IMMUNOMODULATORY OLIGOSACCHARIDES

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority under 35 U.S.C. §119 from Provisional Application Serial No. 62/567,865, filed October 4, 2017, the disclosures of which are incorporated herein by reference.

TECHNICAL FIELD

[0002] The disclosure provides for immunomodulatory oligosaccharides, and uses thereof.

BACKGROUND

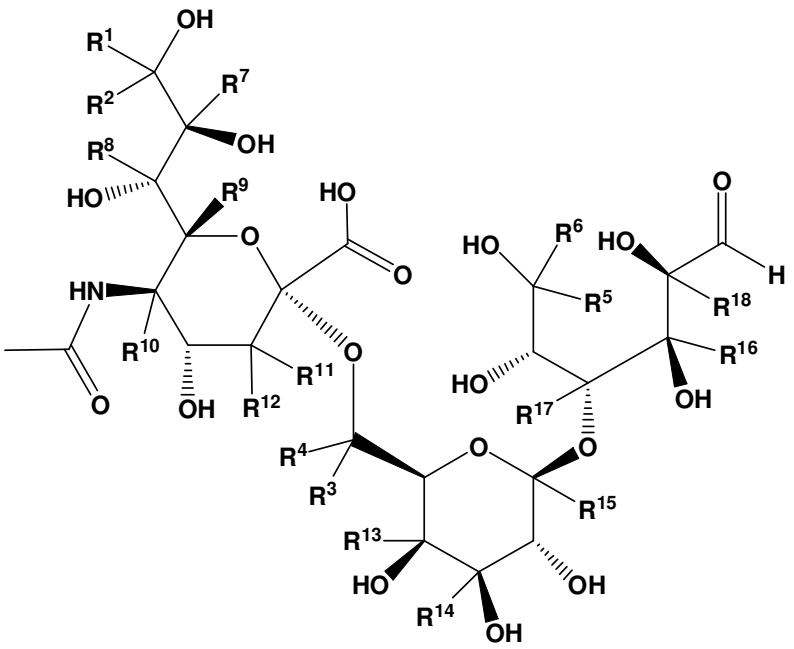
[0003] Rheumatoid arthritis (RA) is a lifelong, systemic autoimmune disease that affects women three times more frequently than men, often in their most productive and childbearing years. Pregnancy in women with RA poses a therapeutic challenge. Some anti-rheumatic drugs can cross the placenta and harm the fetus and/or are transferred into breast milk and harm the breastfed baby. Teratogenic compounds like methotrexate and leflunamide are to be avoided and high dose steroids may be associated with a premature rupture of the membranes. The high risk of drug transfer into breast milk often leads to the recommendation for women to cease breastfeeding.

[0004] 2'-Fucosyllactose (2'FL) and lacto-*N*-(*neo*)tetraose (LN*n*T) have been certified by the FDA for Generally Recognized as Safe (GRAS) status as medical foods and as dietary ingredients for adults. Moreover, these oligosaccharides are well tolerated, remain undigested in the stomach and are absorbed intact in the lower gastrointestinal tract.

SUMMARY

[0005] Chronic macrophage inflammation plays a key role in the development and progression of rheumatoid arthritis. The data presented herein, indicate that 3'-sialyllactose (3'SL) and 6'-sialyllactose (6'SL) based oligosaccharides and purified preparations comprising or consisting of 3'SL and 6'SL attenuate macrophage inflammation and suppress the secretion of pro-inflammatory cytokines, like interleukin (IL)-1beta and IL-6.

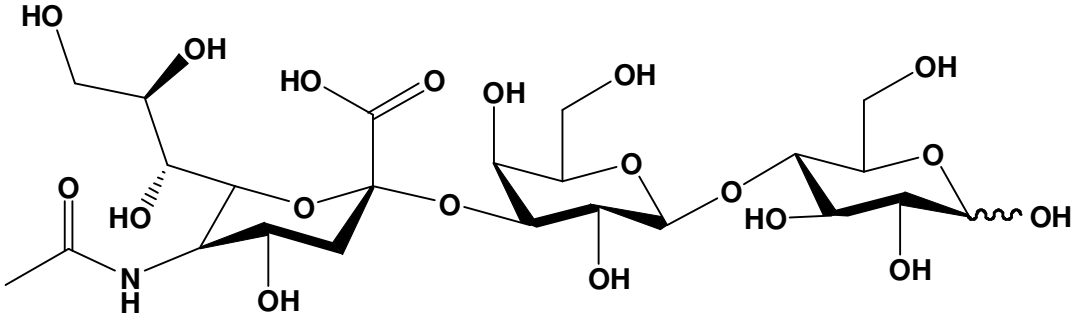
[0006] In a particular example, the disclosure provides a method for treating a subject having or suspected of having an



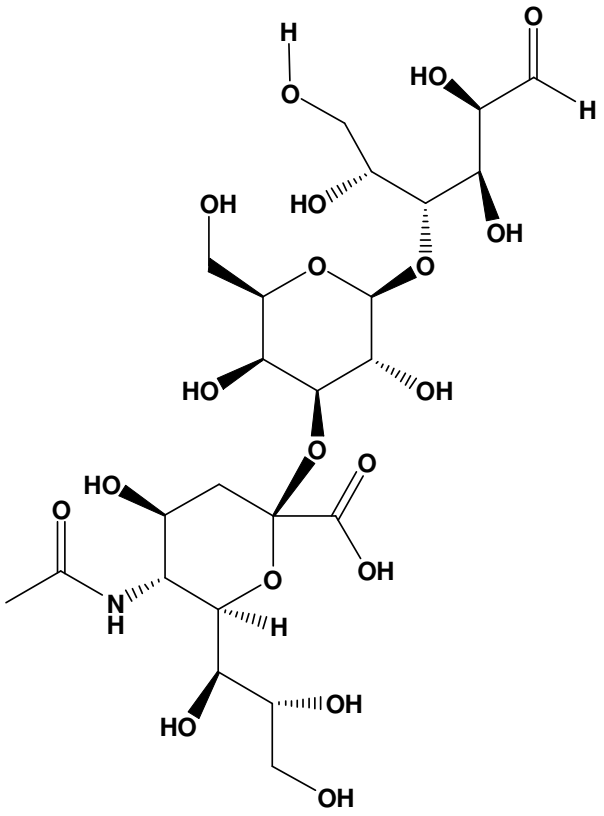
Formula II

or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein, R^1–R^{18} are independently selected from H, D, a halo, an unsubstituted or substituted (C_1–C_6)alkyl, an unsubstituted or substituted (C_1–C_6)heteroalkyl, an unsubstituted or substituted (C_2–C_6)alkenyl, an unsubstituted or substituted (C_2–C_6)heteroalkenyl, an unsubstituted or substituted (C_3–C_6)alkynyl, an unsubstituted or substituted (C_3–C_6)heteroalkynyl, an unsubstituted or substituted (C_4–C_8)cycloalkyl, an unsubstituted or substituted heterocycle, an unsubstituted or substituted aryl, –ROR', –RN(R')$_2$, –RSSR', –SH, –RSOR', –RSO$_2$R', –RSO$_2$H, –RSO$_3$H, –RC(=S)–R', –ROH, –RC(=O)R', –RNO$_2$, –RSR', –RCN, –RNC, –RNNR', –RC(=O)OR', –ROC(=O)R', –RC(=O)H, –RC(=O)OH, –RC(=O)N(R')$_2$, –RN$_3$, –ROCN, –RNCO, –RONO$_2$, –RNO, –ROP(=O)(OH)$_2$, and –RB(OH)$_2$; R is absent or a (C_1–C_5)alkyl; and R' is independently selected from H, D, an unsubstituted or substituted (C_1–C_6) alkyl, an unsubstituted or substituted (C_1–C_6)heteroalkyl, an unsubstituted or substituted (C_2–C_6)alkenyl, an unsubstituted or substituted (C_2–C_6)heteroalkenyl, an unsubstituted or substituted (C_3–C_6)alkynyl, an unsubstituted or substituted (C_3–C_6)heteroalkynyl, an unsubstituted or substituted (C_4–C_8)cycloalkyl, an unsubstituted or substituted heterocycle, and an unsubstituted or substituted aryl. In another example, the disclosure also provides a method

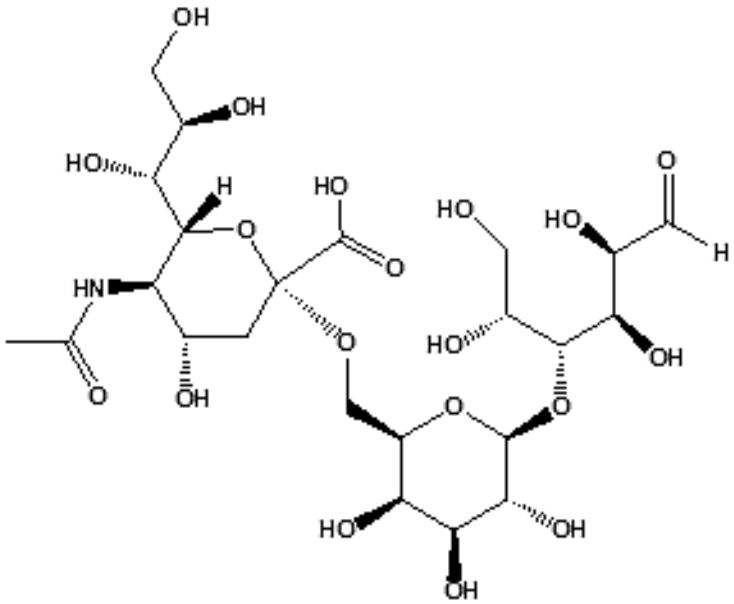
C_6)alkenyl, an unsubstituted or substituted (C_2–C_6)heteroalkenyl, an unsubstituted or substituted (C_3–C_6)alkynyl, an unsubstituted or substituted (C_3–C_6)heteroalkynyl, an unsubstituted or substituted (C_4–C_8)cycloalkyl, an unsubstituted or substituted heterocycle, an unsubstituted or substituted aryl, –ROR', –RN(R')$_2$, –RSSR', –SH, –RSOR', –RSO$_2$R', –RSO$_2$H, –RSO$_3$H, –RC(=S)–R', –ROH, –RC(=O)R', –RNO$_2$, –RSR', –RCN, –RNC, –RNNR', –RC(=O)OR', –ROC(=O)R', –RC(=O)H, –RC(=O)OH, –RC(=O)N(R')$_2$, –RN$_3$, –ROCN, –RNCO, –RONO$_2$, –RNO, –ROP(=O)(OH)$_2$, and –RB(OH)$_2$; R is absent or a (C_1–C_5)alkyl; and R' is independently selected from H, D, an unsubstituted or substituted (C_1–C_6) alkyl, an unsubstituted or substituted (C_1–C_6)heteroalkyl, an unsubstituted or substituted (C_2–C_6)alkenyl, an unsubstituted or substituted (C_2–C_6)heteroalkenyl, an unsubstituted or substituted (C_3–C_6)alkynyl, an unsubstituted or substituted (C_3–C_6)heteroalkynyl, an unsubstituted or substituted (C_4–C_8)cycloalkyl, an unsubstituted or substituted heterocycle, and an unsubstituted or substituted aryl. In yet another example, the disclosure further provides a method for treating a subject having or suspected of having an inflammatory disease or an autoimmune disorder, comprising administering to the subject an effective amount of an oligosaccharide, or a pharmaceutical composition comprising the oligosaccharide, wherein the oligosaccharide comprises a structure of Formula I(d), I(e) or II(a):



Formula I(d)



Formula I(e)



Formula II(a)

or a pharmaceutically acceptable salt, solvate, or prodrug thereof. In a certain example, a method disclosed herein comprises orally administering an oligosaccharide of the disclosure or a pharmaceutical composition comprising an oligosaccharide of the

disclosure to a subject. In yet a further example, a method disclosed herein comprises orally administering to a subject a nutritional composition comprising at least one oligosaccharide of the disclosure. In certain examples, the nutritional composition comprises or consists of 3'SL, 6'SL or a combination of 3'SL and 6'SL. In other examples, the nutritional composition comprise or consists of 3'SL, 6'SL or a combination thereof at 145 mg/L or greater of 3'SL, 6'SL or a combination of 3'SL and 6'SL. In another example, the nutritional composition comprises at least 9% (*e.g.*, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, or 100%; or any value between any of the foregoing) 3'SL, 6'SL or a combination thereof of the total oligosaccharides in the composition. In another example, a pharmaceutical composition comprising the oligosaccharide of the disclosure is formulated as a tablet or a capsule. In another example, the disclosure also provides a method for treating a subject having or suspected of having an inflammatory disease or an autoimmune disorder, comprising administering to the subject an effective amount of an oligosaccharide disclosed herein, or a pharmaceutical composition comprising the oligosaccharide disclosed herein, wherein the autoimmune disorder is selected from the group consisting of autoimmune myocarditis, Dressler's syndrome, postpericardiotomy syndrome, subacute bacterial endocarditis, anti-glomerular basement membrane nephritis, interstitial cystitis, lupus nephritis, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, antisynthetase syndrome, alopecia areata, autoimmune angioedema, autoimmune progesterone dermatitis, autoimmune urticaria, bullous pemphigoid, cicatricial pemphigoid, dermatitis herpetiformis, discoid lupus erythematosus, epidermolysis bullosa acquisita, erythema nodosum, gestational pemphigoid, hidradenitis suppurativa, lichen planus, lichen sclerosus, linear IgA disease, morphea, pemphigus vulgaris, pityriasis lichenoides et varioliformis acuta, Mucha-Habermann disease, psoriasis, Systemic scleroderma, vitiligo, Addison's disease, autoimmune polyendocrine syndrome type 1, autoimmune polyendocrine syndrome type 2, autoimmune polyendocrine syndrome type 3, autoimmune pancreatitis, diabetes mellitus type 1, autoimmune thyroiditis, Ord's thyroiditis, Graves'

disease, autoimmune Oophoritis, endometriosis, Sjögren syndrome, autoimmune enteropathy, antiphospholipid syndrome, aplastic anemia, autoimmune hemolytic anemia, autoimmune lymphoproliferative syndrome, autoimmune neutropenia, autoimmune thrombocytopenic purpura, cold agglutinin disease, essential mixed cryoglobulinemia, Evans syndrome, pernicious anemia, pure red cell aplasia, thrombocytopenia, adiposis dolorosa, adult-onset Still's disease, ankylosing spondylitis, CREST syndrome, drug-induced lupus, enthesitis-related arthritis, eosinophilic fasciitis, Felty syndrome, IgG4-related disease, juvenile arthritis, chronic Lyme disease, mixed connective tissue disease, palindromic rheumatism, Parry Romberg syndrome, Parsonage-Turner syndrome, psoriatic arthritis, reactive arthritis, relapsing polychondritis, retroperitoneal fibrosis, rhematic fever, rheumatoid arthritis, sarcoidosis, Schnitzler syndrome, systemic lupus erythematosus, undifferentiated connective tissue disease, dermatomyositis, fibromyalgia, inclusion body myositis, myositis, myasthenia gravis, neuromyotonia, paraneoplastic cerebellar degeneration, polymyositis, acute disseminated encephalomyelitis, acute motor axonal neuropathy, anti-N-methyl-D-aspartate receptor encephalitis, Balo concentric sclerosis, Bickerstaff's encephalitis, chronic inflammatory demyelinating polyneuropathy, Guillain-Barrè syndrome, Hashimoto's encephalopathy, idiopathic inflammatory demyelinating diseases, Lambert-Eaton myasthenic syndrome, multiple sclerosis, Oshtoran syndrome, pediatric autoimmune neuropsychiatric disorder associated with *Streptococcus*, progressive inflammatory neuropathy, restless leg syndrome, stiff person syndrome, sydenham chorea, transverse myelitis, autoimmune retinopathy, autoimmune uveitis, Cogan syndrome, Graves ophthalmopathy, intermediate uveitis, ligneous conjunctivitis, Mooren's ulcer, neuromyelitis optica, opsoclonus myoclonus syndrome, autoimmune inner ear disease, Ménière's disease, Behçet's disease, eosinophilic granulomatosis with polyangiitis, IgA vasculitis, Kawasaki's disease, leukocytoclastic vasculitis, lupus vasculitis, rheumatoid vasculitis, microscopic polyangiitis, polyarteritis nodosa, polymyalgia rheumatica, urticarial vasculitis, vasculitis, and primary immune deficiency. In yet another example, the disclosure also provides a method for treating a

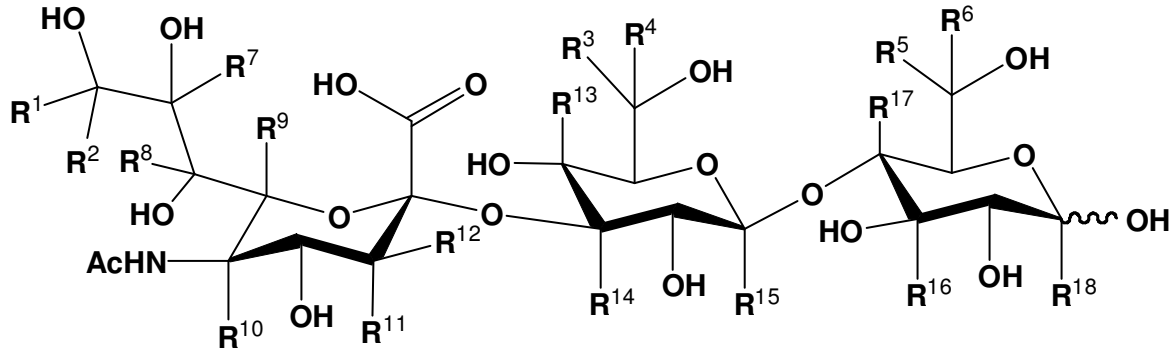
subject having or suspected of having an inflammatory disease or an autoimmune disorder, comprising administering to the subject an effective amount of an oligosaccharide disclosed herein, or a pharmaceutical composition comprising the oligosaccharide disclosed herein, wherein the inflammatory disease is selected from the group consisting of ankylosing spondylitis, antiphospholipid antibody syndrome, gout, myositis, rheumatoid arthritis, scleroderma, systemic lupus erythematosus, vasculitis, Sjögren's syndrome, asthma, tuberculosis, chronic periodontitis, chronic sinusitis, chronic active hepatitis, Alzheimer's, Parkinson's disease, nephritis, fibromyalgia, atherosclerosis, osteoarthritis, psoriatic arthritis, eczema, gastritis, sinusitis, seborrheic dermatitis, and Wegener's granulomatosis. In a further example, the disclosure also provides a method for treating a subject having or suspected of having an inflammatory disease or an autoimmune disorder, comprising administering to the subject an effective amount of an oligosaccharide disclosed herein, or a pharmaceutical composition comprising the oligosaccharide disclosed herein, wherein the inflammatory disease is caused by or associated with macrophage driven chronic inflammation. In yet a further example, the disclosure also provides a method for treating a subject having or suspected of having an inflammatory disease or an autoimmune disorder, comprising administering to the subject an effective amount of an oligosaccharide disclosed herein, or a pharmaceutical composition comprising the oligosaccharide disclosed herein, wherein the inflammatory disease is caused by or associated with macrophage driven chronic inflammation selected from the group consisting of atherosclerosis, chronic obstructive pulmonary disease, insulin resistance, type-2 diabetes, obesity, and systemic juvenile idiopathic arthritis. In a particular example, the disclosure also provides a method for treating a subject having or suspected of having rheumatoid arthritis, comprising administering to the subject an effective amount of an oligosaccharide disclosed herein, or a pharmaceutical composition comprising the oligosaccharide disclosed herein. In another example, the disclosure also provides a method for treating a subject having or suspected of having an inflammatory disease or an autoimmune disorder, comprising

administering to the subject an effective amount of an oligosaccharide disclosed herein, or a pharmaceutical composition comprising the oligosaccharide disclosed herein, with another therapeutic agent. In a further example, the disclosure also provides a method for treating a subject having or suspected of having an inflammatory disease or an autoimmune disorder, comprising administering to the subject an effective amount of an oligosaccharide disclosed herein, or a pharmaceutical composition comprising the oligosaccharide disclosed herein, with a nonsteroidal anti-inflammatory drug, a glucocorticoid, a biologic response modifier or an opioid.

[0007] Examples of nonsteroidal anti-inflammatory drugs include, but are not limited to, Aminophenazone, Ampyrone, Azapropazone, Clofezone, Difenamizole, Famprofazone, Feprazone, Kebuzone, Metamizole, Mofebutazone, Morazone, Nifenazone, Oxyphenbutazone, Phenazone, Phenylbutazone, Propyphenazone, Sulfinpyrazone, Suxibuzone, Aspirin, Aloxiprin, Benorylate, Carbasalate, calcium Diflunisal, Dipyrocetyl, Ethenzamide, Guacetisal, Magnesium salicylate, Methyl salicylate, Salsalate, Salicin, Salicylamide, Salicylic acid (salicylate), Sodium salicylate, Aceclofenac, Acemetacin, Alclofenac, Amfenac, Bendazac, Bromfenac, Bumadizone, Bufexamac, Diclofenac, Difenpiramide, Etodolac, Felbinac, Fenclozic acid, Fentiazac, Indomethacin, Indomethacin farnesil, Isoxepac, Ketorolac, Lonazolac, Oxametacin, Prodolic acid, Proglumetacin, Sulindac, Tiopinac, Tolmetin, Zomepirac, Ampiroxicam, Droxicam, Isoxicam, Lornoxicam, Meloxicam, Piroxicam, Tenoxicam, Alminoprofen, Benoxaprofen, Carprofen, Dexibuprofen, Dexketoprofen, Fenbufen, Fenoprofen, Flunoxaprofen, Flurbiprofen, Ibuprofen, Ibuproxam, Indoprofen, Ketoprofen, Loxoprofen, Miroprofen, Naproxen, Oxaprozin, Pirprofen, Suprofen, Tarenflurbil, Tepoxalin, Tiaprofenic acid, Vedaprofen, Naproxcinod, Azapropazone, Clonixin, Etofenamate, Flufenamic acid, Flunixin, Meclofenamic acid, Mefenamic acid, Morniflumate, Niflumic acid, Tolfenamic acid, Flutiazin, Apricoxib, Celecoxib, Cimicoxib, Deracoxib, Etoricoxib, Firocoxib, Lumiracoxib, Mavacoxib, Parecoxib, Robenacoxib, Rofecoxib, Valdecoxib, Aminopropionitrile, Benzydamine, Chondroitin sulfate, Diacerein, Fluproquazone, Glucosamine, Glycosaminoglycan, Hyperforin,

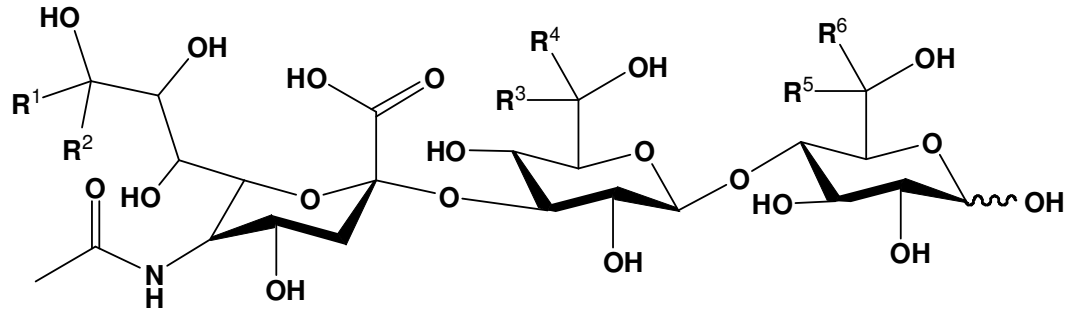
Nabumetone, Nimesulide, Oxaceprol, Proquazone, Superoxide dismutase/Orgotein, and Tenidap. Examples of glucocorticoids include but are limited to betamethasone and prednisone. Examples of biological response modifiers include but are not limited to hydroxychloroquine, leflunomide, methotrexate, tofacitinib, abatacept, adalimumab, adalimumab-atto, anakinra, etanercept, etanercept-szzs, rituximab, infliximab-dyyb, golimumab, certolizumab pegol, tocilizumab, and sarilumab. Example of opioids include but are not limited to tramadol, oxycontin, oxycodone, fentanyl, morphine, codeine, dihydrocodeine, and actiq.

[0008] In a particular example, the disclosure provides for a method to attenuate macrophage inflammation and/or suppress the secretion of pro-inflammatory cytokines in a subject in need thereof, comprising administering to the subject an effective amount of an oligosaccharide, or a pharmaceutical composition comprising the oligosaccharide, wherein the oligosaccharide comprises a structure of Formula I, I(a) or II:



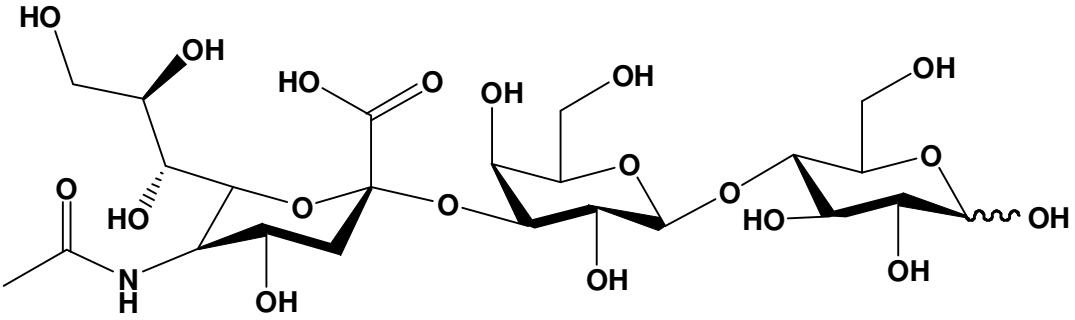
Formula I

substituted (C_1–C_6)heteroalkyl, an unsubstituted or substituted (C_2–C_6)alkenyl, an unsubstituted or substituted (C_2–C_6)heteroalkenyl, an unsubstituted or substituted (C_3–C_6)alkynyl, an unsubstituted or substituted (C_3–C_6)heteroalkynyl, an unsubstituted or substituted (C_4–C_8)cycloalkyl, an unsubstituted or substituted heterocycle, an unsubstituted or substituted aryl, –ROR', –RN(R')$_2$, –RSSR', –SH, –RSOR', –RSO$_2$R', –RSO$_2$H, –RSO$_3$H, –RC(=S)–R', –ROH, –RC(=O)R', –RNO$_2$, –RSR', –RCN, –RNC, –RNNR', –RC(=O)OR', –ROC(=O)R', –RC(=O)H, –RC(=O)OH, –RC(=O)N(R')$_2$, –RN$_3$, –ROCN, –RNCO, –RONO$_2$, –RNO, –ROP(=O)(OH)$_2$, and –RB(OH)$_2$; R is absent or a (C_1–C_5)alkyl; and R' is independently selected from H, D, an unsubstituted or substituted (C_1–C_6) alkyl, an unsubstituted or substituted (C_1–C_6)heteroalkyl, an unsubstituted or substituted (C_2–C_6)alkenyl, an unsubstituted or substituted (C_2–C_6)heteroalkenyl, an unsubstituted or substituted (C_3–C_6)alkynyl, an unsubstituted or substituted (C_3–C_6)heteroalkynyl, an unsubstituted or substituted (C_4–C_8)cycloalkyl, an unsubstituted or substituted heterocycle, and an unsubstituted or substituted aryl. In another example, the disclosure provides for a method to attenuate macrophage inflammation and/or suppress the secretion of pro-inflammatory cytokines in a subject in need thereof, comprising administering to the subject an effective amount of an oligosaccharide, or a pharmaceutical composition comprising the oligosaccharide, wherein the oligosaccharide comprises a structure of Formula I(b) or I(c):

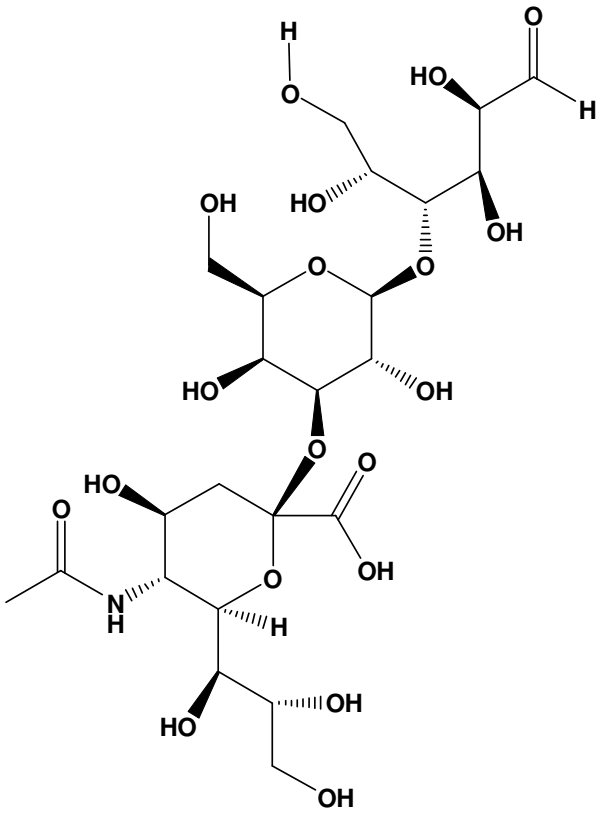


Formula I(b)

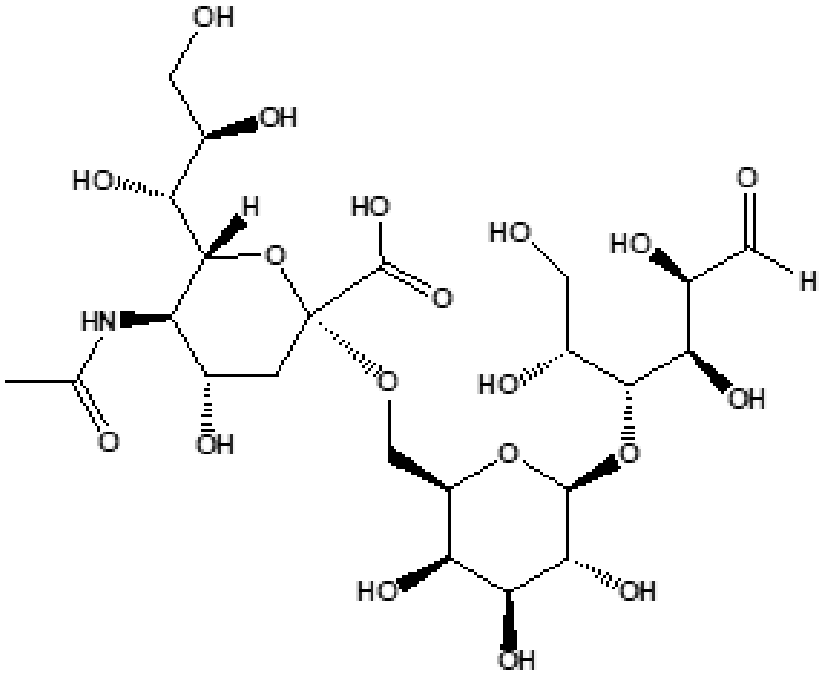
an unsubstituted or substituted (C_4–C_8)cycloalkyl, an unsubstituted or substituted heterocycle, and an unsubstituted or substituted aryl. In yet another example, the disclosure provides for a method to attenuate macrophage inflammation and/or suppress the secretion of pro-inflammatory cytokines in a subject in need thereof, comprising administering to the subject an effective amount of an oligosaccharide, or a pharmaceutical composition comprising the oligosaccharide, wherein the oligosaccharide comprises a structure of Formula I(d), I(e) or II(a):



Formula I(d)



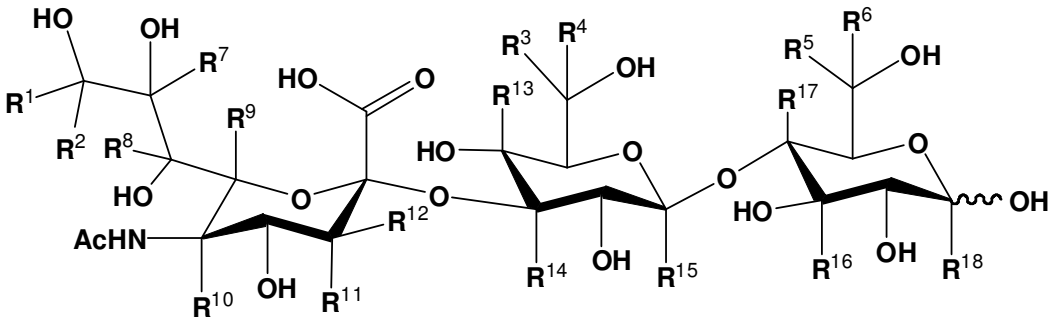
Formula I(e)



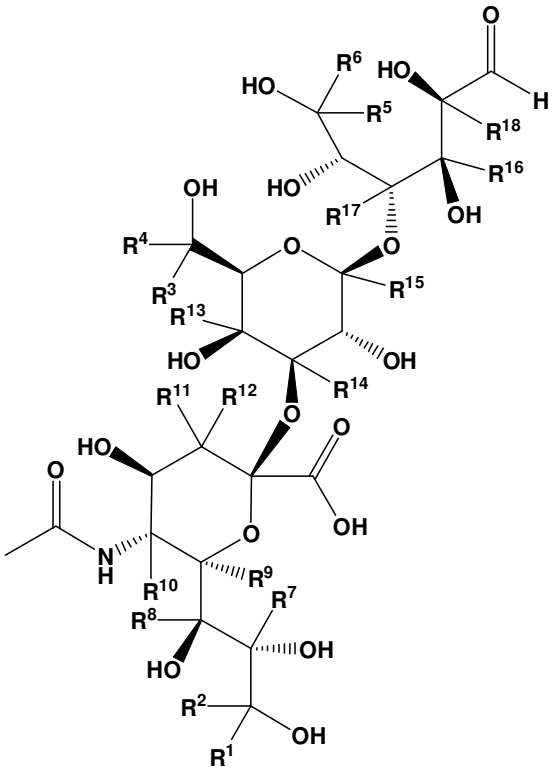
Formula II(a)

or a pharmaceutically acceptable salt, solvate, or prodrug thereof. In yet a further example, the pro-inflammatory cytokines comprise interleukin (IL)-1β and IL-6. In a certain example, for a method disclosed herein an oligosaccharide of disclosure, or a pharmaceutical composition comprising the oligosaccharide of disclosure, is administered to a human subject that is 5 years of age or older (*e.g.*, 6, 7, 8, 9, 10, 11, 12 years of age or older). In an alternative example, the composition comprising the oligosaccharide(s) are administered to a subject less than 5 years of age. In a further example, for a method disclosed herein an oligosaccharide of disclosure, or a pharmaceutical composition comprising the oligosaccharide of disclosure, is administered to a human subject that is 18 years of age or older.

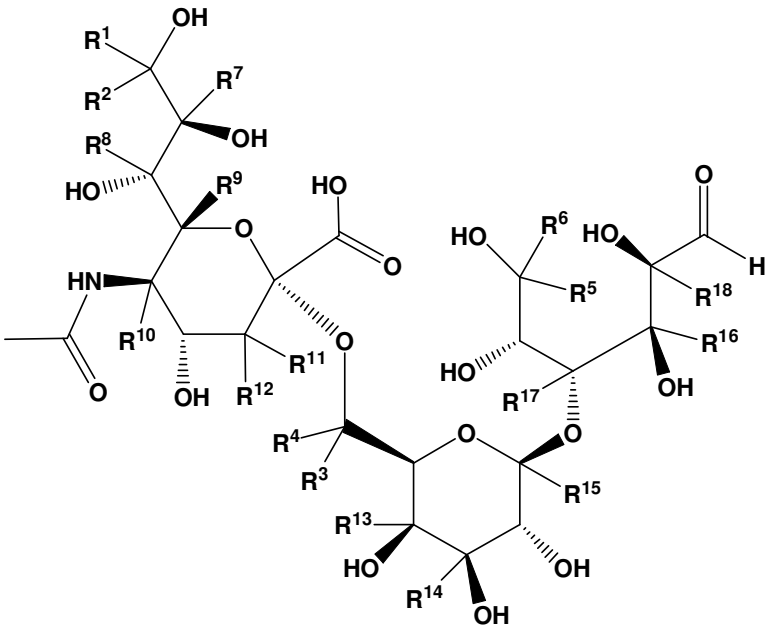
[0008a] In one aspect, the present disclosure refers to use of at least one oligosaccharide, or a pharmaceutical composition comprising the at least one oligosaccharide, in the manufacture of a medicament for treating a subject having or suspected of having an inflammatory disease or an autoimmune disorder, wherein the oligosaccharide comprises a structure of Formula I, I(a) and/or II:



Formula I



Formula I(a)



Formula II

or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein,

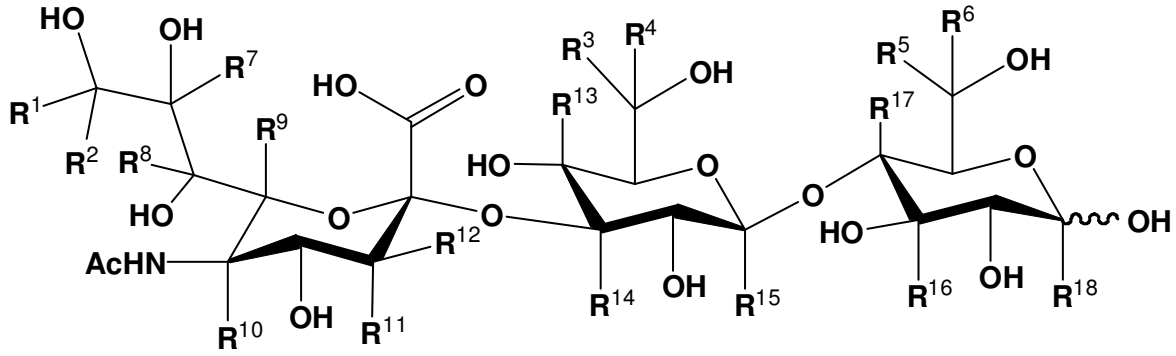
R^1–R^{18} are independently selected from H, D, a halo, an unsubstituted or substituted (C_1–C_6)alkyl, an unsubstituted or substituted (C_1–C_6)heteroalkyl, an unsubstituted or substituted (C_2–C_6)alkenyl, an unsubstituted or substituted (C_2–C_6)heteroalkenyl, an unsubstituted or substituted (C_3–C_6)alkynyl, an unsubstituted or substituted (C_3–C_6)heteroalkynyl, an unsubstituted or substituted (C_4–C_8)cycloalkyl, an unsubstituted or substituted heterocycle, an unsubstituted or substituted aryl, –ROR', –RN(R')$_2$, –RSSR', –SH, –RSOR', –RSO$_2$R', –RSO$_2$H, –RSO$_3$H, –RC(=S)–R', –ROH, –RC(=O)R', –RNO$_2$, –RSR', –RCN, –RNC, –RNNR', –RC(=O)OR', –ROC(=O)R', –RC(=O)H, –RC(=O)OH, –RC(=O)N(R')$_2$, –RN$_3$, –ROCN, –RNCO, –RONO$_2$, –RNO, –ROP(=O)(OH)$_2$, and –RB(OH)$_2$;

R is absent or a (C_1–C_5)alkyl; and

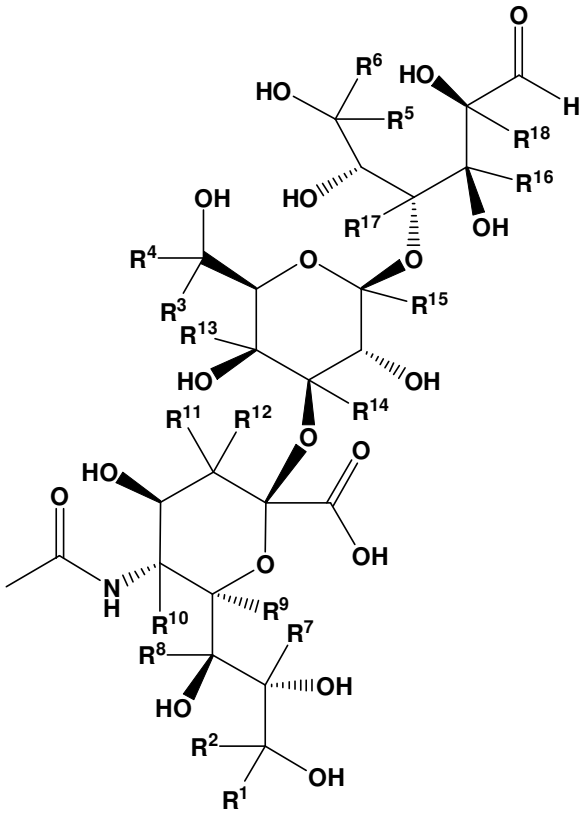
R' is independently selected from H, D, an unsubstituted or substituted (C_1–C_6) alkyl, an unsubstituted or substituted (C_1–C_6)heteroalkyl, an unsubstituted or substituted (C_2–C_6)alkenyl, an unsubstituted or substituted (C_2–C_6)heteroalkenyl, an unsubstituted or substituted (C_3–C_6)alkynyl, an unsubstituted or substituted (C_3–C_6)heteroalkynyl, an unsubstituted or substituted (C_4–C_8)cycloalkyl, an unsubstituted or substituted heterocycle, and an unsubstituted or

substituted aryl.

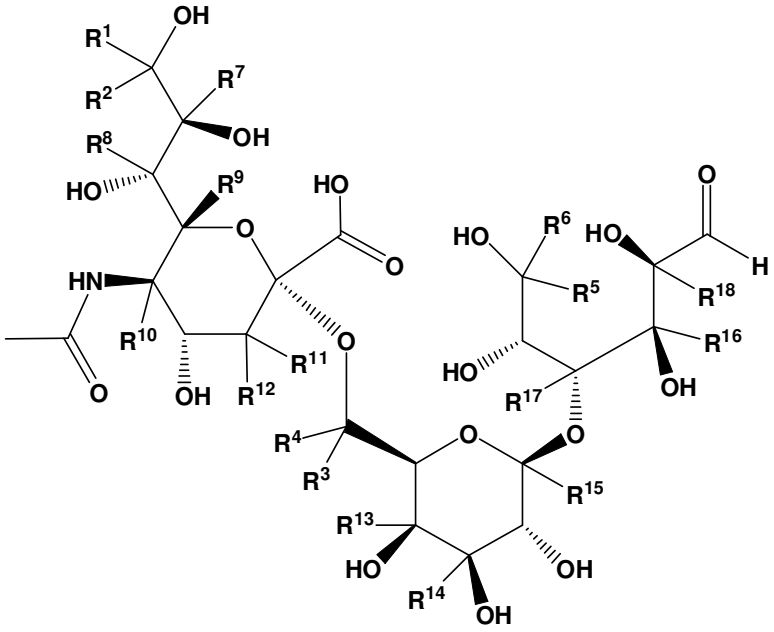
[0008b] In another aspect, the present disclosure refers to use of at least one oligosaccharide, or a pharmaceutical composition comprising the at least one oligosaccharide, in the manufacture of a medicament for attenuating macrophage inflammation and/or suppressing the secretion of pro-inflammatory cytokines in a subject in need thereof, wherein the at least one oligosaccharide comprises a structure of Formula I, I(a) and/or II:



Formula I



Formula I(a)



Formula II

or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein,

R^1–R^{18} are independently selected from H, D, a halo, an unsubstituted or substituted (C_1–C_6)alkyl, an unsubstituted or substituted (C_1–C_6)heteroalkyl, an unsubstituted or substituted (C_2–C_6)alkenyl, an unsubstituted or substituted (C_2–C_6)heteroalkenyl, an unsubstituted or substituted (C_3–C_6)alkynyl, an unsubstituted or substituted (C_3–C_6)heteroalkynyl, an unsubstituted or substituted (C_4–C_8)cycloalkyl, an unsubstituted or substituted heterocycle, an unsubstituted or substituted aryl, –ROR', –RN(R')$_2$, –RSSR', –SH, –RSOR', –RSO$_2$R', –RSO$_2$H, –RSO$_3$H, –RC(=S)–R', –ROH, –RC(=O)R', –RNO$_2$, –RSR', –RCN, –RNC, –RNNR', –RC(=O)OR', –ROC(=O)R', –RC(=O)H, –RC(=O)OH, –RC(=O)N(R')$_2$, –RN$_3$, –ROCN, –RNCO, –RONO$_2$, –RNO, –ROP(=O)(OH)$_2$, and –RB(OH)$_2$;

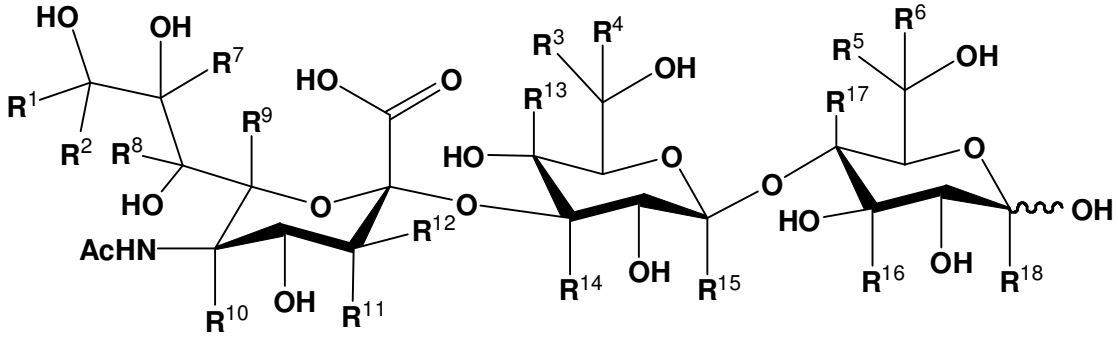
R is absent or a (C_1–C_5)alkyl; and

R' is independently selected from H, D, an unsubstituted or substituted (C_1–C_6) alkyl, an unsubstituted or substituted (C_1–C_6)heteroalkyl, an unsubstituted or substituted (C_2–C_6)alkenyl, an unsubstituted or substituted (C_2–C_6)heteroalkenyl, an unsubstituted or substituted (C_3–C_6)alkynyl, an unsubstituted or substituted (C_3–C_6)heteroalkynyl, an unsubstituted or substituted (C_4–C_8)cycloalkyl,

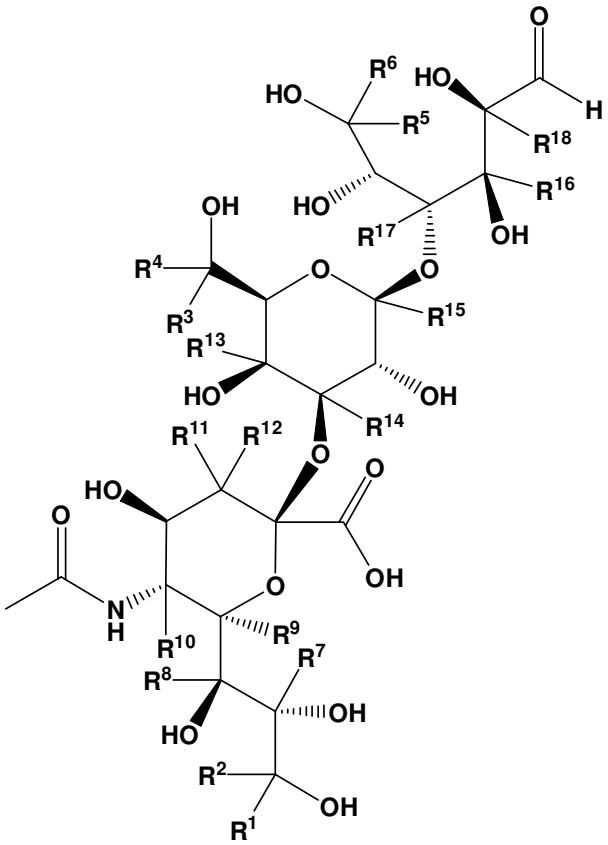
an unsubstituted or substituted heterocycle, and an unsubstituted or substituted aryl.

[0008c] In another aspect, the present disclosure refers to a nutritional supplement comprising at least one oligosaccharide of Formula I, I(a) or II

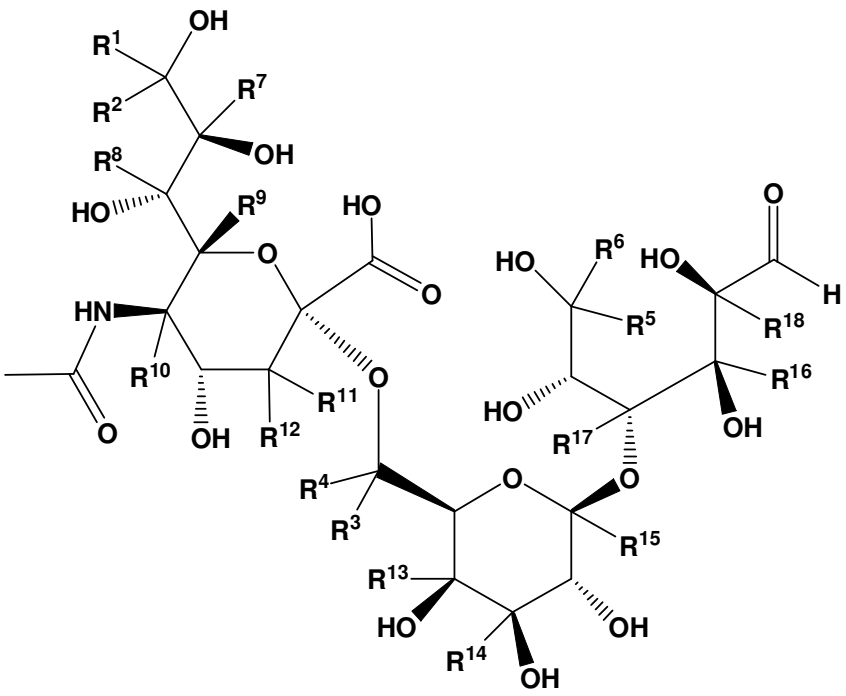
Formula I, I(a) and/or II:



Formula I



Formula I(a)



Formula II

or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein,

R^1–R^{18} are independently selected from H, D, a halo, an unsubstituted or substituted (C_1–C_6)alkyl, an unsubstituted or substituted (C_1–C_6)heteroalkyl, an unsubstituted or substituted (C_2–C_6)alkenyl, an unsubstituted or substituted (C_2–C_6)heteroalkenyl, an unsubstituted or substituted (C_3–C_6)alkynyl, an unsubstituted or substituted (C_3–C_6)heteroalkynyl, an unsubstituted or substituted (C_4–C_8)cycloalkyl, an unsubstituted or substituted heterocycle, an unsubstituted or substituted aryl, –ROR', –RN(R')$_2$, –RSSR', –SH, –RSOR', –RSO$_2$R', –RSO$_2$H, –RSO$_3$H, –RC(=S)–R', –ROH, –RC(=O)R', –RNO$_2$, –RSR', –RCN, –RNC, –RNNR', –RC(=O)OR', –ROC(=O)R', –RC(=O)H, –RC(=O)OH, –RC(=O)N(R')$_2$, –RN$_3$, –ROCN, –RNCO, –RONO$_2$, –RNO, –ROP(=O)(OH)$_2$, and –RB(OH)$_2$;

R is absent or a (C_1–C_5)alkyl; and

R' is independently selected from H, D, an unsubstituted or substituted (C_1–C_6) alkyl, an unsubstituted or substituted (C_1–C_6)heteroalkyl, an unsubstituted or substituted (C_2–C_6)alkenyl, an unsubstituted or substituted (C_2–C_6)heteroalkenyl, an unsubstituted or substituted (C_3–C_6)alkynyl, an unsubstituted or substituted (C_3–C_6)heteroalkynyl, an unsubstituted or substituted (C_4–C_8)cycloalkyl,

an unsubstituted or substituted heterocycle, and an unsubstituted or substituted aryl.

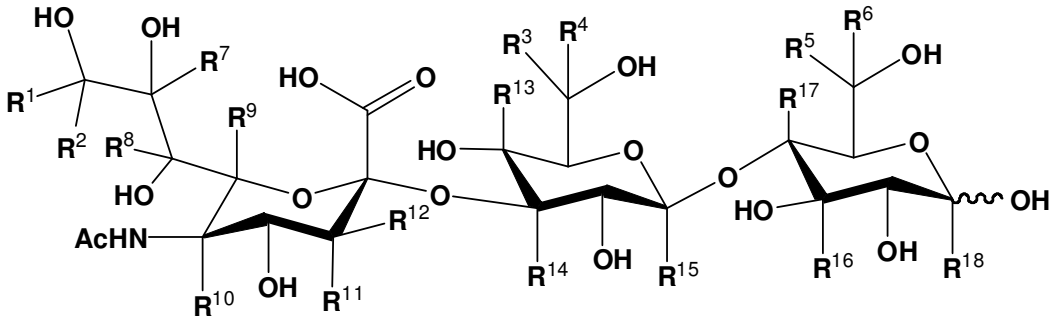
[0008d] In another aspect, the present disclosure refers to a composition consisting of one or both of 3'SL and/or 6'SL and a pharmaceutically acceptable carrier.

DESCRIPTION OF DRAWINGS

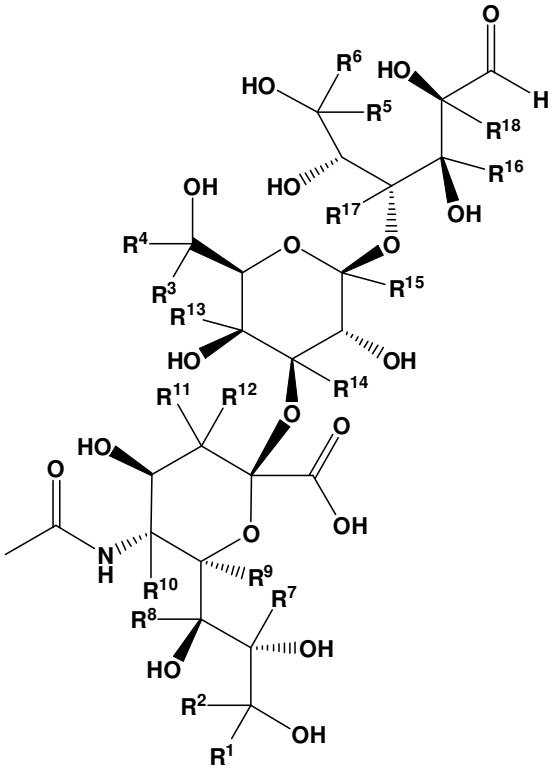
[0009] **Figure 1A–C** demonstrates that 3'–sialyllactose (3'SL) reduces IL–6 and IL–1β mRNA expression in LPS–activated macrophages. RAW246.7 cells were exposed to LPS either alone or in combination with either pooled human milk oligosaccharides (HMOs), or 3'–sialyllactose (3'SL) or 2'–fucosyllactose (2'FL). After 6 hours, IL–6 **(A)** and IL–1β **(B)** mRNA levels were measured by RT–PCR and are plotted as mean ± standard deviation (n=8) relative the respective

WHAT IS CLAIMED IS:

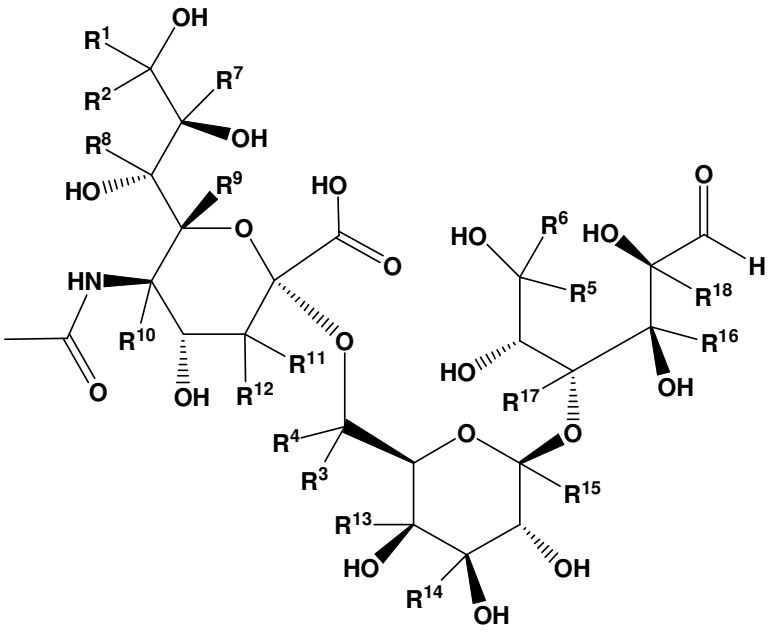
1. Use of at least one oligosaccharide, or a pharmaceutical composition comprising the at least one oligosaccharide, in the manufacture of a medicament for treating a subject having or suspected of having an inflammatory disease or an autoimmune disorder, wherein the oligosaccharide comprises a structure of Formula I, I(a) and/or II:



Formula I



Formula I(a)



Formula II

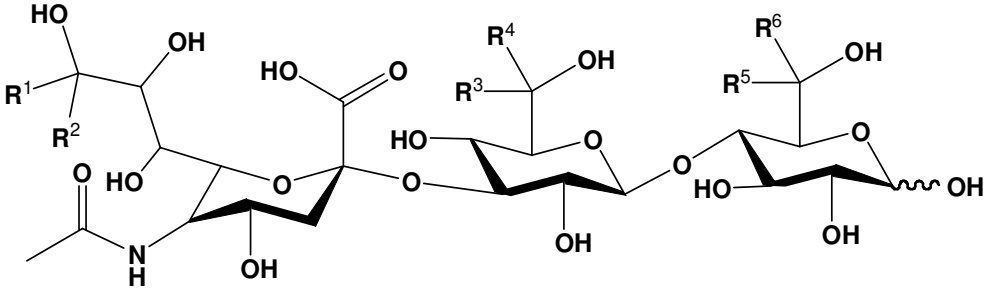
or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein,

R^1–R^{18} are independently selected from H, D, a halo, an unsubstituted or substituted (C_1–C_6)alkyl, an unsubstituted or substituted (C_1–C_6)heteroalkyl, an unsubstituted or substituted (C_2–C_6)alkenyl, an unsubstituted or substituted (C_2–C_6)heteroalkenyl, an unsubstituted or substituted (C_3–C_6)alkynyl, an unsubstituted or substituted (C_3–C_6)heteroalkynyl, an unsubstituted or substituted (C_4–C_8)cycloalkyl, an unsubstituted or substituted heterocycle, an unsubstituted or substituted aryl, –ROR', –RN(R')$_2$, –RSSR', –SH, –RSOR', –RSO$_2$R', –RSO$_2$H, –RSO$_3$H, –RC(=S)–R', –ROH, –RC(=O)R', –RNO$_2$, –RSR', –RCN, –RNC, –RNNR', –RC(=O)OR', –ROC(=O)R', –RC(=O)H, –RC(=O)OH, –RC(=O)N(R')$_2$, –RN$_3$, –ROCN, –RNCO, –RONO$_2$, –RNO, –ROP(=O)(OH)$_2$, and –RB(OH)$_2$;

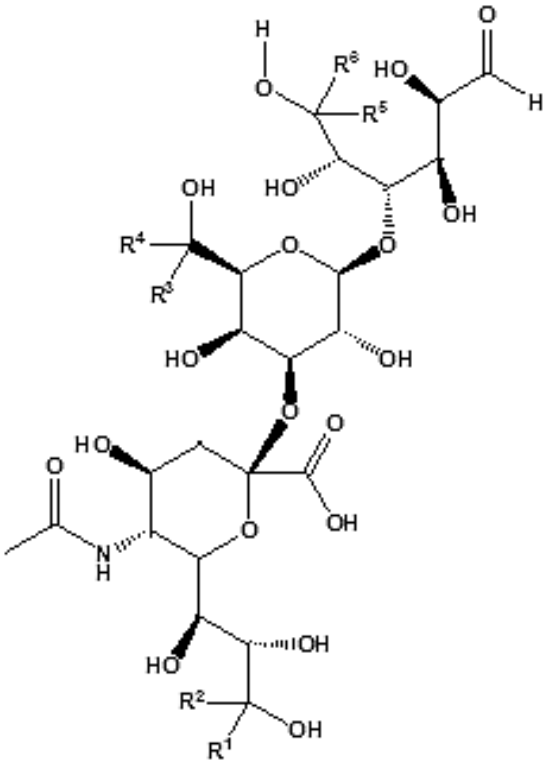
R is absent or a (C_1–C_5)alkyl; and

R' is independently selected from H, D, an unsubstituted or substituted (C_1–C_6) alkyl, an unsubstituted or substituted (C_1–C_6)heteroalkyl, an unsubstituted or substituted (C_2–C_6)alkenyl, an unsubstituted or substituted (C_2–C_6)heteroalkenyl, an unsubstituted or substituted (C_3–C_6)alkynyl, an unsubstituted or substituted (C_3–C_6)heteroalkynyl, an unsubstituted or substituted (C_4–C_8)cycloalkyl, an unsubstituted or substituted heterocycle, and an unsubstituted or substituted aryl.

2. The use of claim 1, wherein the oligosaccharide comprises a structure of Formula I(b) or I(c):



Formula I(b)



Formula I(c)

or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein,

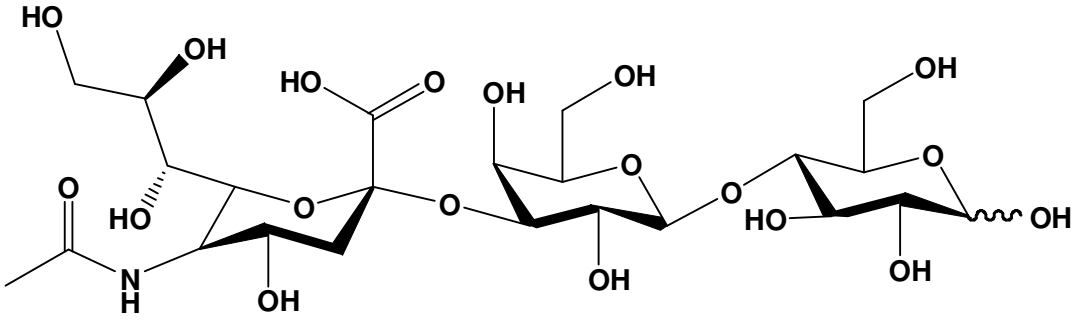
R^1–R^6 are independently selected from H, D, a halo, an unsubstituted or substituted (C_1–C_6)alkyl, an unsubstituted or substituted (C_1–C_6)heteroalkyl, an unsubstituted or substituted (C_2–C_6)alkenyl, an unsubstituted or substituted (C_2–C_6)heteroalkenyl, an unsubstituted or substituted (C_3–C_6)alkynyl, an unsubstituted or substituted (C_3–C_6)heteroalkynyl, an unsubstituted or substituted

(C_4–C_8)cycloalkyl, an unsubstituted or substituted heterocycle, an unsubstituted or substituted aryl, –ROR', –RN(R')$_2$, –RSSR', –SH, –RSOR', –RSO$_2$R', –RSO$_3$H, –RC(=S)–R', –ROH, –RC(=O)R', –RNO$_2$, –RSR', –RCN, –RNC, –RNNR', –RC(=O)OR', –ROC(=O)R', –RC(=O)H, –RC(=O)OH, –RC(=O)N(R')$_2$, –RN$_3$, –ROCN, –RNCO, –RONO$_2$, –RNO, –ROP(=O)(OH)$_2$, and –RB(OH)$_2$;

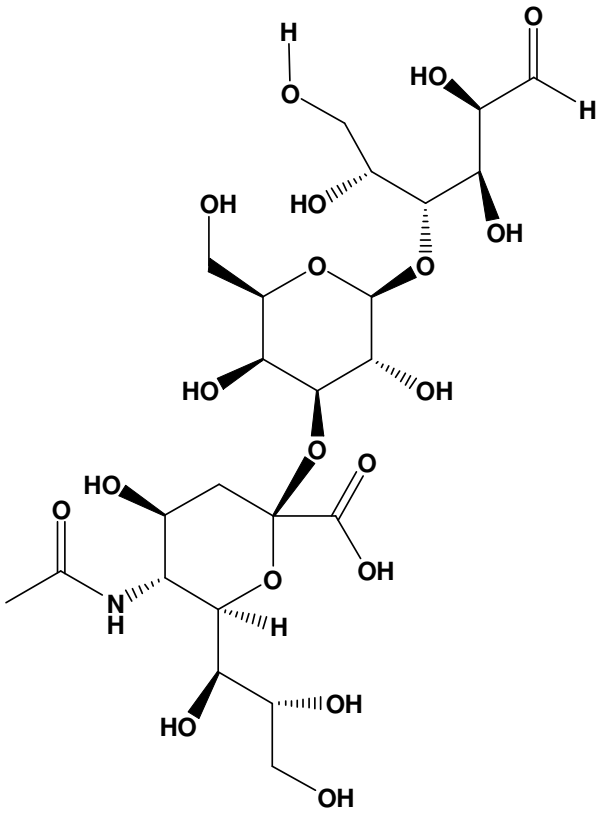
R is absent or a (C_1–C_5)alkyl; and

R' is independently selected from H, D, an unsubstituted or substituted (C_1–C_6) alkyl, an unsubstituted or substituted (C_1–C_6)heteroalkyl, an unsubstituted or substituted (C_2–C_6)alkenyl, an unsubstituted or substituted (C_2–C_6)heteroalkenyl, an unsubstituted or substituted (C_3–C_6)alkynyl, an unsubstituted or substituted (C_3–C_6)heteroalkynyl, an unsubstituted or substituted (C_4–C_8)cycloalkyl, an unsubstituted or substituted heterocycle, and an unsubstituted or substituted aryl.

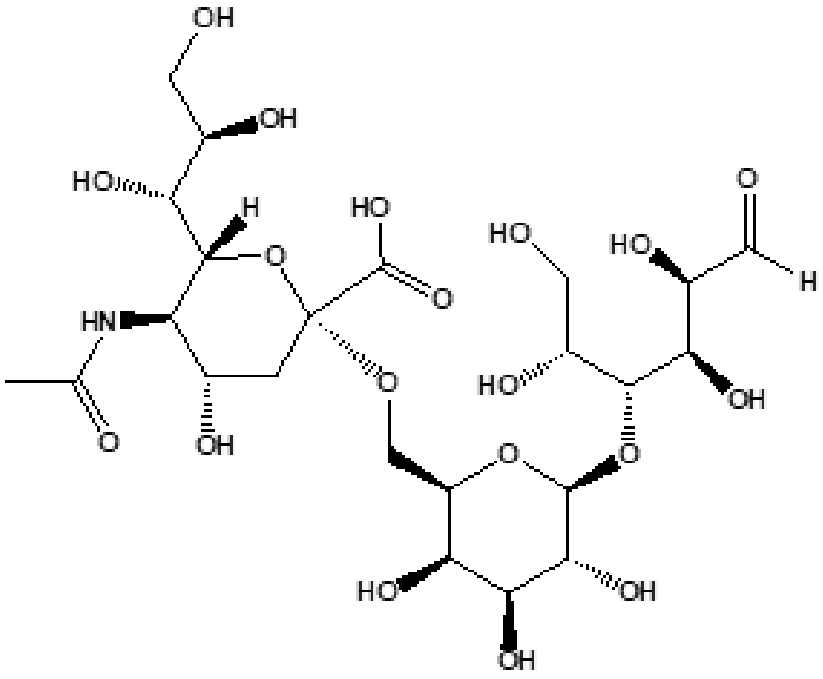
3. The use of claim 1 or claim 2, wherein the oligosaccharide comprises a structure of Formula I(d), I(e) and/or II(a):



Formula I(d)



Formula I(e)



Formula II(a)

or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

4. The use of any one of the preceding claims, wherein the oligosaccharide or the pharmaceutical composition comprising the oligosaccharide is to be orally administered to the subject.

5. The use of claim 4, wherein the oligosaccharide is to be orally administered to the subject as part of a nutritional composition.

6. The use of claim 4, wherein the pharmaceutical composition comprising the oligosaccharide is formulated as a tablet or a capsule.

7. The use of claim 5, wherein the nutritional composition comprises or consists of at least one oligosaccharide of Formula I, I(a), I(b), I(c), I(d), I(e), II and/or II(a).

8. The use of claim 5, wherein the nutritional composition comprises or consists of at least one oligosaccharide of Formula I, I(a), I(b), I(c), I(d), I(e), II and/or II(a) at 145 mg/L or greater.

9. The use of claim 5, wherein the nutritional composition comprises at least 9% of the oligosaccharide of at least one oligosaccharide of Formula I, I(a), I(b), I(c), I(d), I(e), II and/or II(a) of the total oligosaccharides in the nutritional composition.

10. The use of claim 1, wherein the autoimmune disorder is selected from the group consisting of autoimmune myocarditis, Dressler's syndrome, postpericardiotomy syndrome, subacute bacterial endocarditis, anti-glomerular basement membrane nephritis, interstitial cystitis, lupus nephritis, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, antisynthetase syndrome, alopecia areata, autoimmune angioedema, autoimmune progesterone dermatitis, autoimmune urticaria, bullous pemphigoid, cicatricial pemphigoid, dermatitis herpetiformis, discoid lupus erythematosus, epidermolysis bullosa acquisita,

erythema nodosum, gestational pemphigoid, hidradenitis suppurativa, lichen planus, lichen sclerosus, linear IgA disease, morphea, pemphigus vulgaris, pityriasis lichenoides et varioliformis acuta, Mucha-Habermann disease, psoriasis, Systemic scleroderma, vitiligo, Addison's disease, autoimmune polyendocrine syndrome type 1, autoimmune polyendocrine syndrome type 2, autoimmune polyendocrine syndrome type 3, autoimmune pancreatitis, diabetes mellitus type 1, autoimmune thyroiditis, Ord's thyroiditis, Graves' disease, autoimmune Oophoritis, endometriosis, Sjögren syndrome, autoimmune enteropathy, antiphospholipid syndrome, aplastic anemia, autoimmune hemolytic anemia, autoimmune lymphoproliferative syndrome, autoimmune neutropenia, autoimmune thrombocytopenic purpura, cold agglutinin disease, essential mixed cryoglobulinemia, Evans syndrome, pernicious anemia, pure red cell aplasia, thrombocytopenia, adiposis dolorosa, adult-onset Still's disease, ankylosing spondylitis, CREST syndrome, drug-induced lupus, enthesitis-related arthritis, eosinophilic fasciitis, Felty syndrome, IgG4-related disease, juvenile arthritis, chronic Lyme disease, mixed connective tissue disease, palindromic rheumatism, Parry Romberg syndrome, Parsonage-Turner syndrome, psoriatic arthritis, reactive arthritis, relapsing polychondritis, retroperitoneal fibrosis, rhematic fever, rheumatoid arthritis, sarcoidosis, Schnitzler syndrome, systemic lupus erythematosus, undifferentiated connective tissue disease, dermatomyositis, fibromyalgia, inclusion body myositis, myositis, myasthenia gravis, neuromyotonia, paraneoplastic cerebellar degeneration, polymyositis, acute disseminated encephalomyelitis, acute motor axonal neuropathy, anti-N-methyl-D-aspartate receptor encephalitis, Balo concentric sclerosis, Bickerstaff's encephalitis, chronic inflammatory demyelinating polyneuropathy, Guillain-Barrè syndrome, Hashimoto's encephalopathy, idiopathic inflammatory demyelinating diseases, Lambert-Eaton myasthenic syndrome, multiple sclerosis, Oshtoran syndrome, pediatric autoimmune neuropsychiatric disorder associated with *Streptococcus*, progressive inflammatory neuropathy, restless leg syndrome, stiff person syndrome, sydenham chorea, transverse myelitis, autoimmune retinopathy, autoimmune uveitis, Cogan syndrome, Graves ophthalmopathy, intermediate uveitis, ligneous

conjunctivitis, Mooren's ulcer, neuromyelitis optica, opsoclonus myoclonus syndrome, autoimmune inner ear disease, Ménière's disease, Behçet's disease, eosinophilic granulomatosis with polyangiitis, IgA vasculitis, Kawasaki's disease, leukocytoclastic vasculitis, lupus vasculitis, rheumatoid vasculitis, microscopic polyangiitis, polyarteritis nodosa, polymyalgia rheumatica, urticarial vasculitis, vasculitis, and primary immune deficiency.

11. The use of claim 1, wherein the inflammatory disease is selected from the group consisting of ankylosing spondylitis, antiphospholipid antibody syndrome, gout, myositis, rheumatoid arthritis, scleroderma, systemic lupus erythematosus, vasculitis, Sjögren's syndrome, asthma, tuberculosis, chronic periodontitis, chronic sinusitis, chronic active hepatitis, Alzheimer's, Parkinson's disease, nephritis, fibromyalgia, atherosclerosis, osteoarthritis, psoriatic arthritis, eczema, gastritis, sinusitis, seborrheic dermatitis, and Wegener's granulomatosis.

12. The use of claim 1, wherein the inflammatory disease is caused by or associated with macrophage driven chronic inflammation.

13. The use of claim 12, wherein the inflammatory disease is selected from the group consisting of atherosclerosis, chronic obstructive pulmonary disease, insulin resistance, type-2 diabetes, obesity, and systemic juvenile idiopathic arthritis.

14. The use of claim 1, wherein the autoimmune disorder or inflammatory disease is rheumatoid arthritis.

15. The use of claim 1, wherein the at least one oligosaccharide or the pharmaceutical composition comprising the at least one oligosaccharide is to be administered with another therapeutic agent.

16. The use of claim 15, wherein the therapeutic agent is a nonsteroidal anti-inflammatory drug, a glucocorticoid, a biologic response modifier and an opioid.

17. The use of claim 16, wherein the nonsteroidal anti-inflammatory drug is selected from the group consisting of Aminophenazone, Ampyrone, Azapropazone, Clofezone, Difenamizole, Famprofazone, Feprazone, Kebuzone, Metamizole, Mofebutazone, Morazone, Nifenazone, Oxyphenbutazone, Phenazone, Phenylbutazone, Propyphenazone, Sulfinpyrazone, Suxibuzone, Aspirin, Aloxiprin, Benorylate, Carbasalate, calcium Diflunisal, Dipyrocetyl, Ethenzamide, Guacetisal, Magnesium salicylate, Methyl salicylate, Salsalate, Salicin, Salicylamide, Salicylic acid (salicylate), Sodium salicylate, Aceclofenac, Acemetacin, Alclofenac, Amfenac, Bendazac, Bromfenac, Bumadizone, Bufexamac, Diclofenac, Difenpiramide, Etodolac, Felbinac, Fenclozic acid, Fentiazac, Indomethacin, Indomethacin farnesil, Isoxepac, Ketorolac, Lonazolac, Oxametacin, Prodolic acid, Proglumetacin, Sulindac, Tiopinac, Tolmetin, Zomepirac, Ampiroxicam, Droxicam, Isoxicam, Lornoxicam, Meloxicam, Piroxicam, Tenoxicam, Alminoprofen, Benoxaprofen, Carprofen, Dexibuprofen, Dexketoprofen, Fenbufen, Fenoprofen, Flunoxaprofen, Flurbiprofen, Ibuprofen, Ibuproxam, Indoprofen, Ketoprofen, Loxoprofen, Miroprofen, Naproxen, Oxaprozin, Pirprofen, Suprofen, Tarenflurbil, Tepoxalin, Tiaprofenic acid, Vedaprofen, Naproxcinod, Azapropazone, Clonixin, Etofenamate, Flufenamic acid, Flunixin, Meclofenamic acid, Mefenamic acid, Morniflumate, Niflumic acid, Tolfenamic acid, Flutiazin, Apricoxib, Celecoxib, Cimicoxib, Deracoxib, Etoricoxib, Firocoxib, Lumiracoxib, Mavacoxib, Parecoxib, Robenacoxib, Rofecoxib, Valdecoxib, Aminopropionitrile, Benzydamine, Chondroitin sulfate, Diacerein, Fluproquazone, Glucosamine, Glycosaminoglycan, Hyperforin, Nabumetone, Nimesulide, Oxaceprol, Proquazone, Superoxide dismutase/Orgotein, and Tenidap.

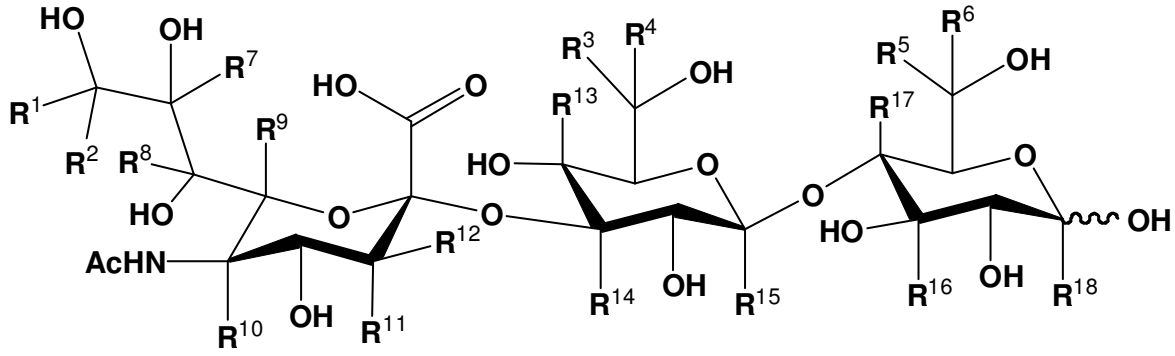
18. The use of claim 16, wherein the glucocorticoid is selected from betamethasone or prednisone.

19. The use of claim 16, wherein the biological response modifier is selected from the group consisting of hydroxychloroquine, leflunomide, methotrexate, tofacitinib, abatacept, adalimumab, adalimumab-atto, anakinra, etanercept, etanercept-szzs, rituximab,

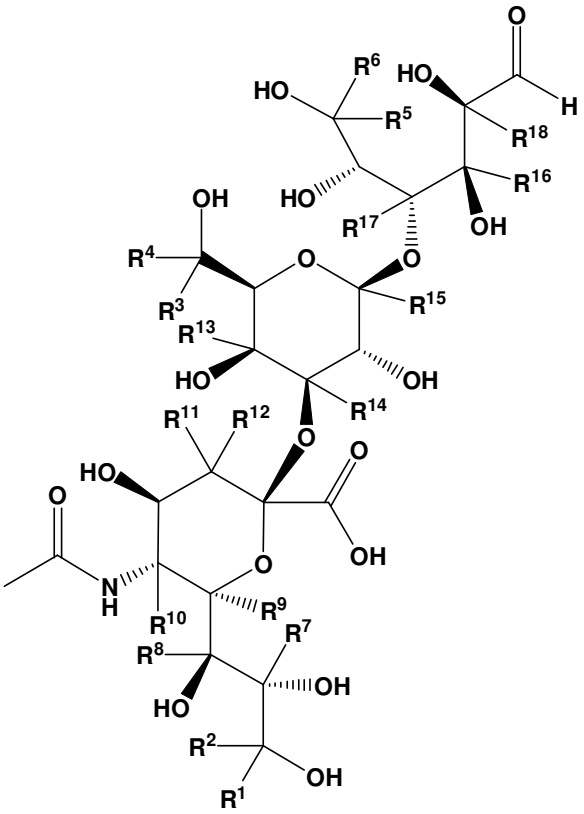
infliximab-dyyb, golimumab, certolizumab pegol, tocilizumab, and sarilumab.

20. The use of claim 16, wherein the opioid is selected from the group consisting of tramadol, oxycontin, oxycodone, fentanyl, morphine, codeine, dihydrocodeine, and actiq.

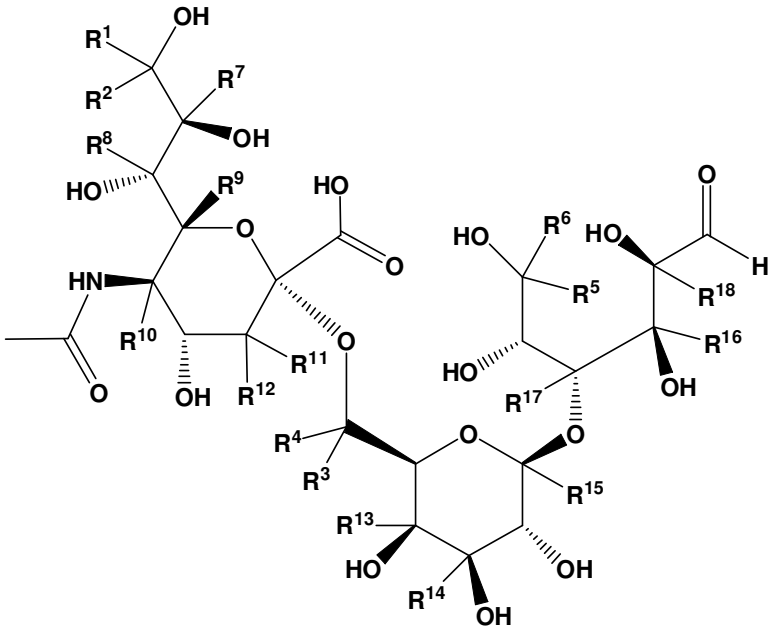
21. Use of at least one oligosaccharide, or a pharmaceutical composition comprising the at least one oligosaccharide, in the manufacture of a medicament for attenuating macrophage inflammation and/or suppressing the secretion of pro-inflammatory cytokines in a subject in need thereof, wherein the at least one oligosaccharide comprises a structure of Formula I, I(a) and/or II:



Formula I



Formula I(a)



Formula II

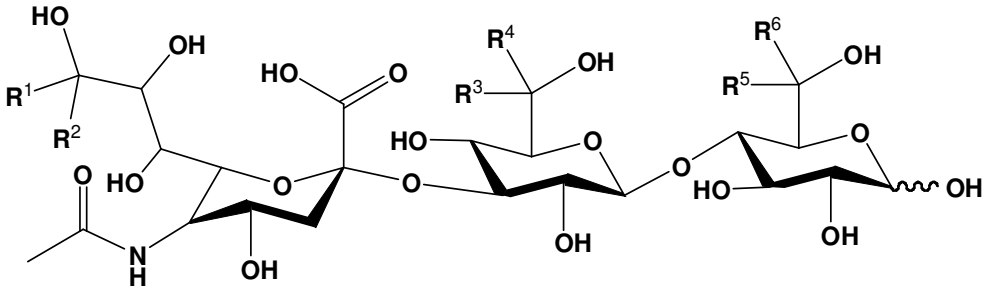
or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein,

R^1–R^{18} are independently selected from H, D, a halo, an unsubstituted or substituted (C_1–C_6)alkyl, an unsubstituted or substituted (C_1–C_6)heteroalkyl, an unsubstituted or substituted (C_2–C_6)alkenyl, an unsubstituted or substituted (C_2–C_6)heteroalkenyl, an unsubstituted or substituted (C_3–C_6)alkynyl, an unsubstituted or substituted (C_3–C_6)heteroalkynyl, an unsubstituted or substituted (C_4–C_8)cycloalkyl, an unsubstituted or substituted heterocycle, an unsubstituted or substituted aryl, –ROR', –RN(R')$_2$, –RSSR', –SH, –RSOR', –RSO$_2$R', –RSO$_2$H, –RSO$_3$H, –RC(=S)–R', –ROH, –RC(=O)R', –RNO$_2$, –RSR', –RCN, –RNC, –RNNR', –RC(=O)OR', –ROC(=O)R', –RC(=O)H, –RC(=O)OH, –RC(=O)N(R')$_2$, –RN$_3$, –ROCN, –RNCO, –RONO$_2$, –RNO, –ROP(=O)(OH)$_2$, and –RB(OH)$_2$;

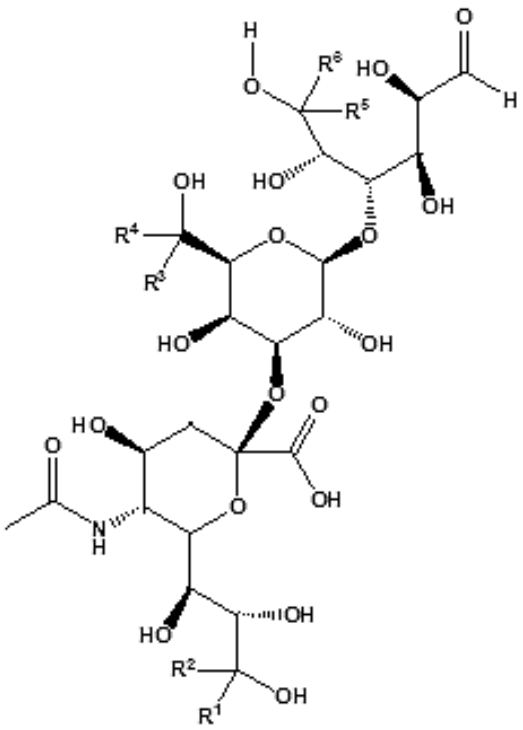
R is absent or a (C_1–C_5)alkyl; and

R' is independently selected from H, D, an unsubstituted or substituted (C_1–C_6) alkyl, an unsubstituted or substituted (C_1–C_6)heteroalkyl, an unsubstituted or substituted (C_2–C_6)alkenyl, an unsubstituted or substituted (C_2–C_6)heteroalkenyl, an unsubstituted or substituted (C_3–C_6)alkynyl, an unsubstituted or substituted (C_3–C_6)heteroalkynyl, an unsubstituted or substituted (C_4–C_8)cycloalkyl, an unsubstituted or substituted heterocycle, and an unsubstituted or substituted aryl.

22. The use of claim 21, wherein the at least one oligosaccharide comprises a structure of Formula I(b) or I(c):



Formula I(b)



Formula I(c)

or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein,

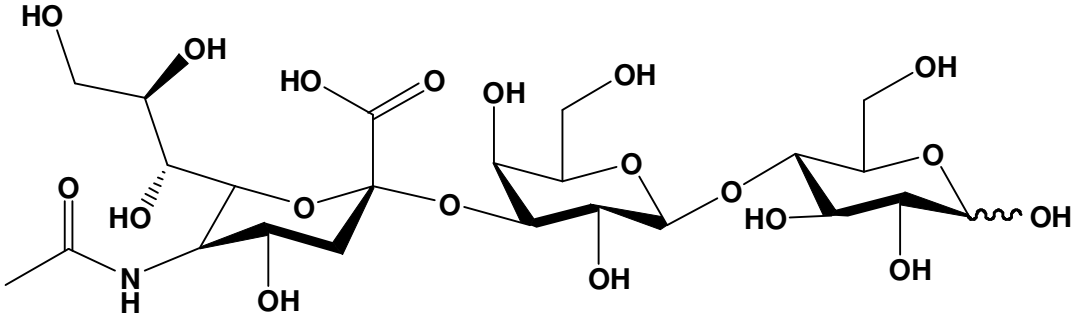
R^1–R^6 are independently selected from H, D, a halo, an unsubstituted or substituted (C_1–C_6)alkyl, an unsubstituted or substituted (C_1–C_6)heteroalkyl, an unsubstituted or substituted (C_2–C_6)alkenyl, an unsubstituted or substituted (C_2–C_6)heteroalkenyl, an unsubstituted or substituted (C_3–C_6)alkynyl, an unsubstituted or substituted (C_3–C_6)heteroalkynyl, an unsubstituted or substituted (C_4–C_8)cycloalkyl, an unsubstituted or substituted heterocycle, an unsubstituted or substituted aryl, –ROR', –RN(R')$_2$, –RSSR', –SH, –RSOR', –RSO$_2$R', –RSO$_2$H, –RSO$_3$H, –RC(=S)–R', –ROH, –RC(=O)R', –RNO$_2$, –RSR', –RCN, –RNC, –RNNR', –RC(=O)OR', –ROC(=O)R', –RC(=O)H, –RC(=O)OH, –RC(=O)N(R')$_2$, –RN$_3$, –ROCN, –RNCO, –RONO$_2$, –RNO, –ROP(=O)(OH)$_2$, and –RB(OH)$_2$;

R is absent or a (C_1–C_5)alkyl; and

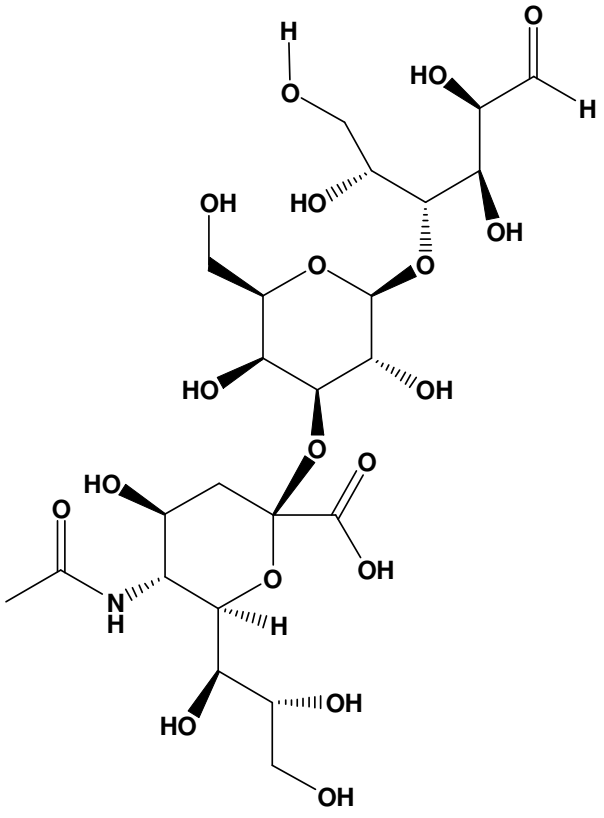
R' is independently selected from H, D, an unsubstituted or substituted (C_1–C_6) alkyl, an unsubstituted or substituted (C_1–C_6)heteroalkyl, an unsubstituted or substituted (C_2–C_6)alkenyl, an unsubstituted or substituted (C_2–C_6)heteroalkenyl, an unsubstituted or substituted (C_3–C_6)alkynyl, an unsubstituted or substituted (C_3–

C_6)heteroalkynyl, an unsubstituted or substituted (C_4-C_8)cycloalkyl, an unsubstituted or substituted heterocycle, and an unsubstituted or substituted aryl.

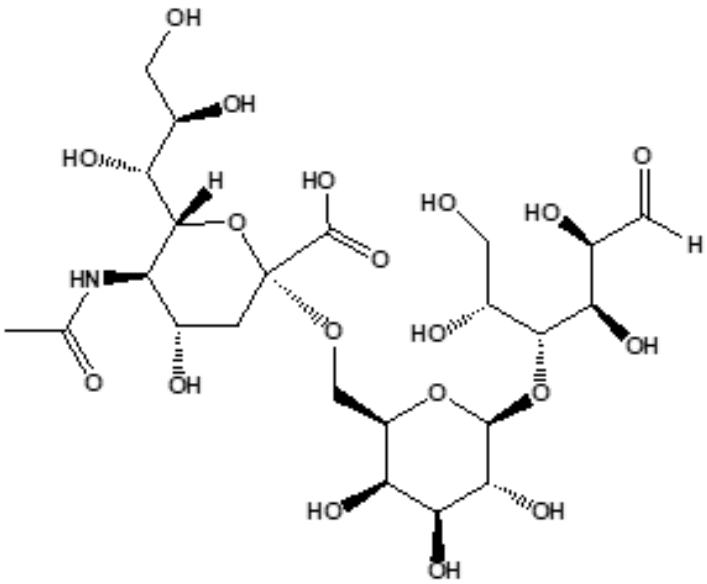
23. The use of claim 21 or claim 22, wherein the at least one oligosaccharide comprises a structure of Formula I(d), I(e), and/or II(a):



Formula I(d)



Formula I(e)



Formula II(a)

or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

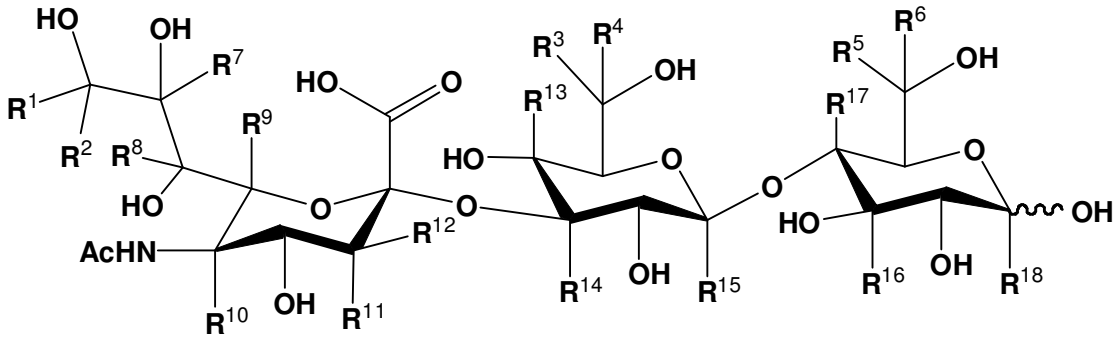
24. The use of claim 21, wherein the pro-inflammatory cytokines comprise interleukin (IL)-1β and IL-6.

25. The use of claim 1 or 21, wherein the subject is a human subject that is 5 years of age or older.

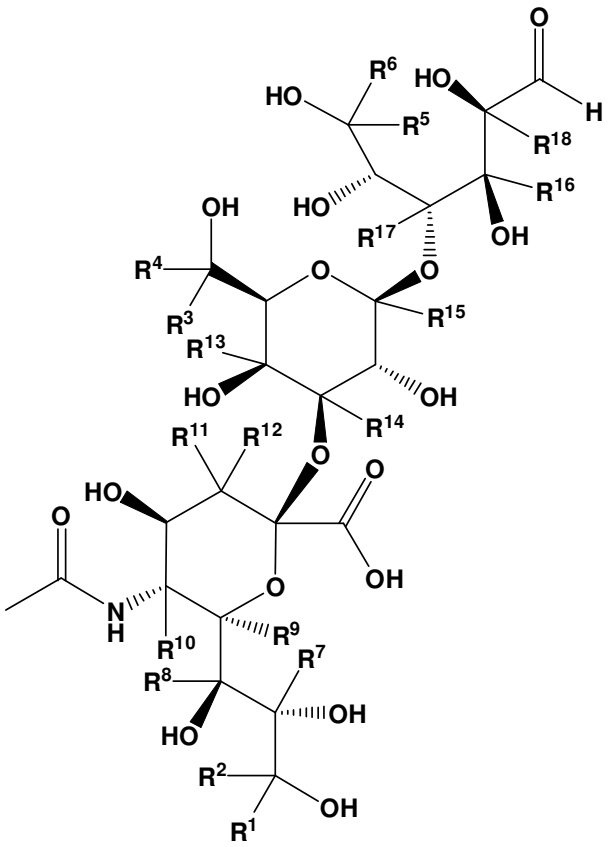
26. The use of claim 25, wherein the subject is a human subject that 18 years of age or older.

27. A nutritional supplement comprising at least one oligosaccharide of Formula I, I(a) or II

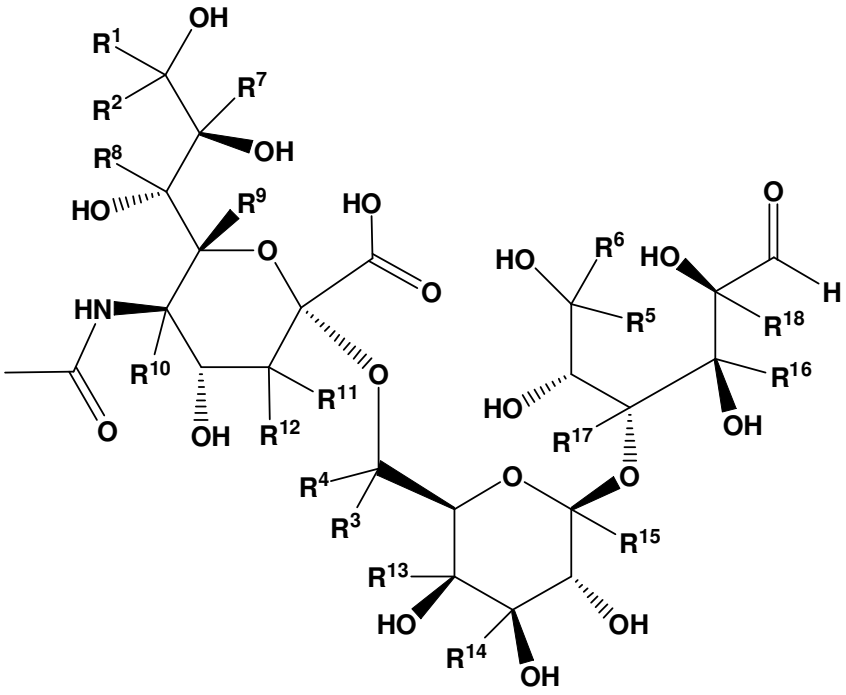
Formula I, I(a) and/or II:



Formula I



Formula I(a)



Formula II

or a pharmaceutically acceptable salt, solvate, or prodrug thereof, wherein,

R^1–R^{18} are independently selected from H, D, a halo, an unsubstituted or substituted (C_1–C_6)alkyl, an unsubstituted or substituted (C_1–C_6)heteroalkyl, an unsubstituted or substituted (C_2–C_6)alkenyl, an unsubstituted or substituted (C_2–C_6)heteroalkenyl, an unsubstituted or substituted (C_3–C_6)alkynyl, an unsubstituted or substituted (C_3–C_6)heteroalkynyl, an unsubstituted or substituted (C_4–C_8)cycloalkyl, an unsubstituted or substituted heterocycle, an unsubstituted or substituted aryl, –ROR', –$RN(R')_2$, –RSSR', –SH, –RSOR', –RSO_2R', –RSO_2H, –RSO_3H, –RC(=S)–R', –ROH, –RC(=O)R', –RNO_2, –RSR', –RCN, –RNC, –RNNR', –RC(=O)OR', –ROC(=O)R', –RC(=O)H, –RC(=O)OH, –$RC(=O)N(R')_2$, –RN_3, –ROCN, –RNCO, –$RONO_2$, –RNO, –$ROP(=O)(OH)_2$, and –$RB(OH)_2$;

R is absent or a (C_1–C_5)alkyl; and

R' is independently selected from H, D, an unsubstituted or substituted (C_1–C_6) alkyl, an unsubstituted or substituted (C_1–C_6)heteroalkyl, an unsubstituted or substituted (C_2–C_6)alkenyl, an unsubstituted or substituted (C_2–C_6)heteroalkenyl, an unsubstituted or substituted (C_3–C_6)alkynyl, an unsubstituted or substituted (C_3–C_6)heteroalkynyl, an unsubstituted or substituted (C_4–C_8)cycloalkyl, an unsubstituted or substituted heterocycle, and an unsubstituted or substituted aryl.

28. The nutritional supplement of claim 27, wherein the nutritional supplement consists of the at least one oligosaccharide of Formula I, I(a), I(b), I(c), I(d), I(e), II and/or II(a) and other non-oligosaccharide components.

29. The nutritional supplement of claim 27, wherein the nutritional supplement comprises or consists of at least one oligosaccharide of Formula I, I(a), I(d), I(e), II and/or II(a) at 145 mg/L or greater.

30. The nutritional supplement of claim 27, wherein the nutritional supplement wherein at least 9% of the total oligosaccharides in the nutritional supplement comprise at least one oligosaccharide of Formula I, I(a), I(d), I(e), II and/or II(a).

31. A composition consisting of one or both of 3'SL and/or 6'SL and a pharmaceutically acceptable carrier.