or coupled to carrier particles and the cGAS-STING activating agent is not encapsulated in or coupled to carrier particles, i.e.,

the cGAS-STING activating agent is “free” or “free in solution”. In some embodiments, the antigens are “free” and the cGAS-STING activating agent is encapsulated in or coupled to carrier particles. In various embodiments, the antigens and cGAS-STING activating agent are both encapsulated in or coupled to carrier particles. In some embodiments, the antigens are encapsulated in or coupled to a first population of carrier particles and the cGAS-STING activating agents are encapsulated in or coupled to a second population of carrier particles. In various embodiments, the composition comprises carrier particles encapsulating or coupled to one or more antigens and cGAS-STING activating agent in the same composition. In various embodiments, the composition is an admixture comprising carrier particles encapsulating or coupled to one or more antigen and carrier particles encapsulating or coupled to cGAS-STING activating agent in different compositions for use in combination. In various embodiments, the carrier particles are coupled to or encapsulate one or more antigens coupled to cGAS-STING activating agents.

[0038] In various embodiments, the administering is performed to treat or prevent a disease or condition. In some embodiments, administering is performed prior to or subsequent to onset of a disease or condition that is caused by said antigen.

[0039] In some embodiments, the disease or condition is selected from the group consisting of: an autoimmune disease, inflammatory disease, an allergy, transplantation rejection, a lysosomal storage disease, an enzyme deficiency, a protein deficiency, inflammatory response and a hyperimmune response. In some embodiments, the disease or condition is selected from the group consisting of: multiple sclerosis, type 1 diabetes, asthma, a food allergy, an environmental allergy, celiac disease, inflammatory bowel disease, including Crohn's disease or ulcerative colitis, primary biliary cholangitis, idiopathic thrombocytopenic purpura, myasthenia gravis, vitiligo, Graves’ disease, thyroid eye disease, narcolepsy, neuromyelitis optica, Addison’s disease, autoimmune myositis, autoimmune hepatitis, rheumatoid arthritis, Sjögrens syndrome, alopecia, granulomatosis, scleroderma, and a condition caused by said antigen in said subject to reduce overreaction to said antigen. In some embodiments, methods further comprise repeating the administration of said composition into said subject.

[0040] In some embodiments the composition is administered intravenously. In some embodiments, the composition is administered subcutaneously, orally, intramuscularly, intra-lymphatically, portally or via aerosol.

[0041] Also provided is a composition comprising one or more antigens and one or more cGAS-STING activating agents for use in inducing antigen specific tolerance in a subject.

[0042] Further contemplated is use of a composition comprising one or more antigens and one or more cGAS-STING activating agents in the manufacture of a medicament for inducing antigen-specific tolerance in a subject.

[0043] It is provided that the composition, carrier particle, antigen, cGAS-STING activating agent, dosing, and/or route of administration referenced above apply to each method, composition or use described herein.

[0044] It is understood that each feature or embodiment, or combination, described herein is a non-limiting, illustrative example of any of the aspects of the invention and, as such, is meant to be combinable with any other feature or embodiment, or combination, described herein. For example, where features are described with language such as "one embodiment", "some embodiments", "certain embodiments", "further embodiment", "specific exemplary embodiments", and/or "another embodiment", each of these types of embodiments is a non-limiting example of a feature that is intended to be combined with any other feature, or combination of features, described herein without having to list every possible combination. Such features or combinations of features apply to any of the aspects of the invention. Where examples of values falling within ranges are disclosed, any of these examples are contemplated as possible endpoints of a range, any and all numeric values between such endpoints are contemplated, and any and all combinations of upper and lower endpoints are envisioned.

BRIEF DESCRIPTION OF FIGURES

[0045] **Figure 1:** Administration of carrier particles containing a STING agonist is safe and leads to dose-dependent increases in cytokines.

[0046] **Figure 2:** Administration of carrier particles containing a STING agonist and peptide leads to induction of antigen-specific tolerance.

[0047] **Figure 3:** Administration of carrier particles containing a STING agonist and protein leads to induction of antigen-specific tolerance.

[0048] **Figure 4**: Administration of carrier particles containing a STING agonist and protein leads to decreases in antigen-specific antibodies.

[0049] **Figure 5**: List of protein antigens identified by Uniprot number.

[0050] **Figure 6**: List of protein or peptide antigens associated with myasthenia gravis.

[0051] **Figure 7**: List of protein or peptide antigens associated with narcolepsy.

[0052] **Figure 8**: List of protein or peptide antigens associated with primary biliary cholangitis.

[0053] **Figure 9**: List of protein antigens associated with autoimmune disease.

DETAILED DESCRIPTION

[0054] The present inventors have found that antigen-specific immune tolerance can be induced or enhanced by activating the cGAS-STING pathway. Agents that activate the cGAS-STING pathway in combination with antigens can induce or enhance tolerance to autoimmune diseases, allergies and other immune-mediated diseases where antigen-specific tolerance might be beneficial like enzyme replacement therapy, gene therapy, anti-drug antibodies. Activation of phagocytes or antigen-presenting cells through the cGAS-STING pathway leads to IFN signaling. IFN signaling phagocytes present the antigen to T-cells in the presence of PD-1, IL-10, type 1 interferon initiating T-cell reprogramming. Via an active process antigen-specific T-cells increase and acquire a stable regulatory phenotype. Antigen-specific tolerance has been described as an attractive strategy to overcome the immunogenicity of gene therapy vectors and the protein therapeutics produced by the vectors. Several methods of inducing antigen-specific tolerance have been described but their translation into the clinic has been elusive. There is a need for interventions that will allow induction of antigen-specific tolerance safely and with greater efficacy.

[0055] Carrier particles comprising one or more antigens, have been previously described for the treatment of immune mediated disorders (e.g. autoimmune diseases and allergies) via induction of antigen-specific immune tolerance (WO20131319253 and WO2015023796 incorporated herein by reference). In several preclinical models of autoimmune diseases and allergies, carrier particles have demonstrated efficacy at inducing T-cell tolerance. Induction of antigen-specific tolerance could potentially cure these immune-mediated diseases.

[0056] The present disclosure provides compositions of (i) one or more antigens and (ii) agents that activate cGAS-STING pathway. In various embodiments, the composition comprises the one or more antigen and cGAS-STING activating agent in the same composition. In various embodiments, the composition is an admixture comprising the one or more antigen and cGAS-STING activating agent in different compositions for use in combination. In various embodiments, the one or more antigens are coupled to cGAS-STING activating agent. In some embodiments, the composition comprises one or more antigens coupled to cGAS-STING

activating agent and liver targeting moieties. In some embodiments, the liver targeting moieties target hepatic antigen presenting cells. In some embodiments, the targeting moieties are selected from the group consisting of N-galactosamine, N-glucosamine, and CD206 targeting agents. Also included are methods of inducing antigen specific tolerance using the compositions described herein.

Definitions

[0057] It is understood that every embodiment of the disclosure described herein may optionally be combined with any one or more of the other embodiments described herein. Every patent literature and every non-patent literature cited herein are incorporated herein by reference in their entirety.

[0058] Unless otherwise stated, the following terms used in this application, including the specification and claims, have the definitions given below.

[0059] As used in the specification and the appended claims, the indefinite articles “a” and “an” and the definite article “the” include plural as well as singular referents unless the context clearly dictates otherwise.

[0060] The term “about” or “approximately” means an acceptable error for a particular value as determined by one of ordinary skill in the art, which depends in part on how the value is measured or determined. In certain embodiments, the term “about” or “approximately” means within 1, 2, 3, or 4 standard deviations. In certain embodiments, the term “about” or “approximately” means within 30%, 25%, 20%, 15%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, 0.5%, or 0.05% of a given value or range. Whenever the term “about” or “approximately” precedes the first numerical value in a series of two or more numerical values, it is understood that the term “about” or “approximately” applies to each one of the numerical values in that series.

[0061] “Particle” as used herein refers to any non-tissue derived composition of matter, suitable for biological use, it may be a sphere or sphere-like entity, bead, lipid nanoparticle, or liposome. The term “particle”, “tolerizing immune modifying particle”, “carrier particle”, and “bead” may be used interchangeably depending on the context. Additionally, the term “particle” may be used to encompass beads and spheres.

[0062] “Negatively charged particle” as used herein refers to particles which have been modified to possess a net surface charge that is less than zero.

[0063] "Positively charged particle" as used herein refers to particles which have been modified to possess a net surface charge that is more than zero.

[0064] The particle may have any particle shape or conformation. However, in some embodiments it is preferred to use particles that are less likely to clump in vivo. Examples of particles within these embodiments are those that have a spherical shape.

[0065] The compositions should generally possess the ability to sequester in the spleen or liver, trigger uptake by neutrophils, or trigger phagocytosis or uptake through receptor or non-receptor mediated mechanism by an antigen presenting cell, including endothelial cell or other mononuclear phagocytic system MPS cell. Preferably, the compositions are microscopic or nanoscopic in size, in order to enhance solubility, avoid possible complications caused by aggregation in vivo and to facilitate pinocytosis.

[0066] In some embodiments, the charge of the carrier (e.g. positive, negative, neutral) is selected to impart application specific benefits. (e.g., physiological compatibility, beneficial surface-peptide interactions, etc.). In some embodiments, a carrier has a net neutral or negative charge (e.g., to reduce non-specific binding to cell surfaces which, in general, bear a net negative charge). In certain embodiments carriers are capable of being conjugated, either directly or indirectly, to an antigen to which tolerance is desired (also referred to herein as an antigen-specific peptide, antigenic peptide, autoantigen, inducing antigen or tolerizing antigen). In some instances, a carrier has multiple binding sites (e.g., 2, 3, 4, 5, 6, 7, 8, 9, 10 . . . 20 . . . 50 . . . 100, or more) in order to have multiple copies of an antigen-specific peptide, or multiple different peptides, exposed on the surface (e.g., to increase the likelihood of a tolerance response). In some embodiments, a carrier displays a single type of antigenic peptide. In some embodiments, a carrier displays multiple different antigenic peptides on the surface. In some embodiments, a carrier surface displays functional groups for the covalent attachment of selected moieties (e.g., antigenic peptides). In some embodiments, carrier surface functional groups provide sites for non-covalent interaction with selected moieties (e.g., antigenic peptides). In some embodiments, a carrier has a surface to which conjugating moieties may be adsorbed without chemical bond formation. In some embodiments, the size and charge are critical for tolerance induction. In some embodiments, the charge is critical for electrostatic interactions.

[0067] "Carboxylated particles" or "carboxylated beads" or "carboxylated spheres" includes any particle that has been modified to contain a carboxyl group on its surface. In some embodiments the addition of the carboxyl group enhances phagocyte/monocyte uptake of the

particles from circulation, for instance through the interaction with scavenger receptors such as MARCO. Carboxylation of the particles can be achieved using any compound which adds carboxyl groups, including, but not limited to, poly (ethylene-maleic anhydride) (PEMA).

[0068] As used herein, the term "Th cell" or "helper T cell" refers to $CD4^+$ cells. $CD4^+$ T cells assist other white blood cells with immunologic processes, including maturation of B cells into plasma cells and memory B cells, and activation of cytotoxic T cells and macrophages. T cells become activated when they are presented with peptide antigens by MHC class II molecules, which are expressed on the surface of antigen-presenting cells (APCs).

[0069] As used herein, the term "Th1 cell" refers to a subset of Th cells which produce pro-inflammatory mediators. Th1 cells secrete cytokines to facilitate immune response and play a role in host defense against pathogens in part by mediating the recruitment of neutrophils and macrophages to infected tissues. Th1 cells secrete cytokines including IFN-gamma, IL-2, IL-10, and TNF alpha/beta to coordinate defense against intracellular pathogens such as viruses and some bacteria.

[0070] As used herein, the term "Th2 cell" refers to a subset of Th cells that mediate the activation and maintenance of the antibody-mediated immune response against extracellular parasites, bacteria, allergens, and toxins. Th2 cells mediate these functions by producing various cytokines such as IL-4, IL-5, IL-6, IL-9, IL-13, and IL-17E (IL-25) that are responsible for antibody production, eosinophil activation, and inhibition of several macrophage functions, thus providing phagocyte-independent protective responses.

[0071] As used herein the term "infectious tolerance" refers to the ability to induce tolerance via Treg cells specific for one Ag that are capable of preventing disease progression due to epitope spreading and autoreactivity to other disease-specific Ags.

[0072] "Polypeptide" and "protein" refer to a polymer composed of amino acid residues, related naturally occurring structural variants, and synthetic non-naturally occurring analogs thereof, linked via peptide bonds or peptide bond isosteres. Synthetic polypeptides can be synthesized, for example, using an automated polypeptide synthesizer. The terms "polypeptide" and "protein" are not limited to a minimum length of the product. The term "protein" typically refers to large polypeptides. The term "peptide" typically refers to short polypeptides. Thus, peptides, oligopeptides, dimers, multimers, and the like, are included within the definition. Both full-length proteins and fragments thereof are encompassed by the definition. The terms "polypeptide" and "protein" also include post-expression modifications of the polypeptide or

protein, for example, glycosylation, acetylation, phosphorylation and the like. Furthermore, for purposes of the present disclosure, a "polypeptide" can include "modifications," such as deletions, additions, substitutions (which may be conservative in nature or may include substitutions with any of the 20 amino acids that are commonly present in human proteins, or any other naturally or non-naturally-occurring or atypical amino acids), and chemical modifications (e.g., addition of or substitution with peptidomimetics), to the native sequence. These modifications may be deliberate, as through site-directed mutagenesis, or through chemical modification of amino acids to remove or attach chemical moieties, or may be accidental, such as through mutations arising via hosts cells that produce the proteins or through errors due to PCR amplification prior to host cell transfection.

[0073] "Antigenic moiety" or "antigen" as used herein refers to any moiety, for example a peptide, that is recognized by the host's immune system. Examples of antigenic moieties include, but are not limited to, autoantigens, allergens, enzymes, and/or bacterial or viral proteins, peptides, drugs or components.

[0074] "Pharmaceutically acceptable carrier" refers to any of the standard pharmaceutical carriers, buffers, and the like, such as a phosphate buffered saline solution, 5% aqueous solution of dextrose, and emulsions (e.g., an oil/water or water/oil emulsion). Non-limiting examples of excipients include adjuvants, binders, fillers, diluents, disintegrants, emulsifying agents, wetting agents, lubricants, glidants, sweetening agents, flavoring agents, and coloring agents. Suitable pharmaceutical carriers, excipients and diluents are described in Remington's Pharmaceutical Sciences, 19th Ed. (Mack Publishing Co., Easton, 1995). Preferred pharmaceutical carriers depend upon the intended mode of administration of the active agent. Typical modes of administration include enteral (e.g., oral) or parenteral (e.g., subcutaneous, intramuscular, intravenous or intraperitoneal injection; or topical, transdermal, or transmucosal administration) or via inhalation.

[0075] By "pharmaceutically acceptable" or "pharmacologically acceptable" is meant a material that is not biologically or otherwise undesirable, i.e., the material may be administered to an individual without causing any undesirable biological effects or without interacting in a deleterious manner with any of the components of the composition in which it is contained or with any components present on or in the body of the individual.

[0076] As used herein, the term "subject" encompasses mammals and non-mammals. Examples of mammals include, but are not limited to, any member of the mammalian class: humans, non-human primates such as chimpanzees, and other apes and monkey species; farm

animals such as cattle, horses, sheep, goats, swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice and guinea pigs, and the like. Examples of non-mammals include, but are not limited to, birds, fish, and the like. The term does not denote a particular age or gender.

[0077] The term "epitope" refers to that portion of any molecule capable of being recognized by and bound by a selective binding agent at one or more of the antigen binding regions of the selective binding agent. Epitopes usually consist of chemically active surface groupings of molecules, such as, amino acids or carbohydrate side chains, and have specific three-dimensional structural characteristics as well as specific charge characteristics. Epitopes as used herein may be contiguous or non-contiguous. Moreover, epitopes may be mimetic (mimotopes) in that they comprise a three-dimensional structure that is identical to the epitope used to generate the antibody, yet comprise none or only some of the amino acid residues found in the target that were used to stimulate the antibody immune response. As used herein, a mimotope is not considered a different antigen from the epitope bound by the selective binding agent; the selective binding agent recognizes the same three-dimensional structure of the epitope and mimotope.

[0078] The term "therapeutically effective amount" is used herein to indicate the amount of antigen-specific composition of the disclosure that is effective to ameliorate or lessen one or more symptoms or signs of disease to be treated.

[0079] The terms "treat", "treated", "treating" and "treatment", as used with respect to methods herein refer to eliminating, reducing, suppressing or ameliorating, either temporarily or permanently, either partially or completely, a clinical symptom, manifestation or progression of an event, disease or condition. Such treating need not be absolute to be useful.

Particles

[0080] Tolerizing Immune Modifying Particles (TIMPs), comprising one or more antigens, have been previously described for the induction of antigen specific tolerance for treating inflammatory conditions (e.g., autoimmune diseases and allergies) (WO20131319253 and WO2015023796 incorporated herein by reference). In several preclinical models of autoimmune diseases and allergies, TIMPs have demonstrated efficacy at inducing antigen specific tolerance and inhibition of pathologic inflammatory immune responses.

[0081] Surprisingly, the combination of one or more cGAS-STING activating agents with an antigen can enhance tolerance induction compared to a particle comprising antigen without a

cGAS STING activating agent. Enhanced tolerance induction can result in a lower dose of antigen needed to induce tolerance, and or in less frequent dosing of compositions or particles comprising the antigen and cGAS-STING activating agent. While particles will differ in size and charge based on the antigen encapsulated within them, in general, particles described herein are effective at inducing tolerance when they encapsulate/are coupled to cGAS-STING activating agents. In general, particles described herein encapsulating or coupled to cGAS-STING activating agents are effective at inducing tolerance when they are between about 100 nanometers and about 1500 nanometers and have a charge of between 0 to about -100 mV. In various embodiments, the particles encapsulating/coupled to cGAS-STING activating agents are about 100 to about 1000 nanometers in diameter and have a charge of between about -15 mV and -40 mV. In various embodiments, the particles encapsulating or coupled to cGAS-STING activating agents are 400-800 nanometers in diameter and have a charge of between about -25mV and -70mV. In various embodiments, the particles encapsulating or coupled to cGAS-STING activating agents are 400-800 nanometers in diameter and have a charge of between about -30mV and -80mV. In various embodiments, the particles encapsulating or coupled to cGAS-STING activating agents are 400-800 nanometers in diameter and have a charge of between about -30mV and -60mV. In various embodiments, the particles encapsulating or coupled to cGAS-STING activating agents are 400-800 nanometers in diameter and have a charge of between about -40mV and -90mV. The average particle size and charge of the particles can be slightly altered in the lyophilization process, therefore, both post-synthesis averages and post-lyophilization averages are described. As used herein, the term "post-synthesis size" and "post synthesis charge" refer to the size and charge of the particle prior to lyophilization. The term "post lyophilization size" and "post lyophilization charge" refer to the size and charge of the particle after lyophilization.

[0082] In some embodiments, the particle is non-metallic. In these embodiments the particle may be formed from a polymer. In a preferred embodiment, the particle is biodegradable in an individual. In this embodiment, the particles can be provided in an individual across multiple doses without there being an accumulation of particles in the individual. Examples of suitable particles include polystyrene particles, PLGA particles, PLURONICS stabilized polypropylene sulfide particles, PLURONICS stabilized dopamine particles, and diamond particles.

[0083] Preferably the particle surface is composed of a material that minimizes non-specific or unwanted biological interactions. Interactions between the particle surface and the interstitium may be a factor that plays a role in lymphatic uptake. The particle surface may be

coated with a material to prevent or decrease non-specific interactions. Steric stabilization by coating particles with hydrophilic layers such as poly(ethylene glycol) (PEG) and its copolymers such as PLURONICS® (including copolymers of poly(ethylene glycol)-bl-poly(propylene glycol)-bl-poly(ethylene glycol)) may reduce the non-specific interactions with proteins of the interstitium as demonstrated by improved lymphatic uptake following subcutaneous injections. All of these facts suggest relevance of the physical properties of the particles in terms of lymphatic uptake. Biodegradable polymers may be used to make all or some of the polymers and/or particles and/or layers. Biodegradable polymers may undergo degradation, for example, by a result of functional groups reacting with the water in the solution. The term "degradation" as used herein refers to becoming soluble, either by reduction of molecular weight or by conversion of hydrophobic groups to hydrophilic groups. Polymers with ester groups are generally subject to spontaneous hydrolysis, e.g., polylactides and polyglycolides.

[0084] Particles disclosed herein may also contain additional components. For example, carriers may have imaging agents incorporated or conjugated to the carrier. An example of a carrier nanosphere having an imaging agent that is currently commercially available is the Kodak X-sight nanospheres. Inorganic quantum-confined luminescent nanocrystals, known as quantum dots (QDs), have emerged as ideal donors in FRET applications: their high quantum yield and tunable size-dependent Stokes Shifts permit different sizes to emit from blue to infrared when excited at a single ultraviolet wavelength. (Bruchez, et al., Science, 1998, 281, 2013; Niemeyer, C. M Angew. Chem. Int. Ed. 2003, 42, 5796; Waggoner, A. Methods Enzymol. 1995, 246, 362; Brus, L. E. J. Chem. Phys. 1993, 79, 5566). Quantum dots, such as hybrid organic/inorganic quantum dots based on a class of polymers known as dendrimers, may be used in biological labeling, imaging, and optical biosensing systems. (Lemon, et al., J. Am. Chem. Soc. 2000, 122, 12886). Unlike the traditional synthesis of inorganic quantum dots, the synthesis of these hybrid quantum dot nanoparticles does not require high temperatures or highly toxic, unstable reagents. (Etienne, et al., Appl. Phys. Lett. 87, 181913, 2005).

[0085] Particles can be formed from a wide range of materials. The particle is preferably composed of a material suitable for biological use. For example, particles may be composed of glass, silica, polyesters of hydroxy carboxylic acids, polyanhydrides of dicarboxylic acids, or copolymers of hydroxy carboxylic acids and dicarboxylic acids. More generally, the carrier particles may be composed of polyesters of straight chain or branched, substituted or unsubstituted, saturated or unsaturated, linear or cross-linked, alkanyl, haloalkyl, thioalkyl, aminoalkyl, aryl, aralkyl, alkenyl, aralkenyl, heteroaryl, or alkoxy hydroxy acids, or

polyanhydrides of straight chain or branched, substituted or unsubstituted, saturated or unsaturated, linear or cross-linked, alkanyl, haloalkyl, thioalkyl, aminoalkyl, aryl, aralkyl, alkenyl, aralkenyl, heteroaryl, or alkoxy dicarboxylic acids. Additionally, carrier particles can be quantum dots, or composed of quantum dots, such as quantum dot polystyrene particles (Joumaa et al. (2006) Langmuir 22: 1810-6). Carrier particles including mixtures of ester and anhydride bonds (e.g., copolymers of glycolic and sebacic acid) may also be employed. For example, carrier particles may comprise materials including polyglycolic acid polymers (PGA), polylactic acid polymers (PLA), polysebacic acid polymers (PSA), poly(lactic-co-glycolic) acid copolymers (PLGA or PLG; the terms are interchangeable), poly(lactic-co-sebacic) acid copolymers (PLSA), poly(glycolic-co-sebacic) acid copolymers (PGSA), polypropylene sulfide polymers, poly(ethylene glycol) (PEG)-*bl*-poly(propylene sulfide polymersomes, poly(caprolactone), chitosan, dextran acetate etc. Other biocompatible, biodegradable polymers useful in the present invention include polymers or copolymers of caprolactones, carbonates, amides, amino acids, orthoesters, acetals, cyanoacrylates and degradable urethanes, as well as copolymers of these with straight chain or branched, substituted or unsubstituted, alkanyl, haloalkyl, thioalkyl, aminoalkyl, alkenyl, or aromatic hydroxy- or di-carboxylic acids. Yet other biocompatible, biodegradable polymers include poly(β-amino esters), hyaluronic acid, citric acid, sialic acid, 3'-sialyllactose, polysaccharide A, glucans, and salicyclic acids.

[0086] In addition, the biologically important amino acids with reactive side chain groups, such as lysine, arginine, aspartic acid, glutamic acid, serine, threonine, tyrosine and cysteine, or their enantiomers, may be included in copolymers with any of the aforementioned materials to provide reactive groups for conjugating to antigen peptides and proteins or conjugating moieties. Biodegradable materials suitable for the present invention include diamond, PLA, PGA, polypropylene sulfide, and PLGA polymers. Biocompatible but non-biodegradable materials may also be used in the carrier particles of the invention. For example, non-biodegradable polymers of acrylates, ethylene-vinyl acetates, acyl substituted cellulose acetates, non-degradable urethanes, styrenes, vinyl chlorides, vinyl fluorides, vinyl imidazoles, chlorosulphonated olefins, ethylene oxide, vinyl alcohols, TEFLON® (DuPont, Wilmington, Del.), and nylons may be employed.

[0087] In certain embodiments, the particle is a co-polymer having a molar ratio from about 80:20 to about 100:0. Suitable co-polymer ratio of present immune modified particles may be 25:75, 30:70, 35:65, 40:60, 45:55, 50:50, 55:45, 60:40, 65:35, 70:30, 75:25, 80:20, 81:19, 82:18, 83:17, 84:16, 85:15, 86:14, 87:13, 88:12, 89:11, 90:10, 91:9, 92:8, 93:7, 94:6, 95:5, 96:4, 97:3,

98:2, 99:1, or 100:0. In various embodiments, the particle is a PLURONICS stabilized polypropylene sulfide particle, a polyglycolic acid particle (PGA), a polylactic acid particle (PLA), or a poly(lactic-co-glycolic acid) (PLGA) particle. In various embodiments, the particle is a carboxylated PLGA particle. In various embodiments, the particle has a copolymer ratio of polylactic acid/polyglycolic acid 80:20: polylactic acid/polyglycolic acid 90:10: or polylactic acid: polyglycolic acid/50:50. In various embodiments, the particle is a poly(lactic-co-glycolic acid) particle and has a copolymer ratio of about 50:50 polylactic acid:polyglycolic acid. In various embodiments, the particle comprises about 50:50, about 80:20 to about 100:0 polylactic acid: polyglycolic acid or from about 50:50, about 80:20 to about 100:0 polyglycolic acid: polylactic acid. In various embodiments, the particle comprises 50:50 polylactic acid: polyglycolic acid. In various embodiments, the particle comprises polylactic acid: polyglycolic acid from about 99:1 to about 1:99, e.g., about 99:1, about 95:5, about 90:10, about 85:15, about 80:20, about 75:25, about 70:30, about 65:35, about 60:40, about 55:45, about 50:50, about 45:55, about 40:60, about 35:65, about 30:70, about 25:75, about 20:80, about 15:85, about 10:90, about 5:95, and about 1:99, including all values and ranges that lie in between these values.

[0088] It is contemplated that the particle may further comprise a surfactant. The surfactant can be anionic, cationic, or nonionic. Surfactants in the poloxamer and poloaxamines family are commonly used in particle synthesis. Surfactants that may be used, include, but are not limited to PEG, Tween-80, gelatin, dextran, pluronic L-63, polyvinyl alcohol (PVA), polyacrylic acid (PAA), methylcellulose, lecithin, didodecyldimethylammonium bromide (DMAB) and poly(ethylene-alt-maleic acid) (PEMA). Additionally, biodegradable and biocompatible surfactants including, but not limited to, vitamin E TPGS (D-α-tocopheryl polyethylene glycol 1000 succinate), poly amino acids (e.g., polymers of lysine, arginine, aspartic acid, glutamic acid, serine, threonine, tyrosine and cysteine, or their enantiomers), and sulfate polymers. In some embodiments, two surfactants are used. For example, if the particle is produced by a double emulsion method, the two surfactants can include a hydrophobic surfactant for the first emulsion, and a hydrophobic surfactant for the second emulsion.

[0089] In various embodiments, the polypeptide antigens are encapsulated in the particles by a single-emulsion process. In various embodiments, the polypeptide antigens are encapsulated in the particles by a double-emulsion process. In a further embodiment, the polypeptide antigens are more hydrophobic. Sometimes, the double emulsion process leads to the formation of large particles which may result in the leakage of the hydrophilic active component and low entrapment efficiencies. The coalescence and Ostwald ripening are two mechanisms that may

destabilize the double-emulsion droplet, and the diffusion through the organic phase of the hydrophilic active component is the main mechanism responsible of low levels of entrapped active component. In some embodiments, it may be beneficial to reduce the nanoparticle size. One strategy to accomplish this is to apply a second strong shear rate. The leakage effect can be reduced by using a high polymer concentration and a high polymer molecular mass, accompanied by an increase in the viscosity of the inner water phase and in increase in the surfactant molecular mass. In certain embodiments, the particles encapsulating antigens are manufactured by nanoprecipitation, co-precipitation, inert gas condensation, sputtering, microemulsion, sol-gel method, layer-by-layer technique or ionic gelation method. Several methods for manufacturing nanoparticles have been described in the literature and are incorporated herein by reference.

[0090] In some embodiments, the particle is a liposome. In some embodiments, the particle is a hybrid polymer liposome. Liposomes may comprise a variety of lipid materials including, but not limited to, lipids of phosphatidyl choline, phosphatidyl serine, phosphatidyl inositol, phosphatidyl glycerol, phosphatidyl ethanolamine, 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC), 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC), 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE), 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP), 1,2-dioleoyl-sn-glycero-3-ethylphosphocholine (EDOPC), dimethyldioctadecylammonium bromide (DDAB), N-[1-(2,3-dioleoyloxy)propyl]-N,N,N-trimethylammonium chloride (DOTMA), dioleoylphosphatidylglycerol (DOPG), phosphatidic acid (PA), cardiolipin, 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-polyethylene glycol (DSPE-PEG), 1,2-dimyristoyl-sn-glycero-3-phosphoethanolamine-polyethylene glycol (DMPE-PEG), DLin-MC3-DMA (MC3), SM-102, ALC-0315, C12-200, sphingomyelin, ceramides, palmitic acid, stearic acid, oleic acid, phosphatidic acid, dicetyl phosphate, monosialoganglioside, polyethylene glycol, stearyl armine, ovolecithin, modified lipids and cholesterol, cholesterol esters, PEGylated cholesterol (e.g., cholesterol-polyethylene glycol) as well as mixtures of these in varying stoichiometries. Liposomes, as used herein, may also be formed from non-lipid amphipathic molecules, such as block copolymers of poly(oxyethylene-b-isoprene-b-oxyethylene) and the like. In some embodiments, the liposomes or hybrid polymer liposomes are prepared from lipids or incorporate lipids that will form negatively charged liposomes, such as those produced from phosphatidyl serine, dicetyl phosphate, and dimyristoyl phosphatidic acid.

[0091] In various embodiments, the negatively charged liposomes have a zeta potential from about -100 mV to about 0 mV, from about -100 mV to about -25 mV, from about -100 to about -30 mV, from about -80 mV to about -30 mV, from about -75 mV to about -30 mV, from about -70 mV to about -30 mV, from about -75 to about -35 mV, from about -70 to about -25 mV, from about -60 mV to about -30 mV, from about -60 mV to about -35 mV, or from about -50 mV to about -30 mV. In various embodiments, the zeta potential is about -25 mV, -30 mV, -35 mV, -40 mV, -45 mV, -50 mV, -55 mV, -60 mV, -65 mV, -70 mV, -75 mV, -80 mV, -85 mV, -90 mV, -95 mV or -100 mV, including all values and ranges therein. In various embodiments, the liposomes have a negative zeta potential of between -30 mV to -80 mV. In various embodiments, the liposomes have a negative zeta potential of between -30 mV to -60 mV. In various embodiments, the liposomes have a negative zeta potential of between -40 mV to -90 mV.

[0092] In some embodiments, the carrier particles encapsulating or coupled to cGAS-STING activating agents comprise a liposome, lipid nanoparticle, polymersomes, micelles, polymeric nanoparticles, manganese ($Mn2^{+}$) based nanoparticles, acid-ionizable iron nanoadjuvant (INOP), mesoporus silica, metal-organic frameworks (MOFs), lipid nanodiscs, supramolecular nanoparticles, extracellular vesicles, sono-driven nanoparticles, or ECDI-coupled splenocytes.

[0093] Conjugates such as ethylene carbodiimide (ECDI), hexamethylene diisocyanate, propyleneglycol di-glycidylether which contain 2 epoxy residues, ultraviolet (UV) irradiation and epichlorohydrin may be used for fixation of peptides or proteins to the carrier particle surface or to cells. Without being bound by theory, ECDI is suspected of carrying out two major functions for induction of tolerance: (a) it chemically couples the protein/peptides to the cell/particle surface via catalysis of peptide bond formation between free amino and free carboxyl groups; and (b) it induces the cell/carrier to mimic apoptotic cell death such that they are picked up by host antigen presenting cells (which may include endothelial cells) in the spleen and induce tolerance. It is this presentation to host T-cells in a non-immunogenic fashion that leads to direct induction of anergy in autoreactive cells. In addition, ECDI serves as a potent stimulus for the induction of specific regulatory T cells.

[0094] The present disclosure contemplates compositions comprising antigens encapsulated in or coupled to albumin and the cGAS-STING activating agent is not encapsulated in or coupled to albumin, i.e., the cGAS-STING activating agent is “free” or “free in solution”. In some embodiments, the antigens are “free” and the cGAS-STING activating agent is encapsulated in or coupled to albumin. In various embodiments, the antigens and cGAS-STING activating agent

are both encapsulated in or coupled to albumin. In some embodiments, the antigens are encapsulated in or coupled to a first population of albumin and the cGAS-STING activating agents are encapsulated in or coupled to a second population of albumin. In various embodiments, the composition comprises the albumin encapsulating or coupled to one or more antigen and cGAS-STING activating agent in the same composition. In various embodiments, the composition is an admixture comprising albumin encapsulating or coupled to one or more antigen and albumin encapsulating or coupled to cGAS-STING activating agent in different compositions for use in combination. In some embodiments, the one or more antigens are coupled to cGAS-STING activating agent. In some embodiments, the albumin is recombinant albumin with enhanced binding to neonatal Fc receptor (FcRn). In some embodiments, the albumin is recombinant albumin with reduced binding to neonatal FcRn.

[0095] The present disclosure also contemplates compositions comprising: (i) one or more antigens, and (ii) one or more agents that activate type 1 interferon pathway i.e., Type 1 interferon activating agent. In various embodiments, the composition comprises the one or more antigen and Type 1 interferon activating agent in the same composition. In various embodiments, the composition is an admixture comprising the one or more antigen and Type 1 interferon activating agent in different compositions for use in combination.

[0096] In some embodiments, the antigen is encapsulated in or coupled to apoptotic cells and the Type 1 interferon activating agent is not encapsulated in or coupled to apoptotic cells, i.e., the Type 1 interferon activating agent is “free” or “free in solution”. In some embodiments, the antigen is not encapsulated in or coupled to apoptotic cells, i.e., the antigen is “free” or “free in solution, and the Type 1 interferon activating agent is encapsulated in or coupled to apoptotic cells. In various embodiments, the antigens and Type 1 interferon activating agent are encapsulated in or coupled to apoptotic cells. In some embodiments, the Type 1 interferon activating agent is encapsulated in apoptotic cells coupled to antigens. In some embodiments, the antigens are encapsulated in or coupled to a first population of apoptotic cells and the Type 1 interferon activating agents are encapsulated in or coupled to a second population of apoptotic cells. In various embodiments, the composition comprises the apoptotic cells encapsulated or coupled to one or more antigen and Type 1 interferon activating agent in the same composition. In various embodiments, the composition is an admixture comprising apoptotic cells encapsulated or coupled to one or more antigen and apoptotic cells encapsulating or coupled to Type 1 interferon activating agent in different compositions for use

in combination. In some embodiments, the one or more antigens are coupled to Type 1 interferon activating agent.

[0097] In some embodiments, the antigens are encapsulated in or coupled to carrier particles and the Type 1 interferon activating agent is not encapsulated in or coupled to carrier particles, i.e., the Type 1 interferon activating agent is "free" or "free in solution". In some embodiments, the antigens are "free" and the Type 1 interferon activating agent is encapsulated in or coupled to carrier particles. In various embodiments, the antigens and Type 1 interferon activating agent are both encapsulated in or coupled to carrier particles. In some embodiments, the antigens are encapsulated in or coupled to a first population of carrier particles and the Type 1 interferon activating agents are encapsulated in or coupled to a second population of carrier particles. In various embodiments, the composition comprises the carrier particles encapsulating or coupled to one or more antigen and Type 1 interferon activating agent in the same composition. In various embodiments, the composition is an admixture comprising carrier particles encapsulating or coupled to one or more antigen and carrier particles encapsulating or coupled to Type 1 interferon activating agent in different compositions for use in combination. In some embodiments, the one or more antigens are coupled to Type 1 interferon activating agent.

[0098] In some embodiments, the antigens are encapsulated in or coupled to albumin and the Type 1 interferon activating agent is not encapsulated in or coupled to albumin, i.e., the Type 1 interferon activating agent is "free" or "free in solution". In some embodiments, the antigens are "free" and the Type 1 interferon activating agent is encapsulated in or coupled to albumin. In various embodiments, the antigens and Type 1 interferon activating agent are both encapsulated in or coupled to albumin. In some embodiments, the antigens are encapsulated in or coupled to a first population of albumin and the Type 1 interferon activating agents are encapsulated in or coupled to a second population of albumin. In various embodiments, the composition comprises the albumin encapsulating or coupled to one or more antigen and Type 1 interferon activating agent in the same composition. In various embodiments, the composition is an admixture comprising albumin encapsulating or coupled to one or more antigen and albumin encapsulating or coupled to Type 1 interferon activating agent in different compositions for use in combination. In some embodiments, the albumin is recombinant albumin with enhanced binding to neonatal Fc receptor (FcRn). In some embodiments, the albumin is recombinant albumin with reduced binding to neonatal FcRn. In some embodiments, the one or more antigens are coupled to Type 1 interferon activating agent.

[0099] Agents inducing type 1 interferons are selected from the group consisting of Toll like receptor activating agents (TLR 2, TLR 3, TLR 4, TLR 7, TLR 8, TLR 9), NOD/12 activating agents, cGAS activating agents, DEXD/H box activating agents, DAI activating agents, RNA polymerase 3 inducing agents, MDA5 activating agent, RIG-1 activating agent.

[0100] The present disclosure also contemplates compositions comprising: (i) one or more antigens, and (ii) one or more agents that activate Wnt-β-catenin i.e., Wnt-β-catenin activating agent. In various embodiments, the composition comprises the one or more antigen and Wnt-β-catenin activating agent in the same composition. In various embodiments, the composition is an admixture comprising the one or more antigen and Wnt-β-catenin activating agent in different compositions for use in combination.

Antigens

[0101] An antigen refers to a discreet portion of a molecule, such as a polypeptide or peptide sequence, a 3-D structural formation of a polypeptide or peptide, a polysaccharide, polynucleotide or a post-translational or post-expression modification that can be recognized by a host immune cells. Antigen-specific refers to the ability of a subject's host cells to recognize and generate an immune response against an antigen alone, or to molecules that closely resemble the antigen, as with an epitope or mimotope. Post-translational modifications include phosphorylation, glycosylation (e.g. O-linked glycosylation, N-linked glycosylation, C-linked glycosylation), ubiquitination, nitrosylation, methylation, acetylation, lipidation, disulfide bonds, oxidation, or, succinylation, malonylation, sumoylation, glutathionylation, hydroxylation, palmitoylation, pyrrolidone carboxymic acid, glutarylation, gamma-carboxyglutamic acid, crotonylation, citrullination, myristoilation, sulfation, formylation or amidation. Epitopes can be linear, discontinuous, or conformational epitopes.

[0102] "Anergy," "tolerance," or "antigen-specific tolerance" refers to insensitivity of T cells to T cell receptor-mediated stimulation. Such insensitivity is generally antigen- specific and persists after exposure to the antigenic peptide has ceased. For example, anergy in T cells is characterized by lack of cytokine production, e.g., IL-2. T-cell anergy occurs when T cells are exposed to antigen and receive a first signal (a T cell receptor or CD-3 mediated signal) in the absence of a second signal (a costimulatory signal). Under these conditions, re-exposure of the cells to the same antigen (even if re-exposure occurs in the presence of a costimulatory molecule) results in failure to produce cytokines and subsequently failure to proliferate. Thus, a

failure to produce cytokines prevents proliferation. Anergic T cells can, however, proliferate if cultured with cytokines (e.g., IL-2).

[0103] It is contemplated that the tolerizing therapy described herein is antigen-specific. For example, compositions described herein administered as tolerizing therapy contain one or more antigens associated with said tolerizing therapy and associated disease or condition being treated. It is contemplated that the compositions used in tolerizing therapy comprise one or more antigens, portions thereof, or combinations thereof.

[0104] In certain embodiments, one, two, three, or a higher number of antigens or antigenic peptides are used in one or more compositions for inducing tolerance. In certain embodiments, the one or more antigens are encapsulated in the carrier particles by covalent linkage to the interior surface of the particle (See e.g., US Patent Publication US20190282707, herein incorporated by reference). In certain embodiments, it is contemplated that sequences of two or more antigens are linked in a fusion protein and coupled to or encapsulated within a carrier particle described herein. Methods for making particles with linked epitopes are described in US Patent Publication US20190365656, herein incorporated by reference. In certain embodiments, the one or more antigens used in one or more compositions for inducing tolerance are encoded by polynucleotides (DNA, RNA, circular RNA). The antigens are selected from the group consisting of autoimmune antigens, allergens, transplant antigens, enzyme replacement therapies, therapeutic proteins, inhaled substances, injected substances, viral proteins, vector for gene therapies, or transgenes coded by the gene therapy. In various embodiments, the composition comprises the carrier particles encapsulating or coupled to polynucleotides encoding one or more antigen, and cGAS-STING activating agent in the same composition. In various embodiments, the composition is an admixture comprising carrier particles encapsulating or coupled to polynucleotides encoding one or more antigen and carrier particles encapsulating or coupled to cGAS-STING activating agent in different compositions for use in combination. In various embodiments, the carrier particles are liposomes or hybrid polymer liposomes.

[0105] Any suitable antigens may find use within the scope of the present invention. In some embodiments, the inducing antigen contributes to the specificity of the tolerogenic response that is induced. The inducing antigen may or may not be the same as the target antigen, which is the antigen present or to be placed in the subject being treated which is a target for the unwanted immunological response, and for which tolerance is desired.

[0106] Where the target antigen is preferentially expressed on a particular organ, cell, or tissue type, the practitioner again has the option of using an inducing antigen which is identical with or immunologically related to the target antigen. However, there is also the additional option of using an antigen which is a bystander for the target. This is an antigen which may not be immunologically related to the target antigen, but is preferentially expressed in a tissue where the target antigen is expressed. A working theory as to the effectiveness of bystander suppression is that suppression is an active cell-mediated process that down-regulates the effector arm of the immune response at the target cells. The suppressor cells are specifically stimulated by the inducer antigen at the mucosal surface, and home to a tissue site where the bystander antigen is preferentially expressed. Through an interactive or cytokine-mediated mechanism, the localized suppressor cells then down-regulate effector cells (or inducers of effector cells) in the neighborhood, regardless of what they are reactive against. If the effector cells are specific for a target different from the inducing antigen, then the result is a bystander effect. For further elaboration of the bystander reaction and a list of tolerogenic peptides having this effect, the reader is referred to International Patent Publication WO 93/16724. An implication of bystander theory is that one of ordinary skill need not identify or isolate a particular target antigen against which tolerance is desired in order to practice the present invention. The practitioner need only be able to obtain at least one molecule preferentially expressed at the target site for use as an inducing antigen.

[0107] In certain embodiments of this disclosure, the inducing antigen is not in the same form as expressed in the individual being treated, but is a fragment or derivative thereof. Inducing antigens of this invention include peptides based on a molecule of the appropriate specificity but adapted by fragmentation, residue substitution, labeling, conjugation, and/or fusion with peptides having other functional properties. The adaptation may be performed for any desirable purposes, including but not limited to the elimination of any undesirable property, such as toxicity or immunogenicity; or to enhance any desirable property, such as mucosal binding, mucosal penetration, or stimulation of the tolerogenic arm of the immune response. Terms such as insulin peptide, collagen peptide, and myelin basic protein peptide, as used herein, refer not only to the intact subunit, but also to allotypic and synthetic variants, fragments, fusion peptides, conjugates, and other derivatives that contain a region that is homologous (preferably 70% identical, more preferably 80% identical and even more preferably 90% identical at the amino acid level) to at least 10 and preferably 20 consecutive amino acids of the respective molecule for which it is an analog, wherein the homologous region of the derivative shares with the respective parent molecule an ability to induce tolerance to the target antigen.

[0108] It is recognized that tolerogenic regions of an inducing antigen are often different from immunodominant epitopes for the stimulation of an antibody response. Tolerogenic regions are generally regions that can be presented in particular cellular interactions involving T cells. Tolerogenic regions may be present and capable of inducing tolerance upon presentation of the intact antigen. Some antigens contain cryptic tolerogenic regions, in that the processing and presentation of the native antigen does not normally trigger tolerance. An elaboration of cryptic antigens and their identification is found in International Patent Publication WO 94/27634.

[0109] In certain embodiments, two, three, or a higher plurality of inducing antigens are used. It may be desirable to implement these embodiments when there are a plurality of target antigens, or to provide a plurality of bystanders for the target. For example, both insulin and glucagon can be mixed with a mucosal binding component in the treatment of diabetes. It may also be desirable to provide a cocktail of antigens to cover several possible alternative targets. For example, a cocktail of histocompatibility antigen fragments could be used to tolerize a subject in anticipation of future transplantation with an allograft of unknown phenotype. Allovariant regions of human leukocyte antigens are known in the art: e.g., Immunogenetics 29:231, 1989.

[0110] Inducing antigens can be prepared by a number of techniques known in the art, depending on the nature of the molecule. Polynucleotide, polypeptide, and carbohydrate antigens can be isolated from cells of the species to be treated in which they are enriched. Short peptides are conveniently prepared by amino acid synthesis. Longer proteins of known sequence can be prepared by synthesizing an encoding sequence or PCR-amplifying an encoding sequence from a natural source or vector, and then expressing the encoding sequence in a suitable bacterial or eukaryotic host cell.

[0111] In various embodiments, the combination comprises a complex mixture of antigens obtained from a cell or tissue, one or more of which plays the role of inducing antigen. The antigens may be in the form of whole cells, either intact or treated with a fixative such as formaldehyde, glutaraldehyde, or alcohol. The antigens may be in the form of a cell lysate, created by detergent solubilization or mechanical rupture of cells or tissue, followed by clarification. The antigens may also be obtained by subcellular fractionation, particularly an enrichment of plasma membrane by techniques such as differential centrifugation, optionally followed by detergent solubilization and dialysis. Other separation techniques are also suitable, such as affinity or ion exchange chromatography of solubilized membrane proteins.

[0112] In one embodiment, the antigenic peptide or protein is an autoantigen, an alloantigen or a transplantation antigen. In yet another particular embodiment, the autoantigen includes, but is not limited to, myelin basic protein, collagen or fragments thereof, DNA, nuclear and nucleolar proteins, mitochondrial proteins and pancreatic β-cell proteins.

[0113] The disclosure provides for the induction of tolerance to an autoantigen for the treatment of autoimmune diseases by administering the antigen for which tolerance is desired. For example, autoantibodies directed against the myelin basic protein (MBP) are observed in patients with multiple sclerosis, and, accordingly, MBP antigenic peptides or proteins may be used in the invention to be delivered using the compositions of the present invention to treat and prevent multiple sclerosis.

[0114] By way of another non-limiting example, an individual who is a candidate for a transplant from a non-identical twin may suffer from rejection of the engrafted cells, tissues or organs, as the engrafted antigens are foreign to the recipient. Prior tolerance of the recipient individual to the intended graft abrogates or reduces later rejection. Reduction or elimination of chronic anti-rejection therapies may be achieved by the practice of the present invention. In another example, many autoimmune diseases are characterized by a cellular immune response to an endogenous or self antigen. Tolerance of the immune system to the endogenous antigen is desirable to control the disease.

[0115] In a further example, sensitization of an individual to an industrial pollutant or chemical, such as may be encountered on-the-job, presents a hazard of an immune response. Prior tolerance of the individual's immune system to the chemical, in particular in the form of the chemical reacted with the individual's endogenous proteins, may be desirable to prevent the later occupational development of an immune response.

[0116] Allergens are other antigens for which tolerance of the immune response thereto is also desirable are provided. Exemplary allergens, include, but are not limited to environmental or food allergens, such as Bahia grass pollen (BaGP), peach allergen Pru p 3, alpha s 1-Casein Milk allergen, peanut allergen (Ara h 1, Ara h 2, Ara h 3, Ara h 4, Ara h 5, Ara h6, Ara h 7, Ara h 8, Ara h 9, Ara h 10, Ara h 11, Ara h 12, Ara h 13, Ara h 14, Ara h15, Ara h 16, Ara h 17, and Ara h 18), Api g 1 celery allergen, Ber e 1 Brazil nut allergen, B-Lactoglobulin Milk allergen, Bovine serum albumin, Cor a 1.04 Hazelnut allergen, Ovalbumin Egg allergen, tree nut allergen, milk allergen, egg allergen, fish allergen, wheat allergen, pollen, Japanese cedar pollen, dust allergen, pet dander allergen, cat allergen, dog allergen, shellfish allergen, soy allergen, sesame allergen, meat allergen, legume allergen, grass allergen, bee venom allergen, or mold allergen.

[0117] Notably, even in diseases where the pathogenic autoantigen is unknown, bystander suppression may be induced using antigens present in the anatomical vicinity. For example, autoantibodies to collagen are observed in rheumatoid arthritis and, accordingly, a collagen-encoding gene may be utilized as the antigen-expressing gene module in order to treat rheumatoid arthritis (see e.g. Choy (2000) Curr Opin Investig Drugs 1: 58-62). Furthermore, tolerance to beta cell autoantigens may be utilized to prevent development of type 1 diabetes (see e.g. Bach and Chatenoud (2001) Ann Rev Immunol 19: 131-161).

[0118] As another example, auto-antibodies directed against myelin oligodendrocyte glycoprotein (MOG) are observed in autoimmune encephalomyelitis and in many other CNS diseases as well as multiple sclerosis (see e.g. Iglesias et al. (2001) Glia 36: 22-34). Accordingly, use of MOG antigen expressing constructs in the invention allows for treatment of multiple sclerosis as well as related autoimmune disorders of the central nervous system.

[0119] Still other examples of candidate autoantigens for use in treating autoimmune disease include those described in WO20131319253 and WO2015023796. In one embodiment, the antigen is gliadin or gliadin epitopes for use in treating celiac disease. In one embodiment, antigens set out in SEQ ID NOs: 1295-1724, SEQ ID NO: 1725, SEQ ID NOs: 1726-1766, SEQ ID NOs: 4983-4985 or SEQ ID NOs: 4986-5140 are provided for use in treating celiac disease. In one embodiment, antigens set out in SEQ ID NOs: 1295-1724, SEQ ID NOs: 1726-1766, or SEQ ID NOs: 4986-5140 are provided for use in treating celiac disease. In one embodiment, gliadin epitopes are selected from SEQ ID NOs: 4983-4985. In one embodiment, protein-glutamine gamma glutamyltransferase 2 epitopes are selected from SEQ ID NO: 1725.

[0120] In one embodiment, the antigen is islet-specific glucose-6-phophatase catalytic subunit-related protein (IGRP), zinc transporter 8 (ZnT8), proinsulin and glutamic acid decarboxylase 65 (GAD65) for use in treating insulin-dependent diabetes mellitus. Antigens set out in Figure 9 are provided for use in treating treat type 1 diabetes or latent autoimmune diabetes of adults. In one embodiment, antigens selected from SEQ ID NOs: 1767-1840, SEQ ID NOs: 1842-1962, SEQ ID NOs: 1964-2027, SEQ ID NOs: 2029-2073, SEQ ID NOs: 2075-2113, SEQ ID NOs: 2115-2197, SEQ ID NOs: 2199-2248, SEQ ID NOs: 2250-2259, SEQ ID NOs: 2261-2420, SEQ ID NOs: 2422-2486, or SEQ ID NOs: 2489-2505 are provided for use in treating type 1 diabetes mellitus. In one embodiment, the insulin epitope is set out in SEQ ID NO: 4981. In one embodiment, the glutamic acid decarboxylase epitope is set out in SEQ ID NO: 4982. In one embodiment, glutamate decarboxylase 2 epitopes are set out in SEQ ID NO: 1841, SEQ ID NO: 1963, SEQ ID NO: 2114, or SEQ ID NO: 2249. In one embodiment, protein

tyrosine phosphatase receptor type N precursor epitopes are set out in SEQ ID NO: 2028 or SEQ ID NO: 2074. In one embodiment, the zinc transporter 8 isoform epitope is set out I SEQ ID NO: 2421. In one embodiment, the receptor type tyrosine- protein phosphatase N2 epitopes are set out in SEQ ID NO: 2198, SEQ ID NO: 2260, or SEQ ID NO: 2487. In one embodiment, the tyrosine phosphatase epitope is set out in SEQ ID NO: 2488.

[0121] In some embodiments, the antigen is collagen type 11, human cartilage gp39 (HCgp39) and gp130-RAPS for use in treating rheumatoid arthritis. In some embodiments, the antigens are citrullinated antigens for use in treating rheumatoid arthritis or hidradenitis suppurativa. In some embodiments, the antigens are set out in SEQ ID NOs: 2506-3260 or SEQ ID NOs: 3262-3693. In some embodiments, the Chain A, crystal structure of human IgM rheumatoid factor Fab in complex with its autoantigen IgG Fc is set out in SEQ ID NO: 3261.

[0122] In one embodiment, the antigens are myelin basic protein (MBP), proteolipid protein (PLP), and myelin oligodendrocyte glycoprotein (MOG, see above) for use in treating multiple sclerosis. In one embodiment, the antigens are selected from myelin oligodendrocyte protein, myelin basic protein, proteolipid protein, myelin associated glycoprotein, 2',3'-cyclic nucleotide 3'-phosphodiesterase for use in treating multiple sclerosis. In one embodiment, antigens for use in treating multiple sclerosis are set out in SEQ ID NO: 2-1294, SEQ ID NO: 4975-4976, SEQ ID NO: 1, SEQ ID NO: 4978, SEQ ID NO: 4977, or SEQ ID NO: 4980. In one embodiment, antigens for use in treating multiple sclerosis are set out in SEQ ID NO: 87, SEQ ID NO: 16, SEQ ID NO: 88, SEQ ID NO: 471, SEQ ID NO: 23, SEQ ID NO: 84, SEQ ID NO: 89, SEQ ID NO: 69, SEQ ID NO: 549, SEQ ID NO: 1092, SEQ ID NO: 1108, SEQ ID NO: 47, SEQ ID NO: 388, SEQ ID NO: 1268, and SEQ ID NO: 1056. In one embodiment, antigens for use in treating multiple sclerosis are set out in SEQ ID NO: 87, SEQ ID NO: 16, SEQ ID NO: 88, SEQ ID NO: 471, SEQ ID NO: 23, SEQ ID NO: 84, SEQ ID NO: 89, and SEQ ID NO: 69. In various embodiments, the myelin basic epitope is set out in SEQ ID NO: 4975 or SEQ ID NO:4976. In various embodiments, the myelin oligodendrocyte glycoprotein epitope is set out in SEQ ID NO: 1 or SEQ ID NO:4978. In one embodiment, the proteolipid protein epitope is set out in SEQ ID NO: 4977. In various embodiments, the myelin associated glycoprotein epitope is set out in SEQ ID NO: 4980.

[0123] In some embodiments, the antigens for use in treating systemic lupus erythematosus are selected from ATP-dependent DNA helicase 2 subunit 1, small nuclear ribonucleoprotein Sm D1, or beta-2-glycoprotein 1. In some embodiments, the antigens for use in treating systemic lupus erythematosus are set out in SEQ ID NOs: 3694-3857 or SEQ ID NOs: 3860-

4565. In some embodiments, the epitopes from ATP-dependent DNA helicase 2 subunit 1 is set out in SEQ ID NO: 3858. In some embodiments, the epitope from small nuclear ribonucleoprotein Sm D1 is set out in SEQ ID NO: 3859. In some embodiments, the epitope from beta-2-glycoprotein 1 is set out in SEQ ID NO: 4357.

[0124] In some embodiments, the antigens for use in treating Good Pasture's syndrome are selected from type IV collagen. In some embodiments, the antigens for use in treating Good Pasture's syndrome are set out in SEQ ID NOs: 4566-4576, SEQ ID NOs: 4578-4610, SEQ ID NOs: 4612-4613, or SEQ ID NOs:5018-5039. In some embodiments, the α3 chain of type IV collagen epitope is set out in SEQ ID NO: 5017, SEQ ID NO: 4577, or SEQ ID NO: 4611.

[0125] In some embodiments, the antigens for use in treating autoimmune uveitis are selected from heat shock protein or αβ-crystallin. In some embodiments, the antigens for use in treating autoimmune uveitis are set out in SEQ ID NOs: 4614-4653. In some embodiments, the antigens for use in treating autoimmune thyroiditis are selected from thyroid peroxidase, or thyrotropin receptor. In some embodiments, the antigens for use in treating autoimmune thyroiditis are set out in SEQ ID NOs: 4654-4694, SEQ ID NOs: 4696-4894, SEQ ID NOs: 4896-4901, SEQ ID NOs: 4695, or SEQ ID NOs: 4895. In some embodiments, the antigen for use in treating autoimmune myositis is synthetase Jo-1. In some embodiments, the antigens for use in treating autoimmune myositis are set out in SEQ ID NOs: 4902-4906. In some embodiments, the antigen for use in treating autoimmune vasculitis are set out in SEQ ID NOs: 4907-4914. In some embodiments, the antigens for use in treating autoimmune pancreatitis are set out in SEQ ID NOs: 4915-4917. In some embodiments, the antigen for use in treating Crohn's Disease are set out in SEQ ID NOs: 4918-4941. In some embodiments, the antigens for use in treating ulcerative colitis are set out in SEQ ID NOs: 4942-4952. In some embodiments, the antigens for use in treating psoriasis are set out in SEQ ID NOs: 4953-4963. In some embodiments, the antigens for use in treating reactive arthritis are set out in SEQ ID NOs: 4964-4974.

[0126] Additional antigens contemplated for use in a composition include fibrillarin, and small nucleolar protein (snoRNP) to treat scleroderma; thyroid stimulating factor receptor (TSH-R) for use in treating Graves' disease; thyroid stimulating factor receptor or IGF-1R for use in treating thyroid eye disease; cytosolic 5'-nucleotidase 1A (cN1A) for use in treating inclusion body myositis, hypocretins such as orexin-1 or orexin-2 for use in treating narcolepsy, nuclear antigens, histones, glycoprotein gp70 and ribosomal proteins for use in treating systemic lupus erythematosus; pyruvate dehydrogenase dehydrolipoamide acetyltransferase (PDC-E2) for use in treating primary biliary cholangitis; tyrosinase, melan-A (MLANA), premelanosome protein

(PMEL) for use in treating vitiligo; aquaporin 4 (e.g. SEQ ID NO:4979) for use in treating neuromyelitis optica spectrum disorder; cN-1A for use in treating inclusion body myositis, MDA5 for use in treating MDA5 myositis, desmoglein 1 and/or desmoglein 3 for use in treating pemphigus vulgaris; BP180 and/or BP230 for use in treating bullous pemphigoid; Gd-IgA1 for use in treating IgA nephropathy; 21-hydroxylase (21OH) for use in treating Addison's disease; acetylcholine receptor for use in treating myasthenia gravis; MuSK for use in treating myasthenia gravis; GPIIb, GPIIIa for use in treating ITP; H+K+ATPase for use in treating autoimmune gastritis; hair follicle antigens for use in treating alopecia areata; and human tropomyosin isoform 5 (hTM5) for use in treating ulcerative colitis. Antigens set out in Figure 6 (SEQ ID NO: 5141-5161)(acetylcholine receptor alpha peptides) are contemplated for use in treating myasthenia gravis, including antigens having amino acid sequences set out in SEQ ID NO: 5143, SEQ ID NO: 5145, SEQ ID NO: 5148, SEQ ID NO: 5153, SEQ ID NO: 5159, SEQ ID NO: 5160, and SEQ ID NO: 5161 listed in Figure 6. Antigens set out in Figure 7 (SEQ ID NO: 5162-5987) (e.g., regulatory factor X4 (RFX4), orexin-1/HCRT, hemagglutinin (HA), neuraminidase (NA), influenza RNA-dependent RNA polymerase subunit 1 (PB1), or influenza nucleoprotein (NP), are contemplated for use in treating narcolepsy. Antigens set out in Figure 8 (SEQ ID NO: 5988-6010) (PDC-E2 peptides) are contemplated for use in treating primary biliary cholangitis.

[0127] In one embodiment, the antigens comprising one or more epitopes are associated with allergies, autoimmune diseases and/or inflammatory diseases or disorders. The antigens may comprise one or more copies of an epitope. In one embodiment, the antigens comprise a single epitope associated with one disease or disorder. In a further embodiment, the antigens comprise more than one epitope associated with the same disease or disorder. In yet a further embodiment, the antigens comprise more than one epitope associated with different diseases or disorders. In a further embodiment, the antigens comprise one or more epitopes associated with one or more allergies.

[0128] Exemplary antigens are also set out in Figure 5, Figure 6, Figure 7, Figure 8, or Figure 9.

[0129] A proxy for tolerogenic activity is the ability of an intact antigen or fragment to stimulate the production of an appropriate cytokine at the target site. The immunoregulatory cytokine released by T suppressor cells at the target site is thought to be TGF-β (Miller et al., Proc. Natl. Acad. Sci. USA 89:421, 1992). Other factors that may be produced during tolerance are the cytokines IL4 and IL-10, and the mediator PGE. In contrast, lymphocytes in tissues

undergoing active immune destruction secrete cytokines such as IL-I, IL-2, IL-6, and γ-IFN. Hence, the efficacy of a candidate inducing antigen can be evaluated by measuring its ability to stimulate the appropriate type of cytokines.

Methods of Use

[0130] Provided herein is a method of inducing tolerance to a subject in need thereof comprising administering to a subject a composition comprising: (i) one or more antigens (ii) one or more agents that activate the cGAS-STING pathway i.e., cGAS-STING activating agent as described herein. In various embodiments, the composition comprises one or more antigen and cGAS-STING activating agent in the same composition. In various embodiments, the composition is an admixture comprising one or more antigen and cGAS-STING activating agent in different compositions for use in combination. In some embodiments, the composition comprises one or more antigens coupled to a cGAS-STING activating agent and liver targeting moieties.

[0131] In various embodiments, the disclosure provides a method of inducing antigen specific tolerance in a subject comprising; administering to said subject, a composition comprising (i) one or more antigens; and (ii) one or more cGAS-STING activating agents. In various embodiments, the composition comprises one or more antigen and cGAS-STING activating agent in the same composition. In various embodiments, the composition is an admixture comprising the one or more antigen and cGAS-STING activating agent in different compositions for use in combination.

[0132] In various embodiments, if the one or more antigens and the one or more cGAS-STING activating agents are in separate compositions to be administered in combination, the one or more cGAS-STING activating agent compositions are administered prior to, concomitantly with or subsequent to the administration of the antigen composition, or vice versa. In various embodiments, one composition is administered 0.5 to 23 hours prior to administration the other composition. In various embodiments, one composition is administered 1, 2, 3, 4, 5, 6, or 7 days prior to administration of the other composition. In various embodiments, one composition is administered 1, 2, 3, or 4 weeks prior to administration of the other composition. In various embodiments, one composition is administered 0.5 to 24 hours subsequent to administration of the other composition. In various embodiments, one composition is administered 1, 2, 3, 4, 5, 6, or 7 days subsequent to administration of the other composition. In various embodiments, one composition is administered 1, 2, 3, or 4 weeks subsequent to administration of the other composition.

[0133] In various embodiments, the compositions are administered at a dose from about 0.001 to about 10 mg/kg, from about 0.005 to about 12 mg/kg, from about 0.01 to about 12 mg/kg, from about 0.05 to about 12 mg/kg, from about 0.1 to about 12 mg/kg, about 0.5 to 10 mg/kg, from about 1 to 8 mg/kg, from about 1.5 to 10 mg/kg, from about 2 to 12 mg/kg, from about 2 to 10 mg/kg, from about 3 to 10 mg/kg, from about 4 to 10 mg/kg, from about 4 to 12 mg/kg, or from about 5 to 12 mg/kg. Optionally, the composition is administered in a dose of about 0.001 mg/kg, about 0.0025 mg/kg, about 0.005 mg/kg, about 0.01 mg/kg, about 0.025 mg/kg, about 0.05 mg/kg, 0.1 mg/kg, 0.25, 0.5 mg/kg, 1.0 mg/kg, 2.0 mg/kg, 4.0 mg/kg, 6 mg/kg, 8.0 mg/kg, 10 mg/kg, or 12 mg/kg. Alternatively, the composition is administered at a dose of about 0.1 mg, 0.25 mg, 0.5 mg, 1mg, 2 mg, 2.5 mg, 5 mg, 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, 300 mg, 325 mg, 350 mg, 400 mg, 425 mg, 450 mg, 475 mg, 500 mg, 525 mg, 550 mg, 575 mg, 600 mg, 625 mg, 650 mg, 675 mg, 700 mg, 725 mg, 750 mg, 775 mg, or 800 mg. In another embodiment, the composition is administered at a concentration of between about 0.0005 mg/mL and about 50 mg/mL between about 0.05 mg/mL and about 50 mg/mL, optionally about 0.0005 mg/mL, 0.001 mg/mL, 0.005 mg/mL, 0.01 mg/mL, 0.05 mg/mL, 0.1 mg/mL, 0.5 mg/mL, 1 mg/mL, 2 mg/mL, 3 mg/mL, 4 mg/mL, 5 mg/mL, 6 mg/mL, 7 mg/mL, 8 mg/mL, 9 mg/mL, 10 mg/mL, 11 mg/mL, 12.5 mg/mL, 15 mg/mL, 17.5 mg/mL, 20 mg/mL, 25 mg/mL, 30 mg/mL, 40 mg/mL, or 50 mg/mL.

[0134] In various embodiments, the composition is administered in a single dose or in multiple doses. In various embodiments, the composition is administered in two doses one-week apart. In various embodiments, the composition is administered once weekly, once every two weeks, once every three weeks, once every 4 weeks, once every two months, once every three months, once every 6 months, once every 9 months, or once per year. In various embodiments, the method further comprises administering at least one booster dose of the composition. In various embodiments, a booster dose of the composition is administered in a single dose or in multiple doses following the loading composition administration. In various embodiments, the booster dose is administered once weekly, once every two weeks, once every three weeks, once every 4 weeks, once every two months, once every three months, once every 4 months, once every 5 months, once every 6 months, or once per year. In various embodiments, the composition is administered in two loading doses one-week apart followed by at least one booster dose administered as a single dose once every one month, every two months or three months. In various embodiments, the composition is administered in two loading doses one-week apart followed by at least one booster dose administered as a single dose once every one month, every two months or three months, once every 4 months, once

every 5 months, once every 6 months, or once per year. In various embodiments, the composition is administered in two loading doses one-week apart followed by a booster dose administered as a single dose once every three months. In various embodiments, one, two, three, four or five booster doses are administered to a subject.

[0135] In various embodiments, the composition is administered intravenously, subcutaneously, intramuscularly, intraperitoneally, intranasally, inhaled, intra-lymphatically, or orally.

[0136] In some embodiments, the antigens are encapsulated in or coupled to carrier particles and the cGAS-STING activating agent is not encapsulated in or coupled to carrier particles, i.e., the cGAS-STING activating agent is "free" or "free in solution". In some embodiments, the antigens are "free" and the cGAS-STING activating agent is encapsulated in or coupled to carrier particles. In various embodiments, the antigens and cGAS-STING activating agent are both encapsulated in or coupled to carrier particles. In some embodiments, the antigens are encapsulated in or coupled to a first population of carrier particles and the cGAS-STING activating agents are encapsulated in or coupled to a second population of carrier particles. In various embodiments, the composition comprises the carrier particles encapsulating or coupled to one or more antigen and cGAS-STING activating agent in the same composition. In various embodiments, the composition is an admixture comprising carrier particles encapsulating or coupled to one or more antigen and carrier particles encapsulating or coupled to cGAS-STING activating agent in different compositions for use in combination. In various embodiments, the one or more antigens are coupled to cGAS-STING activating agents.

[0137] The carrier particles of the current disclosure can be given in any dose effective to dampen the inflammatory immune response in a subject in need thereof. In certain embodiments, about 10^2 to about 10^{20} particles are provided to a subject in need thereof. In a further embodiment between about 10^3 to about 10^{15} particles are provided. In yet a further embodiment between about 10^6 to about 10^{12} particles are provided. In still a further embodiment between about 10^8 to about 10^{10} particles are provided. In a preferred embodiment the preferred dose is 0.1% solids/ml. Therefore, for 0.5 μm beads, a preferred dose is approximately 4×10^9 beads, for 0.05 μm beads, a preferred dose is approximately 4×10^{12} beads, for 3 μm beads, a preferred dose is 2×10^7 beads. However, any dose that is effective in treating the particular condition to be treated is encompassed by the current disclosure.

[0138] In some embodiments, the subject suffers from a disease selected from the group consisting of achalasia, Addison's disease, adult Still's disease, agammaglobulinemia, alopecia areata, Alzheimer's disease, amyloidosis, amyotrophic lateral sclerosis, ankylosing spondylitis, anti-GBM/anti-TBM nephritis, antiphospholipid syndrome, autoimmune angioedema, autoimmune dysautonomia, autoimmune encephalomyelitis, autoimmune hepatitis, autoimmune inner ear disease (AIED), autoimmune myocarditis, autoimmune oophoritis, autoimmune orchitis, autoimmune pancreatitis, autoimmune retinopathy, autoimmune urticaria, axonal & neuronal neuropathy (AMAN), Baló disease, Behcet's disease, benign mucosal pemphigoid, bullous pemphigoid, Castleman disease (CD), celiac disease, Chagas disease, chronic inflammatory demyelinating polyneuropathy (CIDP), chronic recurrent multifocal osteomyelitis (CRMO), Churg-Strauss syndrome (CSS), eosinophilic granulomatosis (EGPA), cicatricial pemphigoid, Cogan's syndrome, cold agglutinin disease, congenital heart block, Coxsackie myocarditis, CREST syndrome, Crohn's disease, dermatitis herpetiformis, dermatomyositis, Devic's disease (neuromyelitis optica), discoid lupus, Dressler's syndrome, endometriosis, eosinophilic esophagitis (EoE), eosinophilic fasciitis, epilepsy, erythema nodosum, essential mixed cryoglobulinemia, Evans syndrome, fibromyalgia, fibrosing alveolitis, giant cell arteritis (temporal arteritis), giant cell myocarditis, glaucoma, glomerulonephritis, Goodpasture's syndrome, granulomatosis with polyangiitis, Graves' disease, Guillain-Barre syndrome, Hashimoto's thyroiditis, hemolytic anemia, Henoch-Schonlein purpura (HSP), herpes gestationis, pemphigoid gestationis (PG), hidradenitis suppurativa (HS) (acne inversa), hypogammalglobulinemia, IgA nephropathy, idiopathic thrombocytopenic purpura (ITP), inclusion body myositis (IBM), anti-melanoma differentiation-associated gene 5 (MDA5 myositis), inflammatory bowel disease, interstitial cystitis (IC), juvenile arthritis, juvenile diabetes (type 1 diabetes), juvenile myositis (JM), Kawasaki disease, latent autoimmune diabetes od adults (LADA), Lambert-Eaton syndrome, leukocytoclastic vasculitis, lichen planus, lichen sclerosus, ligneous conjunctivitis, linear IgA disease (LAD), lupus/systemic lupus, Lyme disease chronic, membranous nephropathy, Meniere's disease, microscopic polyangiitis (MPA), mixed connective tissue disease (MCTD), myelin oligodendrocyte glycoprotein associated disease (MOGAD)Mooren's ulcer, Mucha-Habermann disease or PLEVA, multifocal motor neuropathy (MMN) or MMNCB, multiple sclerosis, myasthenia gravis, myositis, narcolepsy, neonatal lupus, neutropenia, ocular cicatricial pemphigoid, palindromic rheumatism (PR), pediatric acute liver failure (PALF), PANDAS, paraneoplastic cerebellar degeneration (PCD), Parkinson's disease, paroxysmal nocturnal hemoglobinuria (PNH), Parry Romberg syndrome, pars planitis (peripheral uveitis), parsonage-turner syndrome, pemphigus foliaceous, pemphigus vulgaris,

peripheral neuropathy, perivenous encephalomyelitis, pernicious anemia (PA), POEMS syndrome, polyarteritis nodosa, polyglandular syndromes type I, II, III, polymyalgia rheumatica, polymyositis, post-myocardial infarction syndrome, post-pericardiotomy syndrome, primary biliary cholangitis, primary sclerosing cholangitis, progesterone dermatitis, psoriasis, psoriatic arthritis, pure red cell aplasia (PRCA), pyoderma gangrenosum, Raynaud's phenomenon, reactive arthritis, reflex sympathetic dystrophy, relapsing polychondritis, restless legs syndrome (RLS), retroperitoneal fibrosis, rheumatic fever, rheumatoid arthritis, sarcoidosis, Schmidt syndrome, scleritis, scleroderma, Sjögren's syndrome, sperm & testicular autoimmunity, stiff person syndrome (SPS), sub-acute bacterial endocarditis (SBE), Susac's syndrome, sympathetic ophthalmia (SO), Takayasu's arteritis, temporal arteritis/giant cell arteritis, thrombotic thrombocytopenic purpura (TTP), thyroid eye disease (TED), Tolosa-Hunt syndrome (THS), transverse myelitis, ulcerative colitis, undifferentiated connective tissue disease (UCTD), uveitis, vasculitis, vitiligo, PALF/ALF, Rasmussen's encephalitis, Lewy body dementia, encephalitis, Vogt-Koyanagi-Harada disease, a mucopolysaccharide storage disorder, gangliosidosis, alkaline hypophosphatasia, cholesterol ester storage disease, hyperuricemia, growth hormone deficiency, renal anemia, Gaucher's disease, Fabry's disease, Hurler's disease, Hunter's disease, Maroteaux-Lamy disease, hemophilia A, hemophilia B, von Willebrand disease, venous thrombosis, purpura fulminans, Mucopolysaccaridosis VI, Pompe disease, inherited retinal diseases (e.g., Leber congenital amaurosis, RPE65 mutation-associated retinal dystrophy), spinal muscular atrophy (SMA), inherited blood disorders, sickle cell disease, β-thalassemia, severe combined immunodeficiency (SCID), ADA-SCID (adenosine deaminase deficiency SCID), lipoprotein lipase deficiency, neurodegenerative diseases, Genetic Disorders, cystic fibrosis, Duchenne Muscular Dystrophy (DMD), Cardiomyopathies, Hunter Syndrome (MPS II), Mucopolysaccharidosis, Metabolic Disorders, Phenylketonuria (PKU), Crigler-Najjar syndrome type 1, methylmalonic acidemia, propionic acidemia, ornithine transcarbamylase deficiency, or glycogen storage disease type 1a.

[0139] In a further embodiment, administration of the composition promotes cell apoptosis. In a further embodiment, the administration of the composition results in release of cellular debris containing antigen. In a further embodiment, the administration of the composition results in release of oxidized DNA. In a further embodiment, the administration of the composition results in release of neutrophil extracellular traps (NETs). In a further embodiment, administration of the composition results in release of reactive oxygen species. In a further embodiment, administration of the composition results in release of mitochondrial reactive oxygen species. In

a further embodiment, administration of the composition results in intrinsic and/or extrinsic STING signaling. In a further embodiment, administration of the composition results in increases in cGAS-STING signaling pathway expression compared to before administration. In some embodiments, administration of the composition results in increases in anti-inflammatory or regulatory cytokines compared to before the administration. In some embodiments, administration of the composition results in decreases in pro-inflammatory cytokines compared to before the administration. In a further embodiment, the administration of the composition results in increases in IFN signaling. In a further embodiment, the administration of the composition results in increases in interleukin-10 (IL-10) cytokine, PD-1, and/or type 1 interferon expression compared to before administration. In a further embodiment, the administration of the composition results in increases in interferon beta (IFN-B) expression compared to before administration. In a further embodiment, the administration of the composition results in increases in Ki67, CD25, Foxp3, CTLA4, Nrp1, Helios, LAP, CCL3, Lag3, IFNAR1, IFNAR2, TGF-beta, expression compared to before administration. In a further embodiment, the administration of the composition results in decreases in IFN-gamma, IL-17, GM-CSF, IFN-gamma:IL-10 ratio, IFN-gamma:Foxp3 ratio, expression compared to before administration. In a further embodiment, the administration of the composition results in T cell reprograming. In a further embodiment, the administration of the composition results in increases in mitotic sister chromatid segregation pathway, sister chromatid segregation pathway, chromosome organization pathway, nuclear chromosome segregation pathway, meiotic nuclear division pathway, nuclear division pathway, meiotic cell cycle progress pathway, chromosome segregation pathway, meiotic cell cycle pathway, organelle fission pathway expression compared to before administration. In a further embodiment, the administration of the composition results in decreases in G protein-coupled receptor signaling pathway, defense response pathway, positive regulation of cell differentiation pathway, locomotion pathway, regulation of locomotion pathway, regulation of cell mobility pathway, cell activation pathway, and response to external stimulus pathway compared to before administration. In a further embodiment, the administration of the composition results in induction of infectious tolerance. In a further embodiment, the administration of the composition results in decreases in IFN-γ, IL-17, and GM-CSF expression compared to before administration. In an embodiment, administration of the composition results in increases in cells with a Treg/Tr1 phenotype compared to before administration. In a further embodiment, the administration of the composition results in the conversion of effector T cells to regulatory T cells. In a further embodiment, the administration of the composition results in the induction and expansion of both antigen specific and non-specific

regulatory T cells. In a further embodiment, the administration of the composition results in activation induced death of effector T cells. In a further embodiment, the administration of the composition results in anergy of effector T cells. In a further embodiment, the administration of the composition results in apoptosis of effector T cells. In a further embodiment, the administration of the composition results in the isolation of effector T cells in the lymph nodes and spleen inhibiting their ability to traffic to peripheral sites and cause inflammation. In some embodiments, administration of the composition results in decreases in antigen-specific or overall antibody levels compared to before the administration. In some embodiments, administration of the composition results in decreases in pathogenic B-cell levels compared to before the administration.

[0140] In some embodiments, the compositions described herein are administered in combination with one or more immunomodulatory agents. In some embodiments, the immunomodulatory agent is selected from the group consisting of immunosuppressive agents, cytokines or chemokines, immunostimulants, or immune cell function modulators. In some embodiments, the immunomodulatory agent is selected from the group consisting of mTOR inhibitors, glucocorticoids, vitamins and vitamin derivatives, calcineurin inhibitors, nuclear factor kappa B inhibitors, kynurenine, aryl hydrocarbon receptor agonists, glycan and glycan binding proteins, apoptotic signaling pathway agonists, TLR agonists, inhibitory receptor activating agents, T-cell modulators, immunological synapse modulators, or Janus kinase inhibitors. In various embodiments, the immunomodulatory agents are selected from the group consisting of dexamethasone, rapamycin, cyclosporine A, FK506, ITE, andrographolide, tofacitinib, rosiglitazone, iloprost, IL-10, PD-1, PD-L1/L2, IL-2, TGF-β, TGF-β-signaling agonist, GM-CSF, IFN-β, IL-35, IL-27, IL-4, hepatocyte growth factor, Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) agonist, vitamin D, retinoic acid.

[0141] In various embodiments, the subject suffers from an orphan autoimmune condition. In certain embodiments, the individual suffers from a disorder associated with disease therapy.

[0142] In various embodiments, the subject is a subject who has received therapy, a subject who is receiving therapy, or a subject who will receive therapy for an autoimmune disease or allergy.

[0143] In some embodiments, the invention relates to uses of compositions of this disclosure prior to the onset of disease. In other embodiments, the disclosure relates to use of the compositions described herein to inhibit ongoing disease. In some embodiments, relates to use of the compositions described herein to ameliorate disease in a subject. By ameliorating

disease in a subject is meant to include treating, preventing or suppressing the disease in the subject.

[0144] Autoimmune diseases can be divided in two broad categories: organ-specific and systemic. Autoimmune diseases include, without limitation, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), type I diabetes mellitus, type II diabetes mellitus, multiple sclerosis (MS), immune-mediated infertility such as premature ovarian failure, scleroderma, Sjogren's disease, vitiligo, alopecia (baldness), polyglandular failure, Grave's disease, hypothyroidism, autoimmune myositis (includes polymyositis (including anti-synthetase antibody syndrome and myositis associated with other connective tissue disorders), inclusion body myositis, dermatomyositis, necrotizing myopathy, juvenile myositis), IgA nephropathy, pemphigus vulgaris, pemphigus foliaceus, IgA nephropathy, inflammatory bowel disease including Crohn's disease and ulcerative colitis, autoimmune hepatitis including that associated with hepatitis B virus (HBV) and hepatitis C virus (HCV), hypopituitarism, graft-versus-host disease (GvHD), myocarditis, Addison's disease, autoimmune skin diseases, uveitis, pernicious anemia, Celiac disease, hypoparathyroidism, neuromyelitis optica, membranous nephropathy, bullous pemphigoid, myasthenia gravis.

[0145] In various embodiments, the autoimmune disease is selected from the group consisting of multiple sclerosis, Addison's disease, ankylosing spondylitis, alopecia, osteoarthritis, psoriatic arthritis, scleroderma, type-I diabetes, rheumatoid arthritis, thyroiditis, systemic lupus erythematosus, Reynaud's syndrome, Behcet's syndrome, Sjorgen's syndrome, autoimmune uveitis, Eaton Lamberts disease, autoimmune myocarditis, inflammatory bowel disease, Amyotrophic Lateral Sclerosis (ALS), Systemic Lupus, Neuromyelitis Optica, Idiopathic Thrombocytopenic Purpura, Thrombotic Thrombocytopenic Purpura, Nephropathy, Bullous Pemphigoid, Pemphigus Vulgaris, IgA nephropathy, Myasthenia Gravis, Celiac disease, ulcerative colitis, Crohn's disease, erythema nodosa, glomerulonephritis, Goodpasture's syndrome, granulomatosis, Grave's disease, thyroid eye disease (TED), narcolepsy, Guillain-Barre syndrome, Hashimoto disease, hemolytic anemia, Kawasaki Disease, mixed connective tissue disease, multifocal motor neuropathy, peripheral biliary cholangitis, polyangiitis overlap syndrome, scleroderma type 1, sclerosis cholangitis, stiff person syndrome, Takayasu arteritis, or Wegener's granulomatosis.

[0146] In various embodiments, the allergy is a food allergy. In various embodiments, the food allergy is a peanut allergy, tree nut allergy, meat allergy, α-gal syndrome, milk allergy, egg allergy, fish allergy, wheat allergy, celery allergy, or peach allergy.

[0147] In various embodiments, the allergy is an environmental allergy. In various embodiments, the environmental allergy is pollen allergy, Japanese cedar pollen, dust allergy, pet dander allergy, or mold allergy. In various embodiments, the pet allergy is cat allergy or dog allergy.

[0148] In some embodiments, the disclosure relates to preventing the relapse of disease. The present disclosure provides compositions and methods that can prevent the effect of dynamic changing disease, a function of "epitope spreading."

[0149] Other embodiments of this disclosure relate to transplantation. This refers to the transfer of a tissue sample or graft from a donor individual to a recipient individual, and is frequently performed on human recipients who need the tissue in order to restore a physiological function provided by the tissue. Tissues that are transplanted include (but are not limited to) whole organs such as kidney, liver, heart, lung; organ components such as skin grafts and the cornea of the eye; and cell suspensions such as bone marrow cells and cultures of cells selected and expanded from bone marrow or circulating blood, and whole blood transfusions.

[0150] Certain embodiments of the disclosure relate to decreasing the risk of host versus graft disease, leading to rejection of the tissue graft by the recipient. The treatment may be performed to prevent or reduce the effect of a hyperacute, acute, or chronic rejection response. Treatment is preferentially initiated sufficiently far in advance of the transplant so that tolerance will be in place when the graft is installed; but where this is not possible, treatment can be initiated simultaneously with or following the transplant. Regardless of the time of initiation, treatment will generally continue at regular intervals for at least the first month following transplant. Follow-up doses may not be required if a sufficient accommodation of the graft occurs, but can be resumed if there is any evidence of rejection or inflammation of the graft. In various embodiments, the tolerization procedures of this disclosure may be combined with other forms of immunosuppression to achieve an even lower level of risk.

[0151] The compositions of the disclosure are also useful for the regeneration of damaged tissue. In one embodiment, administration of the composition(s) described herein to a patient increases the regeneration of damaged epithelial cells in the digestive tract. In a further embodiment, the patient suffers from celiac disease, colitis, Crohn's disease, or inflammatory bowel disease. In another embodiment, administration of the composition of the invention to a patient increases remyelination of neurons. In a further embodiment, the patient suffers from multiple sclerosis. In another embodiment, administration of the composition of the disclosure to a patient decreases liver fibrosis or liver damage. In a further embodiment, the patient suffers

from primary biliary cholangitis. In another embodiment, administration of the composition of the disclosure to a patient increases or preserves islet ß-cell mass. In a further embodiment, the patient suffers from type 1 diabetes. In another embodiment, administration of the composition of the disclosure to a patient increases or preserves hypocretin secretion from neurons. In a further embodiment, the patient suffers from narcolepsy. In another embodiment, administration of the composition of the disclosure to a patient increases or preserves skin pigmentation. In a further embodiment, the patient suffers from vitiligo. In another embodiment, administration of the composition of the disclosure to a patient increases or preserves platelets. In a further embodiment, the patient suffers from ITP. In another embodiment, administration of the composition of the disclosure to a patient increases or preserves acetylcholine receptor signaling. In a further embodiment, the patient suffers from myasthenia gravis. In another embodiment, administration of the composition of the disclosure to a patient decreases or preserves thyroid stimulating hormone receptor signaling. In a further embodiment, the patient suffers from Grave's disease.

[0152] An important factor influencing the success of antigen specific immune tolerance (ASIT) is the longevity of immune tolerance. Several physiological and immunological factors determine the longevity of immune tolerance induced by therapeutic intervention and immune tolerance may begin to diminish over time. It is therefore important to routinely monitor subjects treated with tolerizing therapies to confirm the maintenance of immunological tolerance and re-dose the subject with the tolerizing therapy if a change, weakening, or loss of immune tolerance is observed. However, to our knowledge, there are no existing methods for monitoring maintenance of immunological tolerance in a subject treated with a therapy capable of inducing true immune tolerance and which help inform re-dosing decisions to ensure maintenance of antigen-specific immune tolerance to prevent disease relapse.

[0153] In various embodiments, the present disclosure provides methods for monitoring the immune tolerance status of a subject undergoing treatment for an inflammatory disease or condition and determining whether the subject requires re-administration of the treatment. In various embodiments, the method comprises the steps of (a) obtaining one or more biological samples from the subject prior to administration of treatment and determining the immune tolerance status of the subject by assaying said biological sample(s), (b) obtaining one or more biological samples from the subject after administration of treatment and determining the immune tolerance status of the subject by assaying the biological sample(s), (c) obtaining one or more biological samples from the subject at regular intervals after administration of treatment

and determining the immune tolerance status of the subject by assaying the biological sample(s), and (d) re-administering treatment if the immune tolerance status determined in step (c) indicates a change, weakening, and/or loss of immunological tolerance. In various embodiments, the results from the assay of one or more biological samples in step (c) are compared to the results from the assay of one or more biological samples in steps (a) and/or (b) to generate a signature of immune tolerance status.

[0154] In various embodiments, the biological sample collected from the subject is whole-blood, peripheral blood, peripheral blood mononuclear cells (PBMCs), serum, plasma, urine, cerebrospinal fluid (CSF), stool, a tissue biopsy, and/or a bone-marrow biopsy. In various embodiments, the assay of the biological sample(s) consists of analyzing levels of, and or presence or absence of cell-surface proteins, extracellular proteins, intracellular proteins, nucleic acids, metabolites, and/or combinations thereof. In various embodiments, the assay of one or more biological sample(s) is used to generate a signature of immune tolerance status.

[0155] In various embodiments, the one or more biological samples of step (a) are collected from the subject 1-7 days, 1-4 weeks, and/or 1-12 months prior to administration of immune tolerizing therapy. In various embodiments, the one or more biological samples of step (b) are collected 1-7 days, 1-4 weeks, and/or 1-12 months after administration of the immune tolerizing therapy. In various embodiments, the one or more biological samples of step (c) are collected every 1-7 days, every 1-4 weeks, and/or every 1-12 months after administration of the immune tolerizing therapy. In various embodiments, the one or more biological samples of step (c) are collected at intervals of 1-7 days, every 1-4 weeks, and/or every 1-12 months after administration of the immune tolerizing therapy. In various embodiments, the samples are collected every week, 2 weeks, 4 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 9 months or 12 months.

[0156] The immune tolerance signature of a subject is generated using one or more of the following parameters assayed from one or more biological samples obtained from the subject and stimulated in vivo and/or ex vivo:

[0157] a. proportion of effector T cells in the total T cell population, b. proportion of Treg cells in the total T cell population, c. proportion of effector B cells in the total B cell population, d. levels and/or ratios of specific IgG, IgA, IgM, and/or IgE, e. levels of inflammatory cytokines and chemokines, f. levels of anti-inflammatory cytokines and chemokines, g. levels of inflammatory metabolites, and h. levels of anti-inflammatory metabolites.

[0158] The immune tolerance signature is indicative of maintenance of immune tolerance if 1, 2, 3, 4, 5, 6, 7, or 8 parameters listed in (a)-(h) above indicate maintenance of immune tolerance. In various embodiments, the immune tolerance signature is indicative of maintenance of immune tolerance if at least 2/8 parameters listed in (a)-(h) indicate maintenance of immune tolerance. In various embodiments, the subject is determined to not require treatment if 1, 2, 3, 4, 5, 6, 7, or 8 parameters listed in (a)-(h) above indicate maintenance of immune tolerance. In various embodiments, the subject is determined to not require treatment if at least 3/8 parameters listed in (a)-(h) above indicate maintenance of immune tolerance.

[0159] The immune tolerance signature of a subject generated using one or more parameters described herein indicates weakening and/or absence of immune tolerance prior to or after treatment with tolerizing therapy, if:

[0160] a. the proportion of effector T cells in the total T cell population is between 5%- 100% (e.g., about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 100%, inclusive of all values and ranges between these values), and/or

[0161] b. the proportion of Treg cells in the total T cell population is between 1-3%, and/or

[0162] c. the proportion of effector B cells in the total B cell population is between 5%- 100% (e.g. about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 100%, inclusive of all values and ranges between these values), and/or

[0163] d. the levels and/or ratios of IgG, IgA, IgM, and/or IgE are increased by about 5%-100% (e.g. about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 100%, inclusive of all values and ranges between these values), 10-95%, 15-90%, 20-85%, 25-75%, 30-70%, 35-65%, 40-60%, 45-55%, or 50% or by about 2-100-fold (e.g., about 2, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100-fold inclusive of all values and ranges between these values) relative to a healthy subject and/or one or more baseline measurements taken from the subject during treatment, and/or

[0164] e. levels of inflammatory cytokines/chemokines are increased by about 5%-100% (e.g. about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 100%, inclusive of all values and ranges between these values), 10-95%, 15-90%, 20-85%, 25-75%, 30-70%, 35-65%, 40-60%, 45-55%, or 50% or by about 2-100-fold (e.g., about 2, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100-fold inclusive of all values and ranges between these values) relative to a healthy subject and/or one or more baseline measurements taken from the subject during treatment, and/or

[0165] f. levels of anti-inflammatory cytokines and chemokines are decreased by about 5%-100% (e.g. about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 100%, inclusive of all values and ranges between these values), 10-95%, 15-90%, 20-85%, 25-75%, 30-70%, 35-65%, 40-60%, 45-55%, or 50% or by about 2-100-fold (e.g., about 2, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100-fold inclusive of all values and ranges between these values) relative to a healthy subject and/or one or more baseline measurements taken from the subject during treatment, and/or

[0166] g. levels of inflammatory metabolites are increased by about 5%-100% (e.g. about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 100%, inclusive of all values and ranges between these values), 10-95%, 15-90%, 20-85%, 25-75%, 30-70%, 35-65%, 40-60%, 45-55%, or 50% or by about 2-100-fold (e.g., about 2, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100-fold inclusive of all values and ranges between these values) relative to a healthy subject and/or one or more baseline measurements taken from the subject during treatment, and/or

[0167] h. levels of anti-inflammatory metabolites are decreased by about 5%-100% (e.g. about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 100%, inclusive of all values and ranges between these values), 10-95%, 15-90%, 20-85%, 25-75%, 30-70%, 35-65%, 40-60%, 45-55%, or 50% or by about 2-100-fold (e.g., about 2, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80,

85, 90, 95, or 100-fold inclusive of all values and ranges between these values) relative to a healthy subject and/or one or more baseline measurements taken from the subject during treatment.

[0168] It is contemplated that the one or more biological samples used in the methods are collected from the subject undergoing tolerizing therapy 1-7 days, 1-4 weeks, and/or 1-12 months prior to administration of immune tolerizing therapy. In various embodiments, the one or more biological samples are collected 1-7 days, 1-4 weeks, and/or 1-12 months after administration of the immune tolerizing therapy. In various embodiments, the one or more biological samples are collected every 1-7 days, every 1-4 weeks, and/or every 1-12 months after administration of the immune tolerizing therapy. In various embodiments, the one or more biological samples are collected at intervals of 1-7 days, every 1-4 weeks, and/or every 1-12 months after administration of the immune tolerizing therapy. In various embodiments, the samples are collected every week, 2 weeks, 4 weeks, 1 month, 2 months, 3 months, 4 months, 5 months, 6 months, 9 months or 12 months.

Pharmaceutical Formulations

[0169] Pharmaceutical compositions of the present disclosure containing the cGAS-STING activating agent and antigens described herein and an antigen may contain pharmaceutically acceptable carriers or additives depending on the route of administration. Examples of such carriers or additives include water, a pharmaceutically acceptable organic solvent, collagen, polyvinyl alcohol, polyvinylpyrrolidone, a carboxy-vinyl polymer, carboxymethylcellulose sodium, polyacrylic sodium, sodium alginate, water-soluble dextran, carboxymethyl starch sodium, pectin, methyl cellulose, ethyl cellulose, xanthan gum, gum Arabic, casein, gelatin, agar, diglycerin, glycerin, propylene glycol, polyethylene glycol, Vaseline®, paraffin, stearyl alcohol, stearic acid, human serum albumin (HSA), mannitol, sorbitol, lactose, a pharmaceutically acceptable surfactant and the like. Additives used are chosen from, but not limited to, the above or combinations thereof, as appropriate, depending on the dosage form of the present disclosure.

[0170] Formulation of the pharmaceutical composition will vary according to the route of administration selected (e.g., solution, emulsion). An appropriate composition comprising the therapeutic to be administered can be prepared in a physiologically acceptable vehicle or carrier. For solutions or emulsions, suitable carriers include, for example, aqueous or alcoholic/aqueous solutions, emulsions or suspensions, including saline and buffered media. Parenteral vehicles can include sodium chloride solution, Ringer's dextrose, dextrose and

sodium chloride, lactated Ringer's or fixed oils. Intravenous vehicles can include various additives, preservatives, or fluid, nutrient or electrolyte replenishers.

[0171] A variety of aqueous carriers, e.g., sterile phosphate buffered saline solutions, bacteriostatic water, water, buffered water, 0.4% saline, 0.3% glycine, and the like, and may include other proteins for enhanced stability, such as albumin, lipoprotein, globulin, etc., subjected to mild chemical modifications or the like.

[0172] Therapeutic formulations of the compositions are prepared for storage by mixing the inhibitor having the desired degree of purity with optional physiologically acceptable carriers, excipients or stabilizers (Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980)), in the form of lyophilized formulations or aqueous solutions. Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyldimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl para-bens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugars such as sucrose, mannitol, trehalose or sorbitol; salt-forming counter-ions such as sodium; metal complexes (e.g., Zn-protein complexes); and/or non-ionic surfactants such as TWEEN™, PLURONICS™ or polyethylene glycol (PEG).

[0173] The formulations to be used for in vivo administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes.

[0174] Aqueous suspensions may contain the active compound in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyl-eneoxycetanol, or condensation products of ethylene oxide with partial esters

derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate.

[0175] The cGAS-STING activating agent and antigen composition as described herein can be lyophilized for storage and reconstituted in a suitable carrier prior to use.

[0176] Solid dosage forms for oral administration include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the modified particles are mixed with at least one inert, pharmaceutically acceptable excipient or carrier such as sodium citrate or dicalcium phosphate and/or a) fillers or extenders such as starches, lactose, sucrose, glucose, mannitol, and silicic acid, b) binders such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinylpyrrolidinone, sucrose, and acacia, c) humectants such as glycerol, d) disintegrating agents such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate, e) solution retarding agents such as paraffin, f) absorption accelerators such as quaternary ammonium compounds, g) wetting agents such as, for example, cetyl alcohol and glycerol monostearate, h) absorbents such as kaolin and bentonite clay, and i) lubricants such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof. In the case of capsules, tablets and pills, the dosage form may also comprise buffering agents.

Kits

[0177] The disclosure also provides kits which comprise one or more compounds or compositions packaged in a manner which facilitates their use to practice methods of the disclosure. In one embodiment, such a kit includes a compound or composition described herein (e.g., a composition comprising cGAS-STING activating agent and antigens alone or in combination with another agent), packaged in a container such as a sealed bottle or vessel, with a label affixed to the container or included in the package that describes use of the compound or composition in practicing the method. Preferably, the compound or composition is packaged in a unit dosage form. The kit may further include a device suitable for administering the composition according to a specific route of administration or for practicing a screening assay. Preferably, the kit contains a label that describes use of the particle compositions.

[0178] Additional aspects and details of the disclosure will be apparent from the following examples, which are intended to be illustrative rather than limiting.

EXAMPLES

Example 1: Particles containing a STING agonist with antigen induce antigen-specific tolerance

[0179] PLGA particles encapsulating a STING agonist, *i.e.,* 5,6-dimethylxanthenone-4-acetic acid (DMXAA) were prepared. The particles had an average diameter of 494.6 nm, a charge of -79.9 ± 10.7 mV, with an approximate load of 50.8 ±10.3 ng DMXAA per mg nanoparticle. This first study tested both general safety of particle-DMXAA dosing and determined if dosing resulted in a dose-dependent increase in cytokines/chemokines within the blood at 24 hours post a single dose of particles (0.0 to 2.5mg per dose; 200 μL saline vehicle). To do so, 6-8 week old naïve female SJL/J mice (n=4) were administered the respective dosage of particles intravenously. Mice were observed for 6 hours post dosing and no changes in activity, grooming, and food/water consumption were noted. Serum was collected at 24 hours post dosing, and the level of cytokines/chemokines were measured via multiplex Luminex assay. The data show that treatment with STING encapsulated particles induced an increase in the level of cytokine/chemokines in a dose-dependent manner (Fig. 1).

[0180] Delayed type hypersensitivity (DTH) assay: To determine if PLGA particles containing a STING agonist, *i.e.*, DMXAA and a peptide antigen had increased efficacy with regard to antigen-specific tolerance induction, 6-8 week old naïve female C57BL/6 mice were primed with 100 μg OVA323-339 peptide emulsified in complete Freund's adjuvant (OVA323-339/CFA) via subcutaneous injection in a final volume of 100 μL per mouse. Mice were randomized into five treatment groups (n=5), with mice receiving:

(i) saline

(ii) 0.25 mg CNP-OVA323-339

(iii) 2.5 mg CNP-OVA323-339

(iv) 0.25 mg CNP-DMXAA-OVA323-339

(v) 2.5 mg CNP-DMXAA-OVA323-3

in 200 μL of saline via intravenous injection on Day 0. To generate CNP-OVA323-339 and CNP-DMXAA-OVA323-339: OVA323-339 peptide was coupled to the surface of unloaded PLGA particles and PLGA particles encapsulating STING activating agent DMXAA with 1-ethyl-

3-(3-dimethylaminopropyl) carbodiimide (ECDI). On Day 14 post OVA323-339/CFA priming, the thickness of the mouse ears was measured, and the mice then received 10 μL of PLP139-151 (1 mg/mL) as a negative control peptide challenge via subcutaneous injection in the left ear, and 10 μL of OVA323-339 (1 mg/mL) as the antigen-specific challenge peptide in the right ear. At 24 hours post injection of peptides within the ear, the thick of the ears were measured to determine the level of antigen-specific T cell-induced swelling. The results show that the inclusion of a STING agonist within antigen-specific CNPs increases treatment efficacy, and thereby decreases the dosage of particles required for antigen-specific tolerance induction (Fig. 2).

[0181] Delayed type hypersensitivity (DTH) assay: A second DTH assay was performed to determine if PLGA particles containing a different STING agonist, *i.e.*, 2'3'-cGAMP, particles possessing a protein antigen had increased efficacy with regard to inducing antigen-specific tolerance. 6-8 week old naïve female C57BL/6 mice were primed with 100 μg OVA protein emulsified in complete Freund's adjuvant (OVA/CFA) via subcutaneous injection in a final volume of 100 μL per mouse. Mice were randomized into the following treatment groups (n=5), with mice receiving the following treatments in 200 μL of saline via intravenous injection on Day 0:

(i) Saline

(ii) Unloaded CNP particles 2.5 mg dose

(iii) CNP-OVA 0.1 mg dose

(iv) CNP-OVA 0.25 mg dose

(v) CNP-OVA 0.5 mg dose

(vi) CNP-OVA 1 mg dose

(vii) CNP-OVA 2.5 mg dose

(viii) Unloaded CNP-STG 2.5 mg dose

(ix) CNP-STG-OVA 0.1 mg dose

(x) CNP-STG-OVA 0.25 mg dose

(xi) CNP-STG-OVA 0.5 mg dose

(xii) CNP-STG-OVA 1 mg dose

(xiii) CNP-STG-OVA 2.5 mg dose

in 200 μL of saline via intravenous injection on Day 0. CNP-OVA particles were generated by encapsulating OVA protein in PLGA particles. The particles had an average size of 879 nm and a negative surface charge (zeta potential -54 mV). CNP-STG-OVA particles were prepared by encapsulating OVA protein in PLGA particles coupled to cGAS-STING agonist 2',3'-cGAMP. PLGA polymers coupled to 2',3'-cGAMP were used to encapsulate whole OVA protein. The CNP-STG-OVA particles had an average size of 619 nm and a negative surface charge (zeta potential -52 mV). Unloaded CNP particles had a size of -582 nm and a charge of -51 mV. CNP-STG particles had a size of 611 nm and a zeta potential of -49 mV. The particles with STING agonist have an approximate load of 50-100 ng of 2',3'-cGAMP per mg nanoparticle. On Day 14 post OVA/CFA priming, the thickness of the mouse ears was measured, and the mice then received 10 μL of KLH protein (1 mg/mL) as a negative control protein challenge via subcutaneous injection in the left ear, and 10 μL of OVA protein (1 mg/mL) as the antigen-specific challenge peptide in the right ear. At 24 hours post injection of protein within the ear, the thickness of the ears were measured to determine the level of antigen-specific T cell-induced swelling. The results show that the inclusion of a STING agonist within antigen containing particles increases treatment efficacy, synergistically compared to PLGA particles containing OVA protein in the absence of additional STING agonist (Fig. 3) (**p<0.05, **p<0.005, ***p<0.001, ****p<0.0001)*.

[0182] Treatment with CNP-STG-OVA decreases OVA-specific IgG production compared to CNP-OVA particles (Fig. 4). The results demonstrate a surprising decrease in the dosage of particles required for antigen-specific tolerance induction with the inclusion of a cGAS-STING agonist.

[0183] It is understood, therefore, that this invention is not limited to the particular embodiments disclosed, but is intended to cover all modifications which are within the spirit and scope of the invention as defined by the appended claims; the above description, and/or shown in the attached drawings. Consequently, only such limitations as appear in the appended claims should be placed on the disclosure.

We claim:

1. A composition comprising: (i) one or more antigens; and (ii) one or more cGAS-STING activating agents.

2. The composition of claim 1, wherein the antigen and cGAS-STING activating agent are in the same composition.

3. The composition of claim 1, wherein the composition is an admixture comprising one or more antigens and cGAS-STING activating agent in different compositions for use in combination.

4. The composition of any one of claims 1-3, wherein the antigens are encapsulated in or coupled to one or more carrier particles and the cGAS-STING activating agent is free or free in solution.

5. The composition of any one of claims 1-3, wherein the antigen is free or free in solution and the cGAS-STING activating agent is encapsulated in or coupled to carrier particles.

6. The composition of any one of claims 1-3, wherein the antigen and cGAS-STING activating agent are encapsulated in or coupled to carrier particles.

7. The composition of claim 6, wherein the antigens and cGAS-STING activating agent are encapsulated in carrier particles.

8. The composition of any one of claims 1-3 or 6-7, wherein (i) one or more antigens are encapsulated in or coupled to a first population of carrier particles and (ii) one or more cGAS-STING activating agents are encapsulated in or coupled to a second population of carrier particles.

9. The composition of claim 8, wherein the carrier particles encapsulating or coupled to one or more antigen and cGAS-STING activating agent are in the same composition.

10. The composition of claim 8, wherein the composition is an admixture comprising carrier particles encapsulating or coupled to one or more antigen and carrier particles

encapsulating or coupled to cGAS-STING activating agents in different compositions for use in combination.

11. The composition of any one of the preceding claims, wherein the cGAS-STING activating agent is MV-626, SR-8314, SR-8291), SYNB1891, STACT-TREX-1, 2'3'-cGAMP, 3'3'cGAMP, c-di-AMP, c-di-GMP), 3'3'-cyclic AIMP, ML RR-CDA, 3'3'-cCAMP, ADU-S100 (2'3'-c-di-AM(PS)2 (Rp,Rp)), BI-STING, BMS-986301, GSK532, JNJ-4412, MK-1454, SB11285), ALG-031048, E7766, JNJ-6196, MK-2118, MSA-1, MSA-2, SNX281, SR-717, TAK676, TT1-10001, flavone acetic acid (FAA), 5,6-dimethylxanthenone-4-acetic acid (DMXAA), 10-carboxymethyl-9-acridanone (CMA), α-mangostin), G10, dispiro diketopiperzine (DSDP), C11, diamidobenzimidazole (ABMZI), benzamide 20 BNBC), antibody-drug conjugates (XMT-2056, CRD-5500), GSK3745417, or exoSTING.

12. The composition of any one of claims 4-11, wherein the carrier particles comprise a liposome, lipid nanoparticle, polymersomes, micelles, polymeric nanoparticles, manganese (Mn2+) based nanoparticles, acid-ionizable iron nanoadjuvant (INOP), mesoporus silica, metal-organic frameworks (MOFs), lipid nanodiscs, supramolecular nanoparticles, extracellular vesicles, or sono-driven nanoparticles.

13. The composition of claim 12, wherein the carrier particles comprise a polymer selected from the group consisting of polyglycolic acid (PGA), polylactic acid (PLA), poly(lactic-co-glycolic) (PLGA), polysebacic acid (PSA), poly(lactic-co-sebacic) acid (PLSA), poly(glycolic-co-sebacic) acid (PGSA), polypropylene sulfide, poly(caprolactone), chitosan, a polysaccharide, or a lipid, polystyrene, diamond, a liposome, PEG, cyclodextran, a lipid or a metal such as iron (Fe), zinc (Zn), cadmium (Cd), gold (Au), silver (Ag), or combinations thereof.

14. The composition of any one of claims 4-13, wherein the carrier particles comprise poly (lactic-co-glycolic acid) (PLGA).

15. The composition of claim 13 or 14, wherein the polymer is a co-polymer with constituent polymer molar ratios selected from 25:75, 30:70, 35:65, 40:60, 45:55, 50:50, 55:45, 60:40, 65:35, 70:30, 75:25, 80:20, 81:19, 82:18, 83:17, 84:16, 85:15, 86:14, 87:13, 88:12, 89:11, 90:10, 91:9, 92:8, 93:7, 94:6, 95:5, 96:4, 97:3, 98:2, 99:1, or 100:0.

16. The composition of any one of claims 4-15, wherein the carrier particles have a negative zeta potential.

17. The composition of claim 16, wherein the zeta potential of the particles is from about -100 mV to about 0 mV, from about -100 mV to about -25 mV, from about -100 to about -30 mV, from about -80 mV to about -30 mV, from about -75 mV to about -30 mV, from about -70 mV to about -30 mV, from about -75 to about -35 mV, from about -70 to about -25 mV, from about -60 mV to about -30 mV, from about -60 mV to about -35 mV, or from about -50 mV to about -30 mV, about -25 mV, about -30 mV, about -35 mV, about -40 mV, about -45 mV, about -50 mV, about -55 mV, about -60 mV, about -65 mV, about -70 mV, about -75 mV, about -80 mV, about -85 mV, about -90 mV, about -95 mV or about -100 mV.

18. The composition of claim 16 or 17, wherein the carrier particles have a negative zeta potential of between -30 mV to -90 mV.

19. The composition of any one of claims 4-18, wherein the carrier particle size or diameter is between 0.05 μm to 10 μm, 0.1 μm to 10 μm, 0.1 μm to 5 μm, 0.1 μm to 3 μm, 0.3 μm to 5 μm, 0.3 μm to 3 μm, or 0.4 μm to 1 μm.

20. The composition of claim 19, wherein the diameter of the carrier particle is between 400 nm to 800 nm or between 350 nm to 800 nm.

21. The composition of any one of claims 4-20, wherein the carrier particles are carboxylate surface functionalized.

22. The composition of any one of the preceding claims, wherein the antigen is an autoimmune antigen, allergen, transplant antigen, enzyme replacement therapy, therapeutic protein, inhaled substance, injected substance, viral protein, vector for gene therapy, or transgene coded by the gene therapy.

23. The composition of any one of the preceding claims, wherein the antigen is selected from the group consisting of myelin basic protein, acetylcholine receptor, endogenous antigen, myelin oligodendrocyte glycoprotein, pancreatic β-cell antigens, insulin, proinsulin, islet-specific glucose-6-phophatase catalytic subunit-related protein (IGRP), glutamic acid decarboxylase (GAD), zinc transporter 8 (ZnT8), collagen type 11, human cartilage gp39, gp130-RAPS, proteolipid protein, fibrillarin, small nucleolar protein, myelin associated glycoprotein, αβ-crystallin, RAS guanyl-releasing protein 2, GDP-l-fucose synthase (TSTA3), β-synuclein, 2',3'-cyclic nucleotide 3'-phosphodiesterase, myelin oligodendrocyte basic protein (MOBP), oligodendrocyte-specific protein (OSP), transaldolase H, S100 beta, contactin 2/TAG-

1, KIR4.1, anoctamin 2, thyroid stimulating factor receptor, IGF-1R, thyroglobulin, thyroid peroxidase, sodium-iodide symporter, cytosolic 5'-nucleotidase 1A (cN1A), galactose-deficient IgA1 (Gd-IgA1), αMyHC, βMyHC, HSP60, synthetase Jo-1, proteinase 3 (PR3), 21-hydroxylase (21OH), Ro/SSA, La/SSB, 17-α-hydroxylase, cholesterol side-chain cleavage enzyme, cytochrome P450 2D6 (CYP2D6), phospholipase A2 receptor (PLA2R),GPIIb, GPIIIa, GABA-A receptor-associated protein (GABARAP), gephyrun, amphiphysin, ADAMTS13, myeloperoxidase, trichohyalin, tyrosinase-related protein 2, no-ncollagenous (NC1) domain of the a3 chain of type IV collagen (a3(IV)NC1), cardiolipin, β2 glycoprotein-I (β2GPI), C1-INH, actin, CYP11A1, laminin 332, β-4-integrin, connexin 26, cell density-enhanced protein tyrosine phosphatase-1 (DEP-1/CD148), and reovirus III major core protein lambda 1, cardiac myosin, GM1, GQ1b, Gd1a, collagen XVII, extracellular matrix protein 1 (ECM1), peptidyl arginine deiminase-4, muscle specific kinase (MuSK), low-density lipoprotein receptor-related protein 4, heat shock proteins (Hsp 90, HSP 70, HSP60, HSP40), alpha-synuclein, parkin, PINK1, LRRK2, platelet derived growth factor receptor beta (PDGFRB), Smith antigen, alpha-fodrin, rhodopsin, gamma-enolase, glutathione-S-transferase, amyloid beta (Aβ), tau, and amyloid precursor protein (APP), dopamine, hydroxytryptamine, glutamate, S100b, glial fibrillary acidic protein (GFAP), rabaptin 5, receptor for advanced glycosylation end products (RAGE), angiotensin 2 type 1 receptor (AT1R), aldolase, ATP synthase, H+K+-ATPase, F-actin, formimidoyltransferase cyclodeaminase, hybrid insulin peptides, C-peptide, histones, glycoprotein gp70, vimentin, fibrinogen, collagen type II, α-enolase, clusterin, PAD2, PAD4, pyruvate dehydrogenase dehydrolipoamide acetyltransferase (PDC-E2), hair follicle antigen, aqua porin 4, Desmoglein 1, Desmoglein 3, BP180 (BPAG2), BP230, nicotinic acetylcholine receptor, orexin-1, orexin-2, protein O-mannosyltransferase 1 (POMT1), regulatory factor X4 (RFX4), Tribbles homologue 2 (TRIB2), hemagglutinin (HA), neuraminidase (NA), influenza RNA-dependent RNA polymerase subunit 1 (PB1), or influenza nucleoprotein (NP), tyrosinase, melan-A (MLANA), premelanosome protein (PMEL), α-elonase, tenascin, fibrinogen, aggrecan, vimentin, gliadin, α-gliadin, and human tropomyosin isoform 5, Bahia grass pollen (BaGP), peach allergen Pru p 3, alpha s 1-Casein Milk allergen, peanut allergen (Ara h 1, Ara h 2, Ara h 3, Ara h 4, Ara h 5, Ara h6, Ara h 7, Ara h 8, Ara h 9, Ara h 10, Ara h 11, Ara h 12, Ara h 13, Ara h 14, Ara h15, Ara h 16, Ara h 17, and Ara h 18), Apig1 celery allergen, Ber e1 Brazil nut allergen, β-Lactoglobulin Milk allergen, Bovine serum albumin, Cor a 1.04 Hazelnut allergen, Ovalbumin Egg allergen, Cor a 8, Cor a 14, Cor a 11, Cor a 9, Cor a 2, Cor a 12, Cor a 13, Cor a 15, Jug r 3, Jug r 8, Jug r 1, Jug r 2, Jug r 6, Jug r 4, Jug r 5, Jug r 7, Jug n 1, Jug n 2, Jug n 4, Car i 1, Car i 2, Car i 4, Ana o 3, Ana o 1, Ana o2, Pis v 1, Pis v 3, Pis v 2, Pis v 5Pru du 3, Pru du 6, Pru du 1, Pru du

4, Ber e 2, Coc n 1, Mac I 1, Mac I 2, Gly m 4, Gly m 7c, Gly m 8a,c, Gly m KTIc, Gly m BBIc, Gly m 2, Gly m 3, Gly m Bd 30k, Bet v 1, Japanese cedar pollen (Cry j 1, Cry j 2, Cry j 3, Cry j 4, Cry j IFR, Cry j Chitinase, Cry j Asp, Cry j LTP, and/or Cry j CPA9), Aldurazyme (laronidase), Cerezyme (imiglucerase), Elelyso (taliglucerase alfa), Vpriv (velaglucerase alfa), Fabrazyme (agalsidase beta), Replagal (agalsidase alfa), Myozyme/Lumizyme (alglucosidase alfa), Naglazyme (galsulfase), Elaprase (idursulfase), Brineura (cerliponase alfa), Kanuma (sebelipase alfa), Strensiq (asfotase alfa), Coagadex (coagulation factor X), Hemlibra (emicizumab), Advate, Eloctate, BeneFIX, Idelvion (albutrepenonacog alfa), Crysvita (burosumab), Nplate (romiplostim), Prolastin/Aralast/Glassia (alpha-1 antitrypsin), Thyrogen (thyrotropin alfa), Pegunigalsidase alfa (PRX-102), DNL310, ORYZON-ERT, Valoctocogene roxaparvovec (Roctavian), SPK-9001 (fidanacogene elaparvovec), AVR-RD-01, AXO-AAV-GM1 and AXO-AAV-GM2, Val-1221, VEGF-B, and M6P replacement therapy.

24. The composition of claim 23, wherein the antigen is post-translationally modified.

25. The composition of claim 22, wherein the vectors for gene therapy are selected from the group comprising adenovirus, AAV-1, AAV-2, AAV-3, AAV-4, AAV-5, AAV-6, AAV-7, AAV-8, AAV-9, AAV-10, AAV-12, AAV capsid protein (VP-1, VP-2, or VP-3), Anc80, herpes simplex virus, hepatitis B virus, lentivirus, retrovirus, alphavirus, flavivirus, rhabdovirus, measles virus, Newcastle disease virus, Coxsackievirus, transfusion transmitted viruses, anellovirus, human papilloma virus, poxvirus, vaccinia virus, modified Ankara virus, vesicular stomatitis virus, picornavirus, tobacco mosaic virus, cowpea mosaic virus, cowpea chlorotic mottle virus, physalis mosaic virus, Red clover necrotic mosaic virus, potato virus x, comovirus, chicken anemia virus or cucumber mosaic virus.

26. The composition of any one of claims 22-24, wherein the antigen is associated with an allergy, an autoimmune disease, an enzyme used in enzyme replacement therapy, a vector used in gene therapy, a target protein of gene therapy, lysosomal storage disease, or an inflammatory disease or disorder.

27. The composition of claim 26 wherein, the antigen is associated with achalasia, Addison's disease, adult Still's disease, agammaglobulinemia, alopecia areata, Alzheimer's disease, amyloidosis, amyotrophic lateral sclerosis, ankylosing spondylitis, anti-GBM/anti-TBM nephritis, antiphospholipid syndrome, autoimmune angioedema, autoimmune dysautonomia, autoimmune encephalomyelitis, autoimmune hepatitis, autoimmune inner ear disease (AIED),

autoimmune myocarditis, autoimmune oophoritis, autoimmune orchitis, autoimmune pancreatitis, autoimmune retinopathy, autoimmune urticaria, axonal & neuronal neuropathy (AMAN), Baló disease, Behcet's disease, benign mucosal pemphigoid, bullous pemphigoid, Castleman disease (CD), celiac disease, Chagas disease, chronic inflammatory demyelinating polyneuropathy (CIDP), chronic recurrent multifocal osteomyelitis (CRMO), Churg-Strauss syndrome (CSS), eosinophilic granulomatosis (EGPA), cicatricial pemphigoid, Cogan's syndrome, cold agglutinin disease, congenital heart block, Coxsackie myocarditis, CREST syndrome, Crohn's disease, dermatitis herpetiformis, dermatomyositis, Devic's disease (neuromyelitis optica), discoid lupus, Dressler's syndrome, endometriosis, eosinophilic esophagitis (EoE), eosinophilic fasciitis, epilepsy, erythema nodosum, essential mixed cryoglobulinemia, Evans syndrome, fibromyalgia, fibrosing alveolitis, giant cell arteritis (temporal arteritis), giant cell myocarditis, glaucoma, glomerulonephritis, Goodpasture's syndrome, granulomatosis with polyangiitis, Graves' disease, Guillain-Barre syndrome, Hashimoto's thyroiditis, hemolytic anemia, Henoch-Schonlein purpura (HSP), herpes gestationis, pemphigoid gestationis (PG), hidradenitis suppurativa (HS) (acne inversa), hypogammalglobulinemia, IgA nephropathy, idiopathic thrombocytopenic purpura (ITP), inclusion body myositis (IBM), anti-melanoma differentiation-associated gene 5 (MDA5 myositis), inflammatory bowel disease, interstitial cystitis (IC), juvenile arthritis, juvenile diabetes (type 1 diabetes), juvenile myositis (JM), Kawasaki disease, latent autoimmune diabetes od adults (LADA), Lambert-Eaton syndrome, leukocytoclastic vasculitis, lichen planus, lichen sclerosus, ligneous conjunctivitis, linear IgA disease (LAD), lupus/systemic lupus, Lyme disease chronic, membranous nephropathy, Meniere's disease, microscopic polyangiitis (MPA), mixed connective tissue disease (MCTD), myelin oligodendrocyte glycoprotein associated disease (MOGAD), Mooren's ulcer, Mucha-Habermann disease or PLEVA, multifocal motor neuropathy (MMN) or MMNCB, multiple sclerosis, myasthenia gravis, myositis, narcolepsy, neonatal lupus, neutropenia, ocular cicatricial pemphigoid, palindromic rheumatism (PR), pediatric acute liver failure (PALF), PANDAS, paraneoplastic cerebellar degeneration (PCD), Parkinson's disease, paroxysmal nocturnal hemoglobinuria (PNH), Parry Romberg syndrome, pars planitis (peripheral uveitis), parsonage-turner syndrome, pemphigus foliaceous, pemphigus vulgaris, peripheral neuropathy, perivenous encephalomyelitis, pernicious anemia (PA), POEMS syndrome, polyarteritis nodosa, polyglandular syndromes type I, II, III, polymyalgia rheumatica, polymyositis, post-myocardial infarction syndrome, post-pericardiotomy syndrome, primary biliary cholangitis, primary sclerosing cholangitis, progesterone dermatitis, psoriasis, psoriatic arthritis, pure red cell aplasia (PRCA), pyoderma gangrenosum, Raynaud's phenomenon, reactive arthritis, reflex sympathetic

dystrophy, relapsing polychondritis, restless legs syndrome (RLS), retroperitoneal fibrosis, rheumatic fever, rheumatoid arthritis, sarcoidosis, Schmidt syndrome, scleritis, scleroderma, Sjögren's syndrome, sperm & testicular autoimmunity, stiff person syndrome (SPS), sub-acute bacterial endocarditis (SBE), Susac's syndrome, sympathetic ophthalmia (SO), Takayasu's arteritis, temporal arteritis/giant cell arteritis, thrombotic thrombocytopenic purpura (TTP), thyroid eye disease (TED), Tolosa-Hunt syndrome (THS), transverse myelitis, ulcerative colitis, undifferentiated connective tissue disease (UCTD), uveitis, vasculitis, vitiligo, PALF/ALF, Rasmussen's encephalitis, Lewy body dementia, encephalitis, Vogt-Koyanagi-Harada disease, a mucopolysaccharide storage disorder, gangliosidosis, alkaline hypophosphatasia, cholesterol ester storage disease, hyperuricemia, growth hormone deficiency, renal anemia, Gaucher's disease, Fabry's disease, Hurler's disease, Hunter's disease, Maroteaux-Lamy disease, hemophilia A, hemophilia B, von Willebrand disease, venous thrombosis, purpura fulminans, Mucopolysaccaridosis VI, Pompe disease, inherited retinal diseases (e.g., Leber congenital amaurosis, RPE65 mutation-associated retinal dystrophy), spinal muscular atrophy (SMA), inherited blood disorders, sickle cell disease, □-thalassemia, severe combined immunodeficiency (SCID), ADA-SCID (adenosine deaminase deficiency SCID), lipoprotein lipase deficiency, neurodegenerative diseases, Genetic Disorders, cystic fibrosis, Duchenne Muscular Dystrophy (DMD), Cardiomyopathies, Hunter Syndrome (MPS II), Mucopolysaccharidosis, Metabolic Disorders, Phenylketonuria (PKU), Crigler-Najjar syndrome type 1, methylmalonic acidemia, propionic acidemia, ornithine transcarbamylase deficiency, or glycogen storage disease type 1a, pediatric autoimmune neuropsychiatric disorders.

28. The composition of any one of claims 1-26, wherein the composition comprises carrier particles comprising PLGA polymer, encapsulating one or more antigens, coupled to a cGAS-STING activating agent, having a diameter between 400 nm to 800 nm, and having a zeta potential between -30 mV and -90 mV.

29. The composition of any one of claims 1-26, wherein the composition comprises carrier particles comprising PLGA polymer, encapsulating one or more antigens and a cGAS-STING activating agent, having a diameter between 400 nm to 800 nm, and having a zeta potential between -30 mV and -100 mV.

30. A method of inducing antigen-specific tolerance in a subject in need thereof, comprising administering a composition of any one of claims 1-29.

31. A method of inducing antigen specific tolerance in a subject comprising; administering to said subject an effective amount of a composition comprising (i) one or more antigens; and (ii) one or more cGAS-STING activating agents.

32. The method of claim 31, wherein the antigens and cGAS-STING activating agent are in the same composition.

33. The method of claim 31, wherein the composition is an admixture comprising (i) one or more antigens and (ii) cGAS-STING activating agent in different compositions for use in combination.

34. The method of any one of claims 31-33, wherein the antigens are encapsulated in or coupled to one or more carrier particles and the cGAS-STING activating agent is free or free in solution.

35. The method of any one of claims 31-33, wherein the antigens are free or free in solution and cGAS-STING activating agent is encapsulated in or coupled to carrier particles.

36. The method of any one of claims 31-33, wherein the antigens and cGAS-STING activating agent are both encapsulated in or coupled to carrier particles.

37. The method of claim 36, wherein (i) one or more antigens are encapsulated in or coupled to a first population of carrier particles (ii) one or more cGAS-STING pathway activators are encapsulated in or coupled to a second population of carrier particles.

38. The method of claim 37 wherein, the carrier particles encapsulating or coupled to one or more antigen and cGAS-STING activating agent are in the same composition.

39. The method of claim 37, wherein the composition is an admixture comprising (i) carrier particles encapsulating or coupled to one or more antigens and (ii) carrier particles encapsulating or coupled to cGAS-STING activating agents, in different compositions for use in combination.

40. The method of any one of claims 31-39, wherein the antigen is an autoimmune antigen, allergen, transplant antigen, enzyme replacement therapy, therapeutic protein, inhaled substance, injected substance, viral protein, vector for gene therapy, or transgene coded by a gene therapy.

41. The method of any one of claims 31-40, wherein the antigen is selected from the group consisting of myelin basic protein, acetylcholine receptor, endogenous antigen, myelin oligodendrocyte glycoprotein, pancreatic β-cell antigens, insulin, proinsulin, islet-specific glucose-6-phophatase catalytic subunit-related protein (IGRP), glutamic acid decarboxylase (GAD), zinc transporter 8 (ZnT8), collagen type 11, human cartilage gp39, gp130-RAPS, proteolipid protein, fibrillarin, small nucleolar protein, myelin associated glycoprotein, αβ-crystallin, RAS guanyl-releasing protein 2, GDP-l-fucose synthase (TSTA3), β-synuclein, 2',3'-cyclic nucleotide 3'-phosphodiesterase, myelin oligodendrocyte basic protein (MOBP), oligodendrocyte-specific protein (OSP), transaldolase H, S100 beta, contactin 2/TAG-1, KIR4.1, anoctamin 2, thyroid stimulating factor receptor, IGF-1R, thyroglobulin, thyroid peroxidase, sodium-iodide symporter, cytosolic 5'-nucleotidase 1A (cN1A), galactose-deficient IgA1 (Gd-IgA1), αMyHC, βMyHC, HSP60, synthetase Jo-1, proteinase 3 (PR3), 21-hydroxylase (21OH), Ro/SSA, La/SSB, 17-α-hydroxylase, cholesterol side-chain cleavage enzyme, cytochrome P450 2D6 (CYP2D6), phospholipase A2 receptor (PLA2R),GPIIb, GPIIIa, GABA-A receptor-associated protein (GABARAP), gephyrun, amphiphysin, ADAMTS13, myeloperoxidase, trichohyalin, tyrosinase-related protein 2, no-ncollagenous (NC1) domain of the a3 chain of type IV collagen (a3(IV)NC1), cardiolipin, β2 glycoprotein-I (β2GPI), C1-INH, actin, CYP11A1, laminin 332, β-4-integrin, connexin 26, cell density-enhanced protein tyrosine phosphatase-1 (DEP-1/CD148), and reovirus III major core protein lambda 1, cardiac myosin, GM1, GQ1b, Gd1a, collagen XVII, extracellular matrix protein 1 (ECM1), peptidyl arginine deiminase-4, muscle specific kinase (MuSK), low-density lipoprotein receptor-related protein 4, heat shock proteins (Hsp 90, HSP 70, HSP60, HSP40), alpha-synuclein, parkin, PINK1, LRRK2, platelet derived growth factor receptor beta (PDGFRB), Smith antigen, alpha-fodrin, rhodopsin, gamma-enolase, glutathione-S-transferase, amyloid beta (Aβ), tau, and amyloid precursor protein (APP), dopamine, hydroxytryptamine, glutamate, S100b, glial fibrillary acidic protein (GFAP), rabaptin 5, receptor for advanced glycosylation end products (RAGE), angiotensin 2 type 1 receptor (AT1R), aldolase, ATP synthase, H+K+-ATPase, F-actin, formimidoyltransferase cyclodeaminase, hybrid insulin peptides, C-peptide, histones, glycoprotein gp70, vimentin, fibrinogen, collagen type II, α-enolase, clusterin, PAD2, PAD4, pyruvate dehydrogenase dehydrolipoamide acetyltransferase (PDC-E2), hair follicle antigen, aqua porin 4, Desmoglein 1, Desmoglein 3, BP180 (BPAG2), BP230, nicotinic acetylcholine receptor, orexin-1, orexin-2, protein O-mannosyltransferase 1 (POMT1), regulatory factor X4 (RFX4), Tribbles homologue 2

(TRIB2), hemagglutinin (HA), neuraminidase (NA), influenza RNA-dependent RNA polymerase subunit 1 (PB1), or influenza nucleoprotein (NP), tyrosinase, melan-A (MLANA), premelanosome protein (PMEL), α-elonase, tenascin, fibrinogen, aggrecan, vimentin, gliadin, α-gliadin, and human tropomyosin isoform 5, Bahia grass pollen (BaGP), peach allergen Pru p 3, alpha s 1-Casein Milk allergen, peanut allergen (Ara h 1, Ara h 2, Ara h 3, Ara h 4, Ara h 5, Ara h6, Ara h 7, Ara h 8, Ara h 9, Ara h 10, Ara h 11, Ara h 12, Ara h 13, Ara h 14, Ara h15, Ara h 16, Ara h 17, and Ara h 18), Apig1 celery allergen, Ber e1 Brazil nut allergen, β-Lactoglobulin Milk allergen, Bovine serum albumin, Cor a 1.04 Hazelnut allergen, Ovalbumin Egg allergen, Cor a 8, Cor a 14, Cor a 11, Cor a 9, Cor a 2, Cor a 12, Cor a 13, Cor a 15, Jug r 3, Jug r 8, Jug r 1, Jug r 2, Jug r 6, Jug r 4, Jug r 5, Jug r 7, Jug n 1, Jug n 2, Jug n 4, Car i 1, Car i 2, Car i 4, Ana o 3, Ana o 1, Ana o2, Pis v 1, Pis v 3, Pis v 2, Pis v 5Pru du 3, Pru du 6, Pru du 1, Pru du 4, Ber e 2, Coc n 1, Mac I 1, Mac I 2, Gly m 4, Gly m 7c, Gly m 8a,c, Gly m KTIc, Gly m BBIc, Gly m 2, Gly m 3, Gly m Bd 30k, Bet v 1, Japanese cedar pollen (Cry j 1, Cry j 2, Cry j 3, Cry j 4, Cry j IFR, Cry j Chitinase, Cry j Asp, Cry j LTP, and/or Cry j CPA9), Aldurazyme (laronidase), Cerezyme (imiglucerase), Elelyso (taliglucerase alfa), Vpriv (velaglucerase alfa), Fabrazyme (agalsidase beta), Replagal (agalsidase alfa), Myozyme/Lumizyme (alglucosidase alfa), Naglazyme (galsulfase), Elaprase (idursulfase), Brineura (cerliponase alfa), Kanuma (sebelipase alfa), Strensiq (asfotase alfa), Coagadex (coagulation factor X), Hemlibra (emicizumab), Advate, Eloctate, BeneFIX, Idelvion (albutrepenonacog alfa), Crysvita (burosumab), Nplate (romiplostim), Prolastin/Aralast/Glassia (alpha-1 antitrypsin), Thyrogen (thyrotropin alfa), Pegunigalsidase alfa (PRX-102), DNL310, ORYZON-ERT, Valoctocogene roxaparvovec (Roctavian), SPK-9001 (fidanacogene elaparvovec), AVR-RD-01, AXO-AAV-GM1 and AXO-AAV-GM2, Val-1221, VEGF-B, M6P replacement therapy.

42. The method of claim 40, wherein the vectors for gene therapy are selected from the group comprising adenovirus, AAV-1, AAV-2, AAV-3, AAV-4, AAV-5, AAV-6, AAV-7, AAV-8, AAV-9, AAV-10, AAV-12, AAV capsid protein (VP-1, VP-2, or VP-3), Anc80, herpes simplex virus, hepatitis B virus, lentivirus, retrovirus, alphavirus, flavivirus, rhabdovirus, measles virus, Newcastle disease virus, Coxsackievirus, transfusion transmitted viruses, anellovirus, human papilloma virus, poxvirus, vaccinia virus, modified Ankara virus, vesicular stomatitis virus, picornavirus, tobacco mosaic virus, cowpea mosaic virus, cowpea chlorotic mottle virus, physalis mosaic virus, Red clover necrotic mosaic virus, potato virus x, comovirus, chicken anemia virus or cucumber mosaic virus.

43. The method of any one of claims 31-42, wherein the antigen is associated with an allergy, an autoimmune disease, an enzyme used in enzyme replacement therapy, a vector used in gene therapy, a target protein of gene therapy, lysosomal storage disease, or an inflammatory disease or disorder.

44. The method of any one of claims 31-43, wherein the antigen is associated with achalasia, Addison's disease, adult Still's disease, agammaglobulinemia, alopecia areata, Alzheimer's disease, amyloidosis, amyotrophic lateral sclerosis, ankylosing spondylitis, anti-GBM/anti-TBM nephritis, antiphospholipid syndrome, autoimmune angioedema, autoimmune dysautonomia, autoimmune encephalomyelitis, autoimmune hepatitis, autoimmune inner ear disease (AIED), autoimmune myocarditis, autoimmune oophoritis, autoimmune orchitis, autoimmune pancreatitis, autoimmune retinopathy, autoimmune urticaria, axonal & neuronal neuropathy (AMAN), Baló disease, Behcet's disease, benign mucosal pemphigoid, bullous pemphigoid, Castleman disease (CD), celiac disease, Chagas disease, chronic inflammatory demyelinating polyneuropathy (CIDP), chronic recurrent multifocal osteomyelitis (CRMO), Churg-Strauss syndrome (CSS), eosinophilic granulomatosis (EGPA), cicatricial pemphigoid, Cogan's syndrome, cold agglutinin disease, congenital heart block, Coxsackie myocarditis, CREST syndrome, Crohn's disease, dermatitis herpetiformis, dermatomyositis, Devic's disease (neuromyelitis optica), discoid lupus, Dressler's syndrome, endometriosis, eosinophilic esophagitis (EoE), eosinophilic fasciitis, epilepsy, erythema nodosum, essential mixed cryoglobulinemia, Evans syndrome, fibromyalgia, fibrosing alveolitis, giant cell arteritis (temporal arteritis), giant cell myocarditis, glaucoma, glomerulonephritis, Goodpasture's syndrome, granulomatosis with polyangiitis, Graves' disease, Guillain-Barre syndrome, Hashimoto's thyroiditis, hemolytic anemia, Henoch-Schonlein purpura (HSP), herpes gestationis, pemphigoid gestationis (PG), hidradenitis suppurativa (HS) (acne inversa), hypogammalglobulinemia, IgA nephropathy, idiopathic thrombocytopenic purpura (ITP), inclusion body myositis (IBM), anti-melanoma differentiation-associated gene 5 (MDA5 myositis), inflammatory bowel disease, interstitial cystitis (IC), juvenile arthritis, juvenile diabetes (type 1 diabetes), juvenile myositis (JM), Kawasaki disease, latent autoimmune diabetes od adults (LADA), Lambert-Eaton syndrome, leukocytoclastic vasculitis, lichen planus, lichen sclerosus, ligneous conjunctivitis, linear IgA disease (LAD), lupus/systemic lupus, Lyme disease chronic, membranous nephropathy, Meniere's disease, microscopic polyangiitis (MPA), mixed connective tissue disease (MCTD), myelin oligodendrocyte glycoprotein associated disease (MOGAD), Mooren's ulcer, Mucha-Habermann disease or PLEVA, multifocal motor neuropathy (MMN) or MMNCB,

multiple sclerosis, myasthenia gravis, myositis, narcolepsy, neonatal lupus, neutropenia, ocular cicatricial pemphigoid, palindromic rheumatism (PR), pediatric acute liver failure (PALF), PANDAS, paraneoplastic cerebellar degeneration (PCD), Parkinson's disease, paroxysmal nocturnal hemoglobinuria (PNH), Parry Romberg syndrome, pars planitis (peripheral uveitis), parsonage-turner syndrome, pemphigus foliaceous, pemphigus vulgaris, peripheral neuropathy, perivenous encephalomyelitis, pernicious anemia (PA), POEMS syndrome, polyarteritis nodosa, polyglandular syndromes type I, II, III, polymyalgia rheumatica, polymyositis, post-myocardial infarction syndrome, post-pericardiotomy syndrome, primary biliary cholangitis, primary sclerosing cholangitis, progesterone dermatitis, psoriasis, psoriatic arthritis, pure red cell aplasia (PRCA), pyoderma gangrenosum, Raynaud's phenomenon, reactive arthritis, reflex sympathetic dystrophy, relapsing polychondritis, restless legs syndrome (RLS), retroperitoneal fibrosis, rheumatic fever, rheumatoid arthritis, sarcoidosis, Schmidt syndrome, scleritis, scleroderma, Sjögren's syndrome, sperm & testicular autoimmunity, stiff person syndrome (SPS), sub-acute bacterial endocarditis (SBE), Susac's syndrome, sympathetic ophthalmia (SO), Takayasu's arteritis, temporal arteritis/giant cell arteritis, thrombotic thrombocytopenic purpura (TTP), thyroid eye disease (TED), Tolosa-Hunt syndrome (THS), transverse myelitis, ulcerative colitis, undifferentiated connective tissue disease (UCTD), uveitis, vasculitis, vitiligo, PALF/ALF, Rasmussen's encephalitis, Lewy body dementia, encephalitis, Vogt-Koyanagi-Harada disease, a mucopolysaccharide storage disorder, gangliosidosis, alkaline hypophosphatasia, cholesterol ester storage disease, hyperuricemia, growth hormone deficiency, renal anemia, Gaucher's disease, Fabry's disease, Hurler's disease, Hunter's disease, Maroteaux-Lamy disease, hemophilia A, hemophilia B, von Willebrand disease, venous thrombosis, purpura fulminans, Mucopolysaccaridosis VI, Pompe disease, inherited retinal diseases (e.g., Leber congenital amaurosis, RPE65 mutation-associated retinal dystrophy), spinal muscular atrophy (SMA), inherited blood disorders, sickle cell disease, β-thalassemia, severe combined immunodeficiency (SCID), ADA-SCID (adenosine deaminase deficiency SCID), lipoprotein lipase deficiency, neurodegenerative diseases, Genetic Disorders, cystic fibrosis, Duchenne Muscular Dystrophy (DMD), Cardiomyopathies, Hunter Syndrome (MPS II), Mucopolysaccharidosis, Metabolic Disorders, Phenylketonuria (PKU), Crigler-Najjar syndrome type 1, methylmalonic acidemia, propionic acidemia, ornithine transcarbamylase deficiency, or glycogen storage disease type 1a, pediatric autoimmune neuropsychiatric disorders.

45. The method of any one of claims 31-33 or 36-44, wherein the composition comprises carrier particles comprising PLGA polymer, encapsulating one or more antigens,

coupled to a cGAS-STING activating agent, having a diameter between 400 nm to 800 nm, and having a zeta potential between -40 mV and -90 mV.

46. The method of any one of claims 31-33 or 36-45, wherein the composition comprises carrier particles comprising PLGA polymer, encapsulating one or more antigens and a cGAS-STING activating agent, having a diameter between 400 nm to 800 nm, and having a zeta potential between -40 mV and -90 mV.

47. The method of any one of claims 31-46, wherein the composition is administered at a dose from about 0.001 to about 10 mg/kg, from about 0.005 to about 12 mg/kg, from about 0.01 to about 12 mg/kg, from about 0.05 to about 12 mg/kg, from about 0.1 to about 12 mg/kg, about 0.5 to 10 mg/kg, from about 1 to 8 mg/kg, from about 1.5 to 10 mg/kg, from about 2 to 12 mg/kg, from about 2 to 10 mg/kg, from about 3 to 10 mg/kg, from about 4 to 10 mg/kg, from about 4 to 12 mg/kg, or from about 5 to 12 mg/kg.

48. The method of any one of claims 31-47, wherein the composition is administered in a dose of about 0.001 mg/kg, about 0.0025 mg/kg, about 0.005 mg/kg, about 0.01 mg/kg, about 0.025 mg/kg, about 0.05 mg/kg, 0.1 mg/kg, 0.25, 0.5 mg/kg, 1.0 mg/kg, 2.0 mg/kg, 4.0 mg/kg, 6 mg/kg, 8.0 mg/kg, 10 mg/kg, or 12 mg/kg.

49. The method of any one of claims 31-46, wherein the composition is administered in a dose of about 0.1 mg, 0.25 mg, 0.5 mg, 1mg, 2 mg, 2.5 mg, 5 mg, 10 mg, 25 mg, 50 mg, 75 mg, 100 mg, 125 mg, 150 mg, 175 mg, 200 mg, 225 mg, 250 mg, 275 mg, 300 mg, 325 mg, 350 mg, 400 mg, 425 mg, 450 mg, 475 mg, 500 mg, 525 mg, 550 mg, 575 mg, 600 mg, 625 mg, 650 mg, 675 mg, 700 mg, 725 mg, 750 mg, 775 mg, or 800 mg.

50. The method of any one of claims 31-46 and 49, wherein the composition is administered in a dose of about 0.0005 mg/mL and about 50 mg/mL between about 0.05 mg/mL and about 50 mg/mL, optionally about 0.0005 mg/mL, 0.001 mg/mL, 0.005 mg/mL, 0.01 mg/mL, 0.05 mg/mL, 0.1 mg/mL, 0.5 mg/mL, 1 mg/mL, 2 mg/mL, 3 mg/mL, 4 mg/mL, 5 mg/mL, 6 mg/mL, 7 mg/mL, 8 mg/mL, 9 mg/mL, 10 mg/mL, 11 mg/mL, 12.5 mg/mL, 15 mg/mL, 17.5 mg/mL, 20 mg/mL, 25 mg/mL, 30 mg/mL, 40 mg/mL, or 50 mg/mL.

51. The method of any one of claims 31-50, wherein the composition is administered in a single dose or in multiple doses.

52. The method of any one of claims 31-51, wherein the composition is administered in two doses one-week apart, once weekly, once every two weeks, once every three weeks, once every 4 weeks, once every two months, once every three months, once every 6 months, or once per year.

53. The method of claim 52, wherein the method further comprises administering at least one booster dose of the composition.

54. The method of claim 53, wherein the booster dose of the composition is administered once weekly, once every two weeks, once every three weeks, once every 4 weeks, once every two months, once every three months, once every 4 months, once every 5 months, once every 6 months, or once per year.

55. The method of claim 54, wherein, the composition is administered in two loading doses one-week apart followed by at least one booster dose administered as a single dose once every one month, every two months or three months.

56. The method of any one of claims 31-55, wherein, the composition is administered intravenously, subcutaneously, intramuscularly, intraperitoneally, intranasally, inhaled, intra-lymphatically, or orally.

57. A composition comprising an effective amount of a composition comprising (i) one or more antigens; and (ii) one or more cGAS-STING activating agents for inducing antigen specific tolerance in a subject.

58. Use of a composition comprising an effective amount of a composition comprising (i) one or more antigens; and (ii) one or more cGAS-STING activating agents in the manufacture of a medicament for inducing antigen specific tolerance in a subject.

59. The composition for use or use of claim 57 or 58, wherein the composition comprises carrier particles comprising PLGA polymer, encapsulating one or more antigens, coupled to a cGAS-STING activating agent, having a diameter between 400 nm to 800 nm, and having a zeta potential between -40 mV and -90 mV.

60. The composition for use or use of claim 57 or 58, wherein the composition comprises carrier particles comprising PLGA polymer, encapsulating one or more antigens and

a cGAS-STING activating agent, having a diameter between 400 nm to 800 nm, and having a zeta potential between -40 mV and -90 mV.

61. A composition comprising antigens and STING activating agent encapsulated in or coupled to carrier particles wherein the carrier particles are liposomes.

62. The composition of claim 61, wherein the liposome comprises lipid selected from the group consisting of phosphatidyl choline, phosphatidyl serine, phosphatidyl inositol, phosphatidyl glycerol, phosphatidyl ethanolamine, 1,2-dipalmitoyl-sn-glycero-3-phosphocholine (DPPC), 1,2-dioleoyl-sn-glycero-3-phosphocholine (DOPC), 1,2-dimyristoyl-sn-glycero-3-phosphocholine (DMPC), 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE), 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP), 1,2-dioleoyl-sn-glycero-3-ethylphosphocholine (EDOPC), dimethyldioctadecylammonium bromide (DDAB), N-[1-(2,3-dioleoyloxy)propyl]-N,N,N-trimethylammonium chloride (DOTMA), dioleoylphosphatidylglycerol (DOPG), phosphatidic acid (PA), cardiolipin, 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-polyethylene glycol (DSPE-PEG), 1,2-dimyristoyl-sn-glycero-3-phosphoethanolamine-polyethylene glycol (DMPE-PEG), DLin-MC3-DMA (MC3), SM-102, ALC-0315, C12-200, sphingomyelin, ceramides, palmitic acid, stearic acid, oleic acid, phosphatidic acid, dicetyl phosphate, monosialoganglioside, polyethylene glycol, stearyl armine, ovolecithin, modified lipids and cholesterol, cholesterol esters, PEGylated cholesterol (e.g., cholesterol-polyethylene glycol) as well as mixtures of these in varying stoichiometries.

63. A composition comprising antigens and STING activating agent encapsulated in or coupled to carrier particles wherein the carrier particles are lipid nanoparticles.

64. The composition of claim 63, wherein the lipids are selected from the group consisting of 1,2-di-O-octadecenyl-3-trimethylammonium-propane (DOTMA), 1,2-dioleoyl-sn-glycero-3-phosphoethanolamine (DOPE), 1,2-dioleoyl-3-trimethylammonium-propane (DOTAP), Dimethyldioctadecylammonium bromide (DDAB), 2,3-dioleyloxy-N-[2-(sperminecarboxamido)ethyl]-N,N-dimethyl-1-propanaminium trifluoroacetate (DOSPA), 2,2-dilinoleyl-4-dimethylaminoethyl-[1,3]-dioxolane (DLin-KC2-DMA), (6Z,9Z,28Z,31Z)-heptatriaconta-6,9,28,31-tetraen-19-yl 4-(dimethylamino)butanoate (DLin-MC3-DMA; MC3), (2S)-2,5-bis(3-aminopropylamino)-N-[2-(dioctadecylamino)acetyl]pentanamide (DOGS; Transfectam), N1-[2-((1S)-1-[(3-aminopropyl)amino]-4-[di(3-

aminopropyl)amino]butylcarboxamido)ethyl]-3,4-di[oleyloxy]-benzamide (MVL5), 3β-[N-(N′,N′-dimethylaminoethane)-carbamoyl]cholesterol (DC-Cholesterol), N4-cholesteryl-spermine (GL67), Di((Z)-non-2-en-1-yl) 9-((4-(dimethylamino)butanoyl)oxy)heptadecanedioate (L319), Heptadecan-9-yl 8-((2-hydroxyethyl)(8-(nonyloxy)-8-oxooctyl)amino)octanoate (Lipid 5), Heptadecan-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate (Lipid H (SM-102)), ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate) (ALC-0315), 1,1′-((2-(4-(2-((2-(bis(2-hydroxydodecyl)amino)ethyl)(2-hydroxydodecyl)amino)ethyl) piperazin-1-yl)ethyl)azanediyl) bis(dodecan-2-ol) (C12-200), Tetrakis (8-methylnonyl) 3,3′,3″,3‴-(((methylazanediyl)bis(propane-3,1 diyl))bis(azanetriyl)) tetrapropionate (306Oi10), 3,6-bis(4-(bis(2-hydroxydodecyl)amino)butyl) piperazine-2,5-dione (cKK-E12), (((3,6-dioxopiperazine-2,5-diyl)bis(butane-4,1-diyl))bis(azanetriyl))tetrakis(ethane-2,1-diyl) (9Z,9′Z,9″Z,9‴Z,12Z,12′Z,12″Z,12‴Z)- tetrakis(octadeca-9,12-dienoate) (OF-Deg-Lin), Ethylphosphatidylcholine (ePC), 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC), Cholesterol, β-sitosterol, 1,2-dimyristoyl-rac-glycero-3-methoxypolyethylene glycol-2000 (PEG2000-DMG), 1,2-distearoyl-rac-glycero-3-methoxypolyethylene glycol-2000 (PEG2000-DSG), DODAP (1,2-dioleoyl-3-dimethylammonium-propane), DODMA (1,2-dioleoyl-3-dimethylammonium-propane), 1,2-dioleoyl-sn-glycero-3-phosphate (18PA), 1,2-dioleoyl-sn-glycero-3-phospho-l-serine (DOPS), Phosphatidic Acid (PA) derivatives, Cardiolipin, 1,2-Dioleoyl-sn-glycero-3-phosphate (DOPA), PEG2000-DSPE (1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000]), PEG2000-DOPE (1,2-dioleoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000]).

65. The composition of claim 63 or 64, wherein the antigens are encoded by RNA, mRNA, circular RNA, or DNA.