CLAIMS

1. An immunomodulatory combination comprising:

a lipid conjugate comprising an immunomodulatory agent covalently linked to a lipid by a cleavable linkage or through a cleavable linker; and

an antigen wherein the antigen is a protein, polypeptide, peptide, lipoprotein, glycolipid, polynucleotide, or polysaccharide, and/or

one or more nucleic acids that encode the antigen wherein the antigen is a protein, polypeptide, peptide, lipoprotein, or polynucleotide,

wherein the antigen is an antigen associated with an allergic reaction, autoimmune disease, organ or tissue rejection, graft versus host disease, anti-drug antibody or gene/protein replacement therapy;

wherein the lipid conjugate and the antigen and/or the one or more nucleic acids that encode the antigen are formulated in separate delivery vehicles or co-formulated in the same delivery vehicle.

2. The immunomodulatory combination as claimed in claim 1, wherein the delivery vehicles are lipid nanoparticles and/or liposomes,

optionally wherein the delivery vehicles are lipid nanoparticles which deliver to antigen presenting cells (APCs).

3. The immunomodulatory combination as claimed in claim 2, wherein:

the antigen or the one or more nucleic acids encoding the antigen is entrapped within a lipid nanoparticle or liposome and has a net charge that is opposite a net charge of a lipid in the lipid nanoparticle, or

the antigen is lipophilic and incorporated into a lipid compartment of a lipid nanoparticle or liposome, or

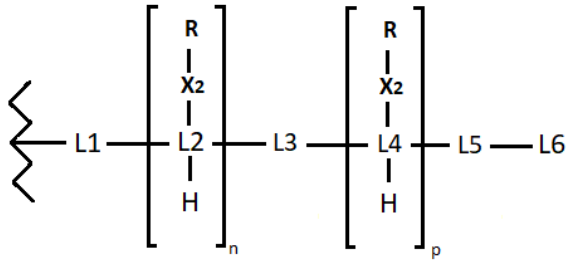
wherein the antigen is hydrophilic and entrapped in a liposome containing an aqueous core.

4. The immunomodulatory combination as claimed in any one of claims 1 to 3, wherein the lipid conjugate is co-formulated in the same delivery vehicle as the antigen or the one or more nucleic acids that encode the antigen.

5. The immunomodulatory combination as claimed in any one of claims 1 to 4, wherein the lipid:

(a) is a linear or branched lipid chain having 5 to 30 carbon atoms, 14 to 20 carbon atoms, or 16 to 18 carbon atoms; or

(b) has the structure of **Formula I**:



(**Formula I**);

wherein backbone L is represented by L1 + L2 + L3 + L4 + L5 + L6 and wherein L comprises 2 to 100, 2 to 75, 2 to 80, 3 to 60, 4 to 50, 5 to 45 or 5 to 40 carbon atoms and 0 to 6 cis or trans C=C double bonds;

wherein L1 is a carbon chain having 0 to 40, 1 to 40, 1 to 35, or 3 to 30 carbon atoms and optionally L1 has one or more cis or trans C=C double bonds or 0 to 2 cis or trans C=C double bonds;

wherein L2 and L4 are carbon atoms;

L3 is 0 to 20 carbon atoms and comprises 0 to 2 cis or trans C=C double bonds;

L5 is 0 to 20 carbon atoms and comprises 0 to 2 cis or trans C=C double bonds;

L6 is $-CH_3$, $=CH_2$ or H;

each R is independently a linear or branched hydrocarbon chain having 0 to 30 carbon atoms and 0 to 3 cis or trans C=C double bonds, optionally 0 to 2 cis or trans C=C double

bonds, wherein if one or more of R is branched, each branch point optionally includes an X2 functional group or is a carbon atom;

wherein n is 0 to 8 and p is 0 to 8, and wherein n + p is 0 or is $\geq$ 1 or 1 to 8, 2 to 6 or 2 to 4; and

wherein each X2 if present is independently an ester, amide, amidine, hydrazone, ether, carbonate, carbamate, thionocarbamate, guanidine, guanine, oxime, isourea, acylsulfonamide, phosphoramide, phosphonamide, phosphoramidate, phosphate, phosphonate, phosphodiester, phosphate phosphonooxymethylether, N-Mannich adduct, N-acyloxyalkylamine, sulfonamide, imine, azo, carbon-based functional groups including an alkane, alkene or alkyne, methylene (CH_2) or urea.

6. The immunomodulatory combination as claimed in any one of claims 1 to 5, wherein the lipid conjugate is a first lipid conjugate, and the immunomodulatory combination further comprises a second lipid conjugate, wherein the second lipid conjugate comprises an immunomodulatory agent covalently linked to a lipid by a cleavable linkage or through a cleavable linker, wherein the immunomodulatory agent of the second lipid conjugate is different from the immunomodulatory agent of the first lipid conjugate, wherein the first lipid conjugate and the second lipid conjugate are formulated in separate delivery vehicles or are co-formulated in the same delivery vehicle,

optionally wherein the immunomodulatory combination comprises a plurality of lipid conjugates, wherein the plurality of lipid conjugates comprise 3, 4, 5, 6, 7, 8, 9, or 10 immunomodulatory agents, wherein each immunomodulatory agent of the plurality of lipid conjugates is different, and wherein each lipid conjugate of the plurality of lipid conjugates is independently formulated in a separate delivery vehicle from the other components of the immunomodulatory combination or is co-formulated with one or more of the other components of the immunomodulatory combination.

7. The immunomodulatory combination as claimed in claim 6, wherein the immunomodulatory agent of the second lipid conjugate targets a different immune pathway than the immunomodulatory agent of the first lipid conjugate.

8. The immunomodulatory combination as claimed in claim 6 or 7, wherein the first lipid conjugate and the second lipid conjugate are co-formulated in the same delivery vehicle.

9. The immunomodulatory combination as claimed in any one of claims 1 to 8, wherein each immunomodulatory agent is a tolerogenic agent or anti-inflammatory agent.

10. The immunomodulatory combination as claimed in any one of claims 1 to 8, wherein each immunomodulatory agent is an immunostimulant or an immunosuppressant.

11. The immunomodulatory combination as claimed in any one of claims 1 to 10, wherein each immunomodulatory agent is independently: a non-steroidal anti-inflammatory drug (NSAID), an inflammasome inhibitor, a Janus kinase (JAK) inhibitor, a corticosteroid, an mTOR inhibitor, a DMARD (disease-modifying antirheumatic drug), a calcineurin inhibitor, or a vitamin D receptor agonist.

12. The immunomodulatory combination as claimed in any one of claims 1 to 10, wherein each immunomodulatory agent is independently prednisone, budesonide, prednisolone, methylprednisolone, hydrocortisone, cortisone, betamethasone, triamcinolone, flunisolide, beclomethasone, fluticasone, mometasone, fludrocortisone, flumethasone, triamcinolone acetonide, isoflupredone, corticosterone, desoxycortone acetate, desoxycortone enanthate, 11-deoxycorticosterone, 11-deoxycortisol, aldosterone, dexamethasone, calcitriol, acetylsalicylic acid, salicylate, mycophenolic acid, sirolimus, tacrolimus, cholecalciferol, calcifediol, alfacalcidol, calcipotriol, falecalcitriol, maxacalcitol, paricalcitol, doxercalciferol, 22-oxacalcitriol, tacalcitol, eldecalcitol, elocalcitol, inecalcitol, becocalcidiol, seocalcital, ergocalciferol, lexacalcitol, retinoic acid, cyclophosphamide (nitrogen mustards), filgotinib, baricitinib, tofacitinib, ruxolitinib, upadacitinib, oclacitinib, peficitinib, fedratinib, delgocitinib, deucravacitinib, abrocitinib, auranofin, apremilast, azathioprine, chloroquine, hydroxychloroquine, ciclosporin, leflunomide, methotrexate, minocycline, sulfasalazine, salicylic acid, diflunisal, salsalate, naproxen, ibuprofen, oxaprozin, loxoprofen, zaltoprofen, indomethacin, tolmetin, sulindac, etodolac, ketorolac, diclofenac, aceclofenac, bromfenac, nabumetone, piroxicam, meloxicam, tenoxicam, droxicam, lornoxicam, isoxicam, phenylbutazone, celecoxib, firocoxib, parecoxib, etoricoxib, clonixin, licofelone, MCC950, glyburide, CY-09, tranilast, oridonin, BOT-4-one (2-cyclohexylimino-6-methyl-6,7-dihydro-5H-benzo[1,3]oxathiol-4-one),

INF39 (Ethyl 2-(2-chlorobenzyl)acrylate), MNS (3,4-Methylenedioxy-β-nitrostyrene), fenamic acid, beta-hydroxybutyric acid, quercetin, JC-171, ibrutinib, OLT1177, FC11A-2, INF58, JC124, or Ethyl 2-((2-chlorophenyl) (hydroxy)methyl)acrylate.

13. The immunomodulatory combination as claimed in any one of claims 1 to 12, wherein the antigen is a first antigen, and the immunomodulatory combination further comprises a second antigen or one or more nucleic acids encoding the second antigen, wherein the first antigen is different than the second antigen,

wherein the second antigen or the one or more nucleic acids encoding the second antigen is formulated in a separate delivery vehicle from the other components of the immunomodulatory combination or is co-formulated with one or more of the other components of the immunomodulatory combination,

optionally wherein the immunomodulatory combination comprises a plurality of antigens or comprises one or more nucleic acids encoding the plurality of antigens, or comprises a combination of antigens and antigen-encoding nucleic acid(s) for providing the plurality of antigens, wherein the plurality of antigens comprises 3, 4, 5, 6, 7, 8, 9, or 10 antigens, and each antigen or antigen-encoding nucleic acid is independently formulated in a separate delivery vehicle from the other components of the immunomodulatory combination or is co-formulated with one or more of the other components of the immunomodulatory combination.

14. The immunomodulatory combination as claimed in claim 13, wherein the one or more nucleic acids encoding the first antigen and the one or more nucleic acids encoding the second antigen are comprised within a single nucleic acid and the first antigen and the second antigen are co-formulated in the same delivery vehicle.

15. The immunomodulatory combination as claimed in any one of claims 1 to 14, for use in treatment of a subject having an antigen-induced disorder or undesired antigen-driven immune response, or for use in manufacture of a medicament for treating the subject,

optionally wherein the antigen-induced disorder or undesired antigen-driven immune response is selected from: autoimmune diseases (T cell and/or antibody responses to self antigen), allergic diseases (T cell and IgE responses to environmental or food antigens),

transplantation (T cell responses against major and minor histocompatibility antigens in donor tissue/organ/cell), anti-drug antibody responses (antibody responses that diminish efficacy of therapeutics), gene/protein replacement therapy (T cell/antibody response against proteins therapeutically replaced in genetic protein deficiencies),

optionally wherein the antigen-induced disorder or undesired antigen-driven immune response is selected from: multiple sclerosis, rheumatoid arthritis, myelin oligodendrocyte glycoprotein antibody disorder, vitiligo, type 1 diabetes, primary biliary cholangitis, anti-GBM nephritis/Goodpasture's disease, celiac disease, psoriasis, myasthenia gravis, immune thrombocytopenia purpura, Grave's disease, neuromyelitis optica, pemphigus vulgaris, bullous pemphigoid, cicatricial pemphigoid, lupus including systemic lupus erythematosus SLE, autoimmune liver disease, myositis, Evan's syndrome, transverse myelitis, Guillain-Barré syndrome, warm autoimmune hemolytic anemia, chronic inflammatory demyelinating polyneuropathy, autoimmune dysautonomia, autoimmune angioedema, Hashimoto's thyroiditis, Lambert-Eaton syndrome, peanut/legume allergy, tree nut allergy (antigens from any of cashew, pistachio, hazelnut, walnut, almond), egg allergy, cow's milk allergy, soy allergy, fish allergy, shellfish allergy, sesame allergy, wheat allergy, allergic airway disease, and allergies caused by environmental allergens (antigens from pollen, dust, pet dander, mold and cockroaches).

16. A method for treating a subject having an antigen-induced disorder or undesired antigen-driven immune response comprising administering the immunomodulatory combination as defined in any one of claims 1 to 14 to the subject, wherein the antigen, or the one or more nucleic acids encoding the antigen, and the lipid conjugate are administered together or sequentially,

optionally wherein the antigen-induced disorder or undesired antigen-driven immune response is selected from: autoimmune diseases (T cell and/or antibody responses to self antigen), allergic diseases (T cell and IgE responses to environmental or food antigens), transplantation (T cell responses against major and minor histocompatibility antigens in donor tissue/organ/cell), anti-drug antibody responses (antibody responses that diminish efficacy of therapeutics), or gene/protein replacement therapy (T cell/antibody response against proteins therapeutically replaced in genetic protein deficiencies),

optionally wherein the antigen-induced disorder is: multiple sclerosis, rheumatoid arthritis, myelin oligodendrocyte glycoprotein antibody disorder, vitiligo, type 1 diabetes, primary biliary cholangitis, anti-GBM nephritis/Goodpasture's disease, celiac disease, psoriasis, myasthenia gravis, immune thrombocytopenia purpura, Grave's disease, neuromyelitis optica, pemphigus vulgaris, bullous pemphigoid, cicatricial pemphigoid, lupus including systemic lupus erythematosus SLE, autoimmune liver disease, myositis, Evan's syndrome, transverse myelitis, Guillain-Barré syndrome, warm autoimmune hemolytic anemia, chronic inflammatory demyelinating polyneuropathy, autoimmune dysautonomia, autoimmune angioedema, Hashimoto's thyroiditis, Lambert-Eaton syndrome, peanut/legume allergy, tree nut allergy (antigens from any of cashew, pistachio, hazelnut, walnut, almond), egg allergy, cow's milk allergy, soy allergy, fish allergy, shellfish allergy, sesame allergy, wheat allergy, allergic airway disease, or allergies caused by environmental allergens (antigens from pollen, dust, pet dander, mold and cockroaches).