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(54) Title: USE OF LIPID CONJUGATES IN THE TREATMENT OF INFECTION

(57) Abstract: This invention provides for the use of a lipid or phospholipid moiety bound to a physiologically acceptable monomer, dimer, oligomer, or polymer in suppressing, inhibiting, preventing, or treating infection with influenza virus, oxvirus, or a combination thereof,in a subject.

USE OF LIPID CONJUGATES IN THE TREATMENT OF INFECTION

FIELD OF THE INVENTION

[001] This invention provides for the use of a lipid or phospholipid moiety bound to a physiologically acceptable monomer, dimer, oligomer, or polymer in suppressing, inhibiting, preventing, or treating influenza, poxvirus, or a combination thereof in a subject.

BACKGROUND OF THE INVENTION

[002] Lipid-conjugates are thought to inhibit the enzyme phospholipase A2 (PLA2, EC 3.1.1.4). Phospholipase A2 catalyzes the breakdown of phospholipids at the sn-2 position to produce a fatty acid and a lysophospholipid. The activity of this enzyme has been correlated with various cell functions, particularly with the production of lipid mediators such as eicosanoid production (prostaglandins, thromboxanes and leukotrienes), platelet activating factor and lysophospholipids. Lipid-conjugates may offer a wider scope of protection of cells and organisms from injurious agents and pathogenic processes, including the prevention and treatment of microbial infections.

[003] Microbial infections (e.g., infections by viral or bacterial species) account for significant morbidity and mortality throughout the world. Although significant resources have been dedicated to identifying compounds having antimicrobial properties, microbial infections continue to present a significant human health risk.

[004] There are relatively few effective pharmaceutical compositions intended or adapted for antiviral, antifungal, or antiparasitic therapy. A major obstacle in the development of antiviral agents is the difficulty in distinguishing viral replicative mechanisms from host replicative processes. An additional limitation of existing antiviral drugs is that they have a narrow antiviral spectrum and are often ineffective against the latent virus.

[005] There are a much larger number of existing antibacterial agents, which has led to a significant decrease in morbidity and mortality from infectious diseases in this century. This important public health contribution has been largely due to the widespread use of

antibiotics that target specific nutrient, cell wall, DNA, RNA and protein biosynthetic pathways that are particular to pathogenic bacteria. However, in recent years the capacity to manage infectious diseases has been threatened by the emergence of bacterial strains that are no longer susceptible to currently available antimicrobial agents. The widespread use of available antibacterial agents has led to the development of increasing numbers of antibiotic resistant bacteria.

[006] In fact, the usefulness of most existing antimicrobial treatments are limited by the development of multidrug resistance and the emergence of long-term toxicities. Other challenges include creating a drug that is broadly applicable in combating many different types of microbial infections, which is especially important in the treatment of immunocompromised individuals.

SUMMARY OF THE INVENTION

[007]In one embodiment, the invention provides a method of suppressing, inhibiting, preventing, or treating infection with an influenza virus in a subject, comprising the step of contacting the cell with a compound comprising a lipid or phospholipid moiety bound to a physiologically acceptable monomer, dimer, oligomer, or polymer, and/or a pharmaceutically acceptable salt or a pharmaceutical product thereof.

[008] In another embodiment, the invention provides a method of suppressing, inhibiting, preventing, or treating a poxvirus infection in a subject, comprising the step of administering an effective amount of a lipid or phospholipid moiety bound to a physiologically acceptable monomer, dimer, oligomer, or polymer, and/or a pharmaceutically acceptable salt or a pharmaceutical product thereof to an infected subject.

DETAILED DESCRIPTION OF THE INVENTION

Methods of Treating Disease Based on Phospholipid Conjugates

[009] In one embodiment, the invention provides a method of suppressing, inhibiting, preventing, or treating a pathogenic effect on a cell, comprising the step of contacting the

cell with a compound comprising a lipid or phospholipid moiety bound to a physiologically acceptable monomer, dimer, oligomer, or polymer, and/or a pharmaceutically acceptable salt or a pharmaceutical product thereof.

[0010] In one embodiment, the compounds for use in the present invention (for e.g., a lipid or phospholipid moiety bound to a physiologically acceptable monomer, dimer, oligomer, or polymer) are referred to herein as "Lipid-conjugates".

[0011] In one embodiment, "suppressing, inhibiting, preventing, or treating" refers to delaying the onset of symptoms, reducing the severity of symptoms, reducing the severity of an acute episode, reducing the number of symptoms, reducing the incidence of disease-related symptoms, reducing the latency of symptoms, preventing the development of a latent infection, ameliorating symptoms, reducing secondary symptoms, reducing secondary infections, prolonging patient survival, preventing relapse to a disease, decreasing the number or frequency of relapse episodes, increasing latency between symptomatic episodes, increasing time to sustained progression, expediting remission, inducing remission, augmenting remission, speeding recovery, or increasing efficacy of or decreasing resistance to alternative therapeutics.

[0012] In one embodiment, symptoms are primary, while in another embodiment, symptoms are secondary. In one embodiment, "primary" refers to a symptom that is a direct result of infection with a pathogen, while in one embodiment, "secondary" refers to a symptom that is derived from or consequent to a primary cause. In another embodiment, "symptoms" may be any manifestation of a disease or pathological condition, comprising inflammation, swelling, fever, pain, bleeding, itching, runny nose, coughing, headache, migraine, difficulty breathing, weakness, fatigue, drowsiness, weight loss, nausea, vomiting, constipation, diarrhea, numbness, dizziness, blurry vision, muscle twitches, convulsions, etc., or a combination thereof.

[0013] In one embodiment, "treating" refers to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or lessen the targeted pathologic condition or disorder as described hereinabove. Thus, in one embodiment,

treating may include suppressing, inhibiting, preventing, treating, or a combination thereof.

[0014] In one embodiment, a pathogenic effect is apoptosis, necrosis, membrane blebbing/protrusion, cell death, permeabilized cell membrane, cell enlargement, dilated organelles, ribosome dissociation from endoplasmic reticulum, nuclear disintegration, chromatin condensation, pyknotic or fragmented nuclei, leakage of cellular contents, tissue inflammation, expression of apoptosis-specific proteins, cell shrinkage, formation of apoptotic bodies, expression of pathogen antigens, granularity, ragged edges, filmy appearance, cell rounding or a combination thereof. In another embodiment, a pathogenic effect is caused by infection with any of the pathogens described hereinbelow. In one embodiment, a pathogenic effect is a cytopathic effect.

[0015] Thus, in one embodiment of the present invention, the compounds for use in the present invention are directed towards the resolution of symptoms of a disease or disorder that result from a pathogenic infection as described hereinabove. In another embodiment, the compounds affect the pathogenesis underlying the pathogenic effect described hereinabove.

[0016] In one embodiment, a pathogenic effect on a cell could be a cell of any tissue, in one embodiment, a vertebrate cell, in another embodiment, a mammalian cell, and in another embodiment, a human cell. In one embodiment, a pathogen may infect a plurality of cell types, tissues or organs. In another embodiment, pathogens have preference for infecting specific cell types, tissues, or organs. It is to be understood that agents of the present invention may be efficacious in treating any cell type in which the pathogen may exert an effect. In one embodiment, a compound for use in the present invention may localize to or act on a specific cell type. In one embodiment, a compound for use in the present invention may be cytoprotective. In one embodiment a compound for use in the present invention may be inserted or partially inserted into a cell membrane. In another embodiment a compound for use in the present invention may be effective in treating a plurality of cell types.

[0017] In another embodiment, the cell exhibiting a pathogenic effect described hereinabove is present in a subject with a pathogenic infection.

[0018] In one embodiment, the invention provides a method of treating a subject suffering from a pathogenic effect, including, *inter alia*, the step of administering to a subject an effective amount of a lipid or phospholipid moiety bonded to a physiologically acceptable monomer, dimer, oligomer, or polymer, thereby treating the subject suffering from a pathogenic effect.

[0019] In another embodiment, the invention provides a method of suppressing, inhibiting, preventing, or treating an infection in a subject comprising the step of administering to said subject an effective amount of a lipid or phospholipid moiety bound to a physiologically acceptable monomer, dimer, oligomer, or polymer, and/or a pharmaceutically acceptable salt or a pharmaceutical product thereof.

[0020] In another embodiment, the invention provides a method of treating a subject suffering from a pathogenic infection, comprising the step of administering to a subject any one of the compounds for use in the present invention, or any combination thereof, in an amount effective to treat the subject suffering from a pathogenic infection.

[0021] In one embodiment, the pathogenic effect is due to an infection of the cell described hereinabove by a pathogen. In one embodiment, the pathogen is a virus and in another embodiment, the pathogen is a bacterium. In one embodiment, the pathogenic effect is the result of a viral infection and in another embodiment, the pathogenic effect is the result of a bacterial infection. In another embodiment, the pathogenic effect is the result of an infection with influenza, poxvirus, or a combination thereof, as is described hereinbelow.

[0022] In another embodiment, the pathogenic effect is due to a cytopathic effect of a pathogen in a cell. In another embodiment, the pathogenic effect in the cell is due to a cell-to-cell spread of a pathogen. In another embodiment, the pathogenic effect is the result of obstructive respiratory disease, cytokine overproduction, sepsis, hemolysis, oxidative injury, central nervous system insult, conjunctivitis, or a combination thereof,

as is described hereinbelow. In another embodiment, the pathogenic effect is the result of cancer. In another embodiment, the pathogenic effect is due to toxic products produced by the pathogen. In one embodiment, the toxic product may be worm eggs.

[0023] In one embodiment, the invention provides a method of treating a subject suffering from a viral infection, including, *inter alia*, the step of administering to a subject an effective amount of a lipid or phospholipid moiety bonded to a physiologically acceptable monomer, dimer, oligomer, or polymer, thereby treating the subject suffering from a viral infection.In another embodiment, said viral infection is caused by an enveloped virus.

[0024] In one embodiment, the invention provides a method of treating a subject suffering from a bacterial infection, including, *inter alia*, the step of administering to a subject an effective amount of a lipid or phospholipid moiety bonded to a physiologically acceptable monomer, dimer, oligomer, or polymer, thereby treating the subject suffering from a bacterial infection.

[0025] In one embodiment, the invention provides a use of a lipid or phospholipid moiety bonded to a physiologically acceptable monomer, dimer, oligomer, or polymer, in the preparation of a pharmaceutical composition for treating a subject afflicted with a viral infection.

[0026] In one embodiment, the invention provides a use of a lipid or phospholipid moiety bonded to a physiologically acceptable monomer, dimer, oligomer, or polymer, in the preparation of a pharmaceutical composition for treating a subject afflicted with a bacterial infection.

[0027] In another embodiment, the viral pathogenic effect, infection, or combination thereof is mediated by any one or more of the following pathogens: hepatitis B virus, hepatitis C virus, human immunodeficiency virus, human herpesviruses, herpes simplex virus-1, herpes simplex virus-2, human cytomegalovirus, Epstein-Barr virus, Varicella-Zoster virus, human herpesvirus-6, human herpesvirus-7, human influenza, measles virus, hantaan virus, pneumonia virus, rhinovirs, poliovirus, human respiratory syncytial

virus, retrovirus, human T-cell leukemia virus, rabies virus, mumps virus, malaria (Plasmodium falciparum), Bordetelia pertussis, Diptheria, Rickettsia prowazekii, Borrelia bergdorferi, Ebola virus. In one embodiment, the viral pathogenic effect, infection or combination thereof is mediated by Pichinde virus, while in another embodiment, it is mediated by Punta Toro virus.

[0028] In one embodiment, the pathogenic effect, infection or combination thereof is mediated by one or more of the following pathogens: Helminths, Bacillus anthracis (anthrax), Clostridium botulinum, Yersinia pestis, Variola major (smallpox) and other pox viruses, Francisella tularensis (tularemia), Arenaviruses, Lymphocytic choriomeningitis, Junin virus, Machupo virus, Guanarito virus, Lassa Fever, Bunyaviruses, Hantaviruses, Rift Valley Fever, Flaviruses, Dengue, Filoviruses, Ebola, Marburg, hemorrhagic fever viruses, Tickborne hemorrhagic fever viruses, Crimean-Congo Hemorrhagic fever virus, Tickborne encephalitis viruses, Yellow fever, Tuberculosis, Multi-drug resistant tuberculosis, Influenza, Rickettsias, Rabies virus, Severe acute respiratory syndrome-associated coronavirus (SARS), Burkholderia pseudomallei, Coxiella burnetii (Q fever), Brucella species (brucellosis), Burkholderia mallei (glanders), Ricin toxin (from Ricinus communis), Epsilon toxin of Clostridium perfringens, Staphylococcus enterotoxin B, Typhus fever (Rickettsia prowazekii), Diarrheagenic E.coli, Pathogenic Vibrios, Shigella species, Salmonella, Listeria monocytogenes, Campylobacter jejuni, Yersinia enterocolitica), Caliciviruses, Hepatitis A, Cryptosporidium parvum, Cyclospora cayatanensis, Giardia lamblia, Entamoeba histolytica, Toxoplasma, Microsporidia, West Nile Virus, LaCrosse, California encephalitis, Western Equine Encephalitis, Eastern Equine Encephalitis, Venezuelan Equine Encephalitis, Japanese Encephalitis Virus, and Kyasanur Forest Virus.

[0029] In another embodiment, the pathogenic effect, infection, or combination thereof is mediated by one or more of the following microorganisms: *Actinobacillus pleuropneumoniae, Aeropyrum pernix, Agrobacterium tumeficians, Anopheles gambiae, Aquifex aeolicus, Arabidopsis thaliana, Archeglobus fulgidis, Bacillus anthracis, bacillus cereus, Baccilus halodurans, Bacillus subtilis, Bacteroides thetaiotaomicron, Bdellovibrio bacteriovorus, Bifidobacterium longum, Bordetella bronchiseptica,*

Bordetella pertussis, Borrelia burgdorferi, Bradyrhizobium japonicum, Brucella melitensis, Brucella suis, Bruchnera aphidicola, Brugia malayi, Caenorhabditis elegans, Canipylobacter jejuni, Candidatus blochmanniafloridanus, Caulobacter crescentus, Chlorobium tepidum, Chromobacterium violaceum, Clostridium acetobutylicum, Clostridium perfringens, Clostridium tetani, Corynebacterium diphtheriae, Corynebacterium efficiens, Corynebacterium glutamicum, Coxiella burnetii, Danio rerio, Dechloromonas aromatica, Deinococcus radiodurans, Drosophila melanogaster, Eimeria tenella, Eimeria acervulina, Entamoeba histolytica, Enterococcus faecalis, Escherichia coli, Fusobacterium nucleatum, Geobacter sururreducens, Gloeobacter violaceus, Haemophilis ducreyi, Haemophilus influenzae, Halobacterium, Helicobacter hepaticus, Helicobacter pylori, Lactobacillus johnsonii, Lactobacillus plantarum, Lactococcus lactis, Leptospira interrogans serovar lai, Listeria innocua, Listeria monocytogenes, Mesorhizobium loti, Methanobacter thermoautotrophicus, Methanocaldocossus jannaschii, Methanococcoides burtonii, Methanopyrus kandleri, Methanosarcina acetivorans, Methanosareina mazei Goel, Mycobacterium avium, Mycobacterium bovis, Mycobacterium leprae, Mycobacterium tuberculosis, Mycoplasma gallisepticum strain R, Mycoplasma genitalium, Mycoplasma penetrans, Mycoplasma pneumoniae, Mycoplasma pulmonis, Nanoarchaeum equitans, Neisseria meningitidis, Nitrosomonas europaea, Nostoc, Oceanobacillus iheyensis, Onion yellows phytoplasma, Oryzias latipes, Oryza sativa, Pasteurella multocida, Photorhabdus luminescens, Pirellula, Plasmodium falciparum, Plasmodium vivax, Plasmodium yoelii, Porphyromonas gingivalis, Prochlorococcus marinus, Pseudomonas aeruginosa, Pseudomonas putida, Pseudomonas syringae, Pyrobaculum aerophilum, Pyrococcus abyssi, Pyrococcus furiosus, Pyrococcus horikoshii, Ralstonia solanacearum, Rhodopseudomonas palustris, Rickettsia conorii, Rickettsia prowazekii, Rickettsia rickettsii, Saccharomyces cerevisiae, Salmonella enterica, Salmonella typhimurium, Sarcocystis cruzi, Schistosoma mansoni, Schizosaccharomyces pombe, Shewanella oneidensis, Shigella flexneri, Sinorhizobium meliloti, Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus agalactiae, Streptococcus agalactiae, Streptococcus mutans, Streptococcus pneumoniae, Streptococcus pyogenes, Streptomyces avermitilis, Streptomyces coelicolor, Suffiblobus tokodaii, Synechocystis sp., Takifugu

rubripes, Tetraodon fluviatilis, Theileria parva, Thermoanaerobacter tengcongensis, Thernzoplasma acidophilum, Thermoplasma voleanium, Thermosynechococcus elongatus, Aermotoga maritima, Toxoplasma gondii, Treponema denticola, Treponema pallidum, Tropheryma whipplei, Tryponosoma brucei, Trypanosoma cruzi, Ureaplasma urealyticum, Vibrio cholerae, Vibro parahaemolyticus, Pbro vulnificus, Wigglesworthia brevipalpis, Wolbachia endosymbiont of Drosophilia melanogaster, W01inella succinogenes, Xanthomonas axonopodis pv. Citri, Xanthomonas campestris pv. Campestris, Xylella fastidiosa, or *Yersinia pestis*.

[0030] In one embodiment, the pathogenic effect, infection or combination thereof is mediated by a parasite. In one embodiment, the parasite is a worm. In one embodiment, the parasitic worm is a helminth, Acanthocephala, Clonorchis sinensis (the Chinese liver fluke), Dracunculiasis (Guinea Worm Disease), or Enterobius vermicularis (pinworm). In another embodiment, the parasite is a fish, which is, in one embodiment, a Candiru (Vampire fish of Brazil). In another embodiment, the parasite is a fungi, which is, in one embodiment, a Tinea (ringworm). In one embodiment, the parasite is a protist. In one embodiment, the protist parasite is a Plasmodium (malaria), Balantidium coli, or Giardia lamblia. In one embodiment, the parasite is Hirudinea (leech), Phthiraptera (lice), Siphonaptera (fleas), or Acarina (ticks).

[0031] In another embodiment, the parasite is an intracellular bacterial parasite. In one embodiment, the intracellular bacterial parasite is Rickettsias, while in another embodiment, it's *Mycobacterium leprae*. In one embodiment, the intracellular bacterial parasite is *Rickettsia prowazekii*, while in another embodiment, it's *Rickettsia rickettsii* (Rocky mountain spotted fever).

[0032] In one embodiment, the methods of the present invention may be used to treat a pathogenic infection acquired via zoonotic transmission. In one embodiment, the methods of the present invention may be used to treat pathogenic infections acquired from avian, swine, bovine, or bat. In another embodiment, the methods of the present invention may be used to treat Menangle, Hendra, Australian Bat Lyssavirus, Nipah, or Tioman. In another embodiment, the methods of the present invention may be used to

diminish pathogen reservoirs in animal species. In another embodiment, the methods of the present invention may be used to treat a human infected with a pathogen.

Influenza

[0033] In one embodiment, the viral pathogenic effect described hereinabove is mediated by influenza virus. In another embodiment, the infection described hereinabove is mediated by an orthomyxovirus, which in one embodiment, is an influenza virus.

[0034] Thus, in one embodiment, the methods of the present invention include the treatment of symptoms of infection by influenza virus comprising fever (usually high), headache, tiredness (can be extreme), cough, sore throat, runny or stuffy nose, body aches, diarrhea, vomiting, or a combination thereof.

[0035] In one embodiment, the methods of the present invention treat secondary complications related to influenza infection, which may comprise, inter alia, bacterial pneumonia, bronchitis, dehydration, sinus infections, and ear infections. In another embodiment, the methods of the present invention treat chronic health problems that are exacerbated in a subject with influenza infection which may comprise, inter alia, asthma.

[0036] In one embodiment, influenza viruses for treatment by the methods of the present invention may be of type A or type B. In one embodiment, the viral pathogenic effect, infection, or combination thereof is mediated by Influenza Type A virus, in another embodiment, it's mediated by Influenza Type B virus, while in another embodiment, it's mediated by Influenza Type C virus. In one embodiment, it's mediated by H1N1 strain of Influenza Type A, in another embodiment, it's mediated by H2N2 strain of Influenza Type A, in another embodiment, it's mediated by H3N2 strain of Influenza Type A, while in another embodiment, it's mediated by H5N1 strain of Influenza Type A. In one embodiment, it's mediated by any combination of strains of the subtypes listed hereinabove.

[0037] In one embodiment, the methods of the present invention may be used to treat influenza infections that were acquired via zoonotic transmission. In one embodiment,

the methods of the present invention may be used to treat zoonotic avian influenza or zoonotic swine influenza.

[0038] In another embodiment, the invention provides a method of suppressing, inhibiting, preventing, or treating infection with an influenza virus in a subject comprising the step of administering to said subject an effective amount of a lipid or phospholipid moiety bound to a physiologically acceptable monomer, dimer, oligomer, or polymer, and/or a pharmaceutically acceptable salt or a pharmaceutical product thereof. In one embodiment, the phospholipid moiety is phosphatidylethanolamine and the physiologically acceptable monomer, dimer, oligomer, or polymer is a glycosaminoglycan. In another embodiment, the phospholipid moiety is dipalmitoyl phosphatidylethanolamine and the physiologically acceptable monomer, dimer, oligomer, or polymer is heparin. In another embodiment, the phospholipid moiety is dipalmitoyl phosphatidylethanolamine and the physiologically acceptable monomer, dimer, oligomer, or polymer is chondroitin sulfate. In another embodiment, the phospholipid moiety is dipalmitoyl phosphatidylethanolamine and the physiologically acceptable monomer, dimer, oligomer, or polymer is hyaluronic acid. In another embodiment, the phospholipid moiety is dimyristoyl phosphatidylethanolamine and the physiologically acceptable monomer, dimer, oligomer, or polymer is hyaluronic acid.

[0039] In another embodiment, the invention provides a method of suppressing, inhibiting, preventing, or treating infection with an influenza virusof a cell, comprising the step of contacting the cell with a compound comprising a lipid or phospholipid moiety bound to a physiologically acceptable monomer, dimer, oligomer, or polymer, and/or a pharmaceutically acceptable salt or a pharmaceutical product thereof.

[0040] In one embodiment, the invention provides a method of treating a subject afflicted with an influenza infection, including, *inter alia*, the step of administering to a subject an effective amount of a lipid or phospholipid moiety bonded to a physiologically acceptable monomer, dimer, oligomer, or polymer, thereby treating the subject afflicted with an influenza infection.

[0041] In another embodiment, the invention provides a use of a lipid or phospholipid moiety bonded to a physiologically acceptable monomer, dimer, oligomer, or polymer, in the preparation of a pharmaceutical composition for treating a subject afflicted with an influenza infection.

[0042] In one embodiment, Lipid-conjugates of the present invention suppress, inhibit, prevent, or treat influenza infection. In another embodiment, Lipid-conjugates decrease morphological changes that result from cytotoxicity of influenza infection. This is exemplified in Example 1.1 and represents an embodiment of this invention. In another embodiment, Lipid-conjugates decrease cell membrane permeability as is demonstrated by a neutral red dye uptake assay. This is exemplified in Example 1.1 and represents an embodiment of this invention. In one embodiment, Compound XXIV (see compound descriptions hereinbelow) is useful to treat infection with influenza, in another embodiment, influenza Type A, while in another embodiment, influenza Type A, Strain H1N1. This is exemplified in Tables 1.2 and 1.4 and represents an embodiment of this invention.

Poxvirus

[0043] In one embodiment, the viral pathogenic effect described hereinabove is mediated by poxviridae, while in another embodiment, the viral pathogenic effect is mediated by chordopoxvirinae. In another embodiment, the infection described hereinabove is mediated by poxviridae while in another embodiment, the infection is mediated by chordopoxvirinae.

[0044] In one embodiment, a range of pox viruses cause febrile illnesses in man and animals with a prominent vesicular rash. In one embodiment, "pox virus", "poxvirus" and "Poxviridae" refer to the Poxviridae family of viruses.

[0045] In one embodiment, methods of the present invention comprise treating secondary complications of infection, which may comprise progressive necrosis at the site of infection, skin disorders such as eczema, vesicular rash, neurological complications, conjunctivitis, or a combination thereof.

[0046] In one embodiment, methods of the present invention comprise treating variola major or variola minor. In another embodiment, the methods of the present invention comprise treating ordinary, modified, flat, and hermorrhagic types of variola major. In one embodiment, the methods of the present invention may be used to treat variola virus used as an agent of bioterrorism.

[0047] In another embodiment, the methods of the present invention may be used to treat secondary complications of variola infection comprising fever, malaise, head and body aches, vomiting, rash in the tongue and mouth, rash on the skin, pustule formation, scabbing, scarring, or a combination thereof.

[0048] In one embodiment, the methods of the present invention may be used to treat poxvirus infections that were acquired via zoonotic transmission. In one embodiment, the methods of the present invention may be used to treat *Molluscum contagiosum*, Cowpox, Monkey pox, pseudocowpox and orf. In one embodiment, the methods of the present invention may be used to treat ulcerative or non-ulcerating lesions (sometimes called "milkers nodules") on the hands of dairy workers or to treat a papulo-vesicular lesion on the hand, forearm or face of a subject.

[0049] In another embodiment, the viral pathogenic effect, infection or combination thereof is mediated by Vaccinia virus. In another embodiment, it's mediated by a poxvirus, while in another embodiment, it's mediated by a chordopoxvirinae. In another embodiment, it's mediated by Orf virus, Fowlpox virus, Sheep pox virus, Myxoma virus, Swinepox virus, Molluscum contagiosum virus, Yaba monkey tumor virus, Melolontha melolontha entomopoxvirus, Amsacta moorei entomopoxvirus, or Chironomus luridus entomopoxvirus.

[0050] In another embodiment, the invention provides a method of suppressing, inhibiting, preventing, or treating a vaccinia infection in a subject comprising the step of administering to said subject an effective amount of a lipid or phospholipid moiety bound to a physiologically acceptable monomer, dimer, oligomer, or polymer, and/or a pharmaceutically acceptable salt or a pharmaceutical product thereof. In one

embodiment, the phospholipid moiety is phosphatidylethanolamine and the physiologically acceptable monomer, dimer, oligomer, or polymer is a glycosaminoglycan. In another embodiment, the phospholipid moiety is dipalmitoyl phosphatidylethanolamine and the physiologically acceptable monomer, dimer, oligomer, or polymer is heparin. In another embodiment, the phospholipid moiety is dipalmitoyl phosphatidylethanolamine and the physiologically acceptable monomer, dimer, oligomer, or polymer is chondroitin sulfate. In another embodiment, the phospholipid moiety is dipalmitoyl phosphatidylethanolamine and the physiologically acceptable monomer, dimer, oligomer, or polymer is hyaluronic acid. In another embodiment, the phospholipid moiety is dimyristoyl phosphatidylethanolamine and the physiologically acceptable monomer, dimer, oligomer, or polymer is hyaluronic acid.

[0051] In another embodiment, the invention provides a method of suppressing, inhibiting, preventing, or treating a vaccinia infection of a cell, comprising the step of contacting the cell with a compound comprising a lipid or phospholipid moiety bound to a physiologically acceptable monomer, dimer, oligomer, or polymer, and/or a pharmaceutically acceptable salt or a pharmaceutical product thereof.

[0052] In another embodiment, the invention provides a method of suppressing, inhibiting, preventing, or treating a smallpox infection in a subject comprising the step of administering to said subject an effective amount of a lipid or phospholipid moiety bound to a physiologically acceptable monomer, dimer, oligomer, or polymer, and/or a pharmaceutically acceptable salt or a pharmaceutical product thereof. In one embodiment, the phospholipid moiety is phosphatidylethanolamine and the physiologically acceptable monomer, dimer, oligomer, or polymer is a glycosaminoglycan. In another embodiment, the phospholipid moiety is dipalmitoyl phosphatidylethanolamine and the physiologically acceptable monomer, dimer, oligomer, or polymer is heparin. In another embodiment, the phospholipid moiety is dipalmitoyl phosphatidylethanolamine and the physiologically acceptable monomer, dimer, oligomer, or polymer is chondroitin sulfate. In another embodiment, the phospholipid moiety is dipalmitoyl phosphatidylethanolamine and the physiologically acceptable monomer, dimer, oligomer, or polymer is hyaluronic acid. In another embodiment, the phospholipid

moiety is dimyristoyl phosphatidylethanolamine and the physiologically acceptable monomer, dimer, oligomer, or polymer is hyaluronic acid.

[0053] In another embodiment, the invention provides a method of suppressing, inhibiting, preventing, or treating a smallpox infection of a cell, comprising the step of contacting the cell with a compound comprising a lipid or phospholipid moiety bound to a physiologically acceptable monomer, dimer, oligomer, or polymer, and/or a pharmaceutically acceptable salt or a pharmaceutical product thereof.

[0054] In another embodiment, the invention provides a method of suppressing, inhibiting, preventing, or treating a poxvirus infection in a subject comprising the step of administering to said subject an effective amount of a lipid or phospholipid moiety bound to a physiologically acceptable monomer, dimer, oligomer, or polymer, and/or a pharmaceutically acceptable salt or a pharmaceutical product thereof. In one embodiment, the phospholipid moiety is phosphatidylethanolamine and the physiologically acceptable monomer, dimer, oligomer, or polymer is a glycosaminoglycan. In another embodiment, the phospholipid moiety is dipalmitoyl phosphatidylethanolamine and the physiologically acceptable monomer, dimer, oligomer, or polymer is heparin. In another embodiment, the phospholipid moiety is dipalmitoyl phosphatidylethanolamine and the physiologically acceptable monomer, dimer, oligomer, or polymer is chondroitin sulfate. In another embodiment, the phospholipid moiety is dipalmitoyl phosphatidylethanolamine and the physiologically acceptable monomer, dimer, oligomer, or polymer is hyaluronic acid. In another embodiment, the phospholipid moiety is dimyristoyl phosphatidylethanolamine and the physiologically acceptable monomer, dimer, oligomer, or polymer is hyaluronic acid.

[0055] In another embodiment, the invention provides a method of suppressing, inhibiting, preventing, or treating a poxvirus infection of a cell, comprising the step of contacting the cell with a compound comprising a lipid or phospholipid moiety bound to a physiologically acceptable monomer, dimer, oligomer, or polymer, and/or a pharmaceutically acceptable salt or a pharmaceutical product thereof.

[0056] In another embodiment, the invention provides a method of suppressing, inhibiting, preventing, or treating a chordopoxvirinae infection in a subject comprising the step of administering to said subject an effective amount of a lipid or phospholipid moiety bound to a physiologically acceptable monomer, dimer, oligomer, or polymer, and/or a pharmaceutically acceptable salt or a pharmaceutical product thereof. In one embodiment, the phospholipid moiety is phosphatidylethanolamine and the physiologically acceptable monomer, dimer, oligomer, or polymer is a glycosaminoglycan. In another embodiment, the phospholipid moiety is dipalmitoyl phosphatidylethanolamine and the physiologically acceptable monomer, dimer, oligomer, or polymer is heparin. In another embodiment, the phospholipid moiety is dipalmitoyl phosphatidylethanolamine and the physiologically acceptable monomer, dimer, oligomer, or polymer is chondroitin sulfate. In another embodiment, the phospholipid moiety is dipalmitoyl phosphatidylethanolamine and the physiologically acceptable monomer, dimer, oligomer, or polymer is hyaluronic acid. In another embodiment, the phospholipid moiety is dimyristoyl phosphatidylethanolamine and the physiologically acceptable monomer, dimer, oligomer, or polymer is hyaluronic acid.

[0057] In another embodiment, the invention provides a method of suppressing, inhibiting, preventing, or treating a chordopoxvirinae infection of a cell, comprising the step of contacting the cell with a compound comprising a lipid or phospholipid moiety bound to a physiologically acceptable monomer, dimer, oligomer, or polymer, and/or a pharmaceutically acceptable salt or a pharmaceutical product thereof.

[0058] In one embodiment, the invention provides a method of treating a subject suffering from a vaccinia infection, including, *inter alia*, the step of administering to a subject an effective amount of a lipid or phospholipid moiety bonded to a physiologically acceptable monomer, dimer, oligomer, or polymer, thereby treating the subject suffering from a vaccinia infection.

[0059] In one embodiment, the invention provides a method of treating a subject suffering from a smallpox infection, including, *inter alia*, the step of administering to a subject an effective amount of a lipid or phospholipid moiety bonded to a physiologically

acceptable monomer, dimer, oligomer, or polymer, thereby treating the subject suffering from a vaccinia infection.

[0060] In one embodiment, the invention provides a method of treating a subject suffering from a poxvirus infection, including, *inter alia*, the step of administering to a subject an effective amount of a lipid or phospholipid moiety bonded to a physiologically acceptable monomer, dimer, oligomer, or polymer, thereby treating the subject suffering from a poxvirus infection.

[0061] In one embodiment, the invention provides a method of treating a subject suffering from a chordopoxvirinae infection, including, *inter alia*, the step of administering to a subject an effective amount of a lipid or phospholipid moiety bonded to a physiologically acceptable monomer, dimer, oligomer, or polymer, thereby treating the subject suffering from a chordopoxvirinae infection.

[0062] In one embodiment, the invention provides a use of a lipid or phospholipid moiety bonded to a physiologically acceptable monomer, dimer, oligomer, or polymer, in the preparation of a pharmaceutical composition for treating a subject afflicted with a vaccinia infection.

[0063] In one embodiment, the invention provides a use of a lipid or phospholipid moiety bonded to a physiologically acceptable monomer, dimer, oligomer, or polymer, in the preparation of a pharmaceutical composition for treating a subject afflicted with a smallpox infection.

[0064] In one embodiment, the invention provides a use of a lipid or phospholipid moiety bonded to a physiologically acceptable monomer, dimer, oligomer, or polymer, in the preparation of a pharmaceutical composition for treating a subject afflicted with a poxvirus infection.

[0065] In one embodiment, the invention provides a use of a lipid or phospholipid moiety bonded to a physiologically acceptable monomer, dimer, oligomer, or polymer, in the

preparation of a pharmaceutical composition for treating a subject afflicted with a chordopoxvirinae infection.

[0066] In one embodiment, Lipid-conjugates of the present invention suppress, inhibit, prevent, or treat vaccinia infection. In another embodiment, Lipid-conjugates decrease vaccinia virus titer. This is exemplified in Table 1.6 and represents an embodiment of this invention. In one embodiment, Compound XXII (see compound descriptions hereinbelow) is useful to treat vaccinia infection. This is exemplified in Table 1.6 and represents an embodiment of this invention. In another embodiment, Compound XXV (see compound descriptions hereinbelow) is useful to treat vaccinia infection. This is exemplified in Table 1.6 and represents an embodiment of this invention. In another embodiment, Compound XXIII (see compound descriptions hereinbelow) is useful to treat vaccinia infection. This is exemplified in Table 1.6 and represents an embodiment of this invention.

Other Pathogen-mediated Diseases and Conditions

Obstructive Respiratory Disease

[0067] In one embodiment, the methods of the present invention treat obstructive respiratory disease, which in one embodiment, can be caused or exacerbated by microbial infections. In one embodiment, obstructive respiratory disease is a disease of luminal passages in the lungs, which in one embodiment, is marked by dyspnea, tachypnea, or ausculatory or radiological signs of airway obstruction. In one embodiment, the methods of the present invention treat obstruction of air flow due to constriction of airway lumen smooth muscle, accumulation of infiltrates in and around the airway lumen, or a combination thereof.

[0068] In one embodiment, microbial-induced respiratory diseases may include influenza infection, which may, in one embodiment, exacerbate chronic asthma. In one embodiment, microbial-induced respiratory diseases may include tuberculosis (TB), as is described hereinbelow.

[0069] In one embodiment, the invention provides a method of treating a subject suffering from obstructive respiratory disease, including, *inter alia*, the step of administering to a subject an effective amount of a lipid or phospholipid moiety bonded to a physiologically acceptable monomer, dimer, oligomer, or polymer, thereby treating the subject suffering from obstructive respiratory disease.

[0070] In one embodiment, the invention provides a use of a lipid or phospholipid moiety bonded to a physiologically acceptable monomer, dimer, oligomer, or polymer, in the preparation of a pharmaceutical composition for treating a subject suffering from obstructive respiratory disease.

[0071] In one embodiment, obstructive respiratory disease is due to a pathogenic effect, while in another embodiment, it's due to a pathogenic infection. In another embodiment, it is due to a microbial infection, in another embodiment, it's due to a viral infection, while in another embodiment, it's due to a bacterial infection. In one embodiment, it's due to influenza, tuberculosis, schistosomiasis, chronic bronchitis, pneumonia, SARS, respiratory syncitial virus, Empyema Thoracis, whooping cough, or a combination thereof.

[0072] In one embodiment, the bacterial pathogenic effect described hereinabove is mediated by tuberculosis. In another embodiment, the infection described hereinabove is mediated by tuberculosis.

[0073] In one embodiment, the microbial-induced obstructive respiratory disease is tuberculosis (TB; *Mycobacterium tuberculosis*). In another embodiment, the methods of the present invention may be used to treat tuberculosis that is acquired via zoonotic transmission, which may include inter alia *Mycobacterium bovis*. In another embodiment, the invention provides a method of suppressing, inhibiting, preventing, or treating a pathogenic effect on a cell from a subject afflicted with a mycobacterial infection, which in one embodiment is tuberculosis, comprising the step of contacting the cell with a compound comprising a lipid or phospholipid moiety bound to a physiologically acceptable monomer, dimer, oligomer, or polymer, and/or a pharmaceutically acceptable

salt or a pharmaceutical product thereof. In another embodiment, the invention provides a method of suppressing, inhibiting, preventing, or treating a mycobacterial infection in a subject comprising the step of administering to said subject an effective amount of a lipid or phospholipid moiety bound to a physiologically acceptable monomer, dimer, oligomer, or polymer, and/or a pharmaceutically acceptable salt or a pharmaceutical product thereof. In another embodiment, the invention provides a method of suppressing, inhibiting, preventing, or treating tuberculosis in a subject comprising the step of administering to said subject an effective amount of a lipid or phospholipid moiety bound to a physiologically acceptable monomer, dimer, oligomer, or polymer, and/or a pharmaceutically acceptable salt or a pharmaceutical product thereof. In another embodiment, the mycobacterial infection may *M. tuberculosis, M. Bovis, M. Avium, M. leprae, M. smegmatis,* or a combination thereof. In one embodiment, the compounds for use in treating a mycobacterial infection may be administered in topical form.

[0074] In one embodiment, the invention provides a use of a lipid or phospholipid moiety bonded to a physiologically acceptable monomer, dimer, oligomer, or polymer, in the preparation of a pharmaceutical composition for suppressing, inhibiting, preventing, or treating tuberculosis in a subject. In one embodiment, said phospholipid moiety is phosphatidylethanolamine and said physiologically acceptable monomer, dimer, oligomer, or polymer is a glycosaminoglycan. In another embodiment, said phosphatidylethanolamine is dipalmitoyl phosphatidylethanolamine and said glycosaminoglycan is heparin. In another embodiment, said phosphatidylethanolamine is dipalmitoyl phosphatidylethanolamine and said glycosaminoglycan is chondroitin sulfate. In another embodiment, said phosphatidylethanolamine is dipalmitoyl phosphatidylethanolamine and said glycosaminoglycan is hyaluronic acid. In another embodiment, said phosphatidylethanolamine is dimyristoyl phosphatidylethanolamine and said glycosaminoglycan is hyaluronic acid.

Cytokine overproduction

[0075] In one embodiment, the methods of the present invention are useful by treating cytokine overproduction in the infected subject, which in one embodiment, can be caused

or exacerbated by microbial infections. In one embodiment, microbial infections refers to bacterial, viral, parasitic, worm, or fungal infections.

[0076] In another embodiment, the methods of the present invention treat secondary complications including, inter alia, tissue damage. In one embodiment, cytokine overproduction is due to blood bourne bacteria (septicemia) or to the pulmonary condition known as acute (or adult) respiratory distress syndrome (ARDS). In one embodiment, the methods of the present invention prevent monocytic phagocytes and leukocytes from adhering to endothelial surfaces or undergoing a respiratory burst. In another embodiment, the methods prevent oxidant injury or release of chemokines such as Gro α, ENA-78, CX3X and MCP-1, leukotrienes, thromboxanes, prostaglandins, or a combination thereof. In another embodiment, the methods prevent the release of oxidants, mediators, or degradative enzymes, in another embodiment prevent endothelial cell damage or release of lysosomal enzymes by leukocytes. In one embodiment, the methods of the present invention treat vaginal bacterial infection in which cytokine overproduction plays a role.

[0077] In one embodiment, the invention provides a method for treating a subject with an infection marked by unchecked inflammation, inappropriate cytokine response, or a combination thereof, including inter alia, influenza, tuberculosis, schistosomiasis, chronic bronchitis, pneumonia, SARS, respiratory syncitial virus, Empyema Thoracis, whooping cough, etc.

[0078] In one embodiment, the invention provides a method for treating a subject with an infection marked by overproduction of TNF. In one embodiment, the method comprises the step of administering to a subject an effective amount of a lipid or phospholipid moiety bonded to a physiologically acceptable monomer, dimer, oligomer, or polymer, thereby treating the subject requiring an anti-TNF therapy. In one embodiment, the invention provides a use of a lipid or phospholipid moiety bonded to a physiologically acceptable monomer, dimer, oligomer, or polymer, in the preparation of a pharmaceutical composition for treating a subject requiring an anti-TNF therapy.

Sepsis

[0079] In one embodiment, the methods of the present invention treat sepsis, which in one embodiment, can be caused by the microbial infection. In one embodiment, sepsis refers to sepsis, septicemia or septic shock. In one embodiment, sepsis syndrome and shock are triggered by the interactions of various microbial products in the blood, which in one embodiment are gram-negative endotoxins, with host mediator systems. In one embodiment, the methods of the present invention prevent activation of host mediators, including inter alia, cytokines, tumor necrosis factor-α (TNF), Gro α, ENA-78, CX3X and MCP-1, NFκß transcription factor, lysosomal enzymes, oxidants from leukocytes, products of the metabolism of arachidonic acid, or a combination thereof.

[0080] In one embodiment, the invention provides a method of treating a subject suffering from sepsis, including, *inter alia*, the step of administering to a subject an effective amount of a lipid or phospholipid moiety bonded to a physiologically acceptable monomer, dimer, oligomer, or polymer, thereby treating the subject suffering from sepsis. In one embodiment, the invention provides a use of a lipid or phospholipid moiety bonded to a physiologically acceptable monomer, dimer, oligomer, or polymer, in the preparation of a pharmaceutical composition for treating a subject suffering from sepsis. In one embodiment, sepsis is due to a pathogenic effect. In another embodiment, it's due to a pathogenic infection, in another embodiment, a viral infection, in another embodiment, a bacterial infection. In one embodiment, the compounds for use in the present invention may protect against bacterial or viral induced septic shock.

Hemolysis

[0081] In one embodiment, the methods of the present invention treat hemolytic infections. In one embodiment, hemolytic infections are marked by red blood cell lysis, which in one embodiment may be an acquired disorder. In one embodiment, the methods of the present invention may be used to treat membrane anomalies, which in one embodiment, are due to infectious agents, including inter alia, viral, bacterial and

parasitic etiologies. In one embodiment, the pathogen causing hemolysis is malaria, while in another embodiment, it's hemorrhagic fevers.

[0082] In one embodiment, the invention provides a method of treating a subject with a hemolytic infection, including, *inter alia*, the step of administering to the subject an effective amount of a lipid or phospholipid moiety bonded to a physiologically acceptable monomer, dimer, oligomer, or polymer, thereby treating the subject with hemolysis. In one embodiment, the invention provides a use of a lipid or phospholipid moiety bonded to a physiologically acceptable monomer, dimer, oligomer, or polymer, in the preparation of a pharmaceutical composition for treating a subject with hemolysis. In one embodiment, hemolysis is due to a pathogenic effect. In another embodiment, it's due to a pathogenic infection, in another embodiment, a viral infection, in another embodiment, a bacterial infection. In one embodiment, the compounds for use in the present invention may protect against cytopathic effects due to infection or cell to cell spread.

Oxidative Injury

[0083] In one embodiment, the methods of the present invention treat oxidative injury, which is caused or exacerbated by microbial infections in the subject. In one embodiment, oxidative injury refers to the effect of peroxidation and free radical production on body tissues. In one embodiment, peroxide production is produced by the body in response to pathogenic infections, such as viral or bacterial infections. In one embodiment, free radicals are unpaired electrons that can damage cell proteins, DNA and lipids that may be formed as biological weapons against viruses, bacteria and cancer cells. In one embodiment, the methods of the present invention treat oxidative injury to membrane components or, in another embodiment, to blood proteins.

[0084] In one embodiment, the invention provides a method of treating a subject requiring anti-oxidant therapy, including, *inter alia*, the step of administering to a subject an effective amount of a lipid or phospholipid moiety bonded to a physiologically acceptable monomer, dimer, oligomer, or polymer, thereby treating the subject requiring

an anti-oxidant therapy. In one embodiment, the invention provides a use of a lipid or phospholipid moiety bonded to a physiologically acceptable monomer, dimer, oligomer, or polymer, in the preparation of a pharmaceutical composition for treating a subject requiring an anti-oxidant therapy. In one embodiment, oxidative tissue damage is due to a pathogenic effect. In another embodiment, it's due to a pathogenic infection, in another embodiment, a viral infection, in another embodiment, a bacterial infection. In one embodiment, the compounds for use in the present invention may protect against tissue damage induced by viruses, bacteria or a combination thereof.

Central Nervous System Insult

[0085] In one embodiment, the methods of the present invention treat Central Nervous System Insult, which is caused or exacerbated by microbial infections in the subject. In one embodiment, the methods of the present invention treat physiological responses to stress resulting from tissue injury, which is a by-product of the infection. In one embodiment, the methods prevent the release of or treat the damage caused by chemical substances released by support tissue in response to infection.

[0086] In one embodiment, central nervous system (CNS) tissue insult is due to a pathogenic infection, which in one embodiment, is viral or in another embodiment, bacterial or in another embodiment, parasitical. In one embodiment, CNS insult is due to viral meningitis, Encephalitis, Poliomyelitis, bacterial meningitis, subdural empyema, CNS helminthic infections, lyme disease, toxplamosis, tuberculosis, measles, or any combination thereof.

[0087] In one embodiment, the invention provides a method of treating a subject suffering from central nervous system tissue insult, including, *inter alia*, the step of administering to the subject an effective amount of a lipid or phospholipid moiety bonded to a physiologically acceptable monomer, dimer, oligomer, or polymer, thereby treating the subject suffering from a central nervous system insult. In one embodiment, the invention provides a use of a lipid or phospholipid moiety bonded to a physiologically acceptable

monomer, dimer, oligomer, or polymer, in the preparation of a pharmaceutical composition for treating a subject suffering from central nervous system insult.

[0088] Thus, in one embodiment, the invention provides a treatment method that utilizes a lipid or phospholipid moiety bound to a physiologically acceptable monomer, dimer, oligomer, or polymer. These Lipid-conjugates display a wide-range combination of cytoprotective pharmacological activities. These compounds may in some embodiments, interfere with bacterial and viral spread and signs of infection, alleviate airway obstruction, attenuate oxidative damage to tissue proteins and cell membranes, reduce intracellular levels of chemokines and cytokines after exposure to bacterial endotoxins, and protect CNS cells by reducing release of neurotoxic agents.

[0089] In one embodiment of the present invention, the useful pharmacological properties of the Lipid-conjugates, some of which are described hereinabove, may be applied for clinical use, and disclosed herein as methods for the prevention or treatment of a disease. The biological basis of these methods may be readily demonstrated by standard cellular and animal models of disease, for example, as described in Example 1, hereinbelow.

[0090] In one embodiment, the pharmacological activities of Lipid-conjugates, including membrane stabilization, anti-inflammation, anti-oxidant action, and attenuation of chemokine levels, may contribute to a Lipid-conjugate-treated cell's resistance to pathogenic infection, such as influenza, vaccinia, smallpox, poxvirus, and chordopoxvirinae infection. In one embodiment, cell membrane stabilization may ameliorate or prevent tissue injury arising in the course of a pathological disease state. In another embodiment, anti-oxidant action may limit oxidative damage to cell and blood components arising in the course of a pathological disease state. In another embodiment, attenuation of chemokines levels may attenuate physiological reactions to stress that arise in the course of a pathological disease state.

[0091] In one embodiment, the present invention provides for use of a lipid moiety bonded to a physiologically acceptable monomer, dimer, oligomer, or polymer, in the preparation of a pharmaceutical composition for treating a subject afflicted with a pathogenic

infection, which in one embodiment is a viral infection, and in another embodiment, a bacterial infection. In another embodiment, the use of the compounds is for treating symptoms or secondary complications related to the pathogenic infection.

[0092] In one embodiment, the methods of the present invention include a composition comprising the compounds as described and may be formulated for administration by topical, oral, nasal, aerosol, intravenous, intraocular, intra-arterial, subcutaneous, or suppository routes as will be described hereinbelow.

[0093] In one embodiment of the invention, the Lipid-conjugates described herein can be used to treat disease, through amelioration, or prevention, of tissue injury arising in the course of pathological disease states by stabilizing cell membranes; limiting oxidative damage to cell and blood components; or attenuating physiological reactions to stress, as expressed in elevated chemokine levels.

[0094] The medicinal properties of the compounds for use in the present invention are readily exemplified using animal models of particular diseases of interest. The patients to whom the lipid or phospholipid conjugates should be administered are those that are experiencing symptoms of disease or who are at risk of contracting the disease or experiencing a recurrent episode or exacerbation of the disease. Thus, the lipid or phospholipid conjugates of the present invention may be used to treat an individual with a disease or disorder or to prevent an individual from contracting a disease or developing a disorder.

[0095] The combination of lipids, such as, but not limited to phosphatidylethanolamine and phosphatidylserine, with additional monomer or polymer moieties, is thus a practical route to the production of new drugs for medical purposes, provided that the resultant chemical composition displays the desired range of pharmacological properties. In one embodiment, the Lipid-conjugates of this invention possess a combination of multiple and potent pharmacological effects in addition to the ability to inhibit the extracellular form of the enzyme phospholipase A2. While the pharmacological activity of the Lipid-conjugates described herein may be due in part to the nature of the lipid moiety, the

multiple and diverse combination of pharmacological properties observed for the Lipid-conjugates emerges from the ability of the compound structure to act essentially as several different drugs in one chemical entity.

[0096] In the cases described herein, the diversity of biological activities and the effectiveness in disease exhibited by the compounds for use in the present invention far exceed the properties anticipated by use of the starting materials themselves, when administered alone or in combination. However, the phospholipid conjugate compounds, alone or in combination, are valuable when used in the methods of treating diseases and conditions specifically described herein.

[0097] In one embodiment, methods of the present invention involve treating a subject by inter alia controlling the expression, production, and activity of phospholipases such as PLA2; controlling the production and/or action of lipid mediators, such as eicosanoids, platelet activating factor (PAF) and lyso-phospholipids; amelioration of damage to cell surface glycosaminoglycans (GAG) and proteoglycans; controlling the production of oxidants, oxygen radicals and nitric oxide; protection of cells, tissues, and plasma lipoproteins from damaging agents, such as reactive oxygen species (ROS) and phospholipases; controlling the expression, production, and activity of cytokines, chemokines and interleukins; anti-oxidant therapy; anti-endotoxin therapy or any combination thereof.

[0098] In one embodiment of the invention, the term "controlling" refers to inhibiting the production and action of the above mentioned factors in order to maintain their activity at the normal basal level and suppress their activation in pathological conditions.

[0099] In one embodiment of the invention, infection is characterized by the presence of damaging agents, which comprise, inter alia, phospholipases, reactive oxygen species (ROS), free radicals, lysophospholipids, fatty acids or derivatives thereof, hydrogen peroxides, phospholipids, oxidants, cationic proteins, streptolysins, proteases, hemolysins, or sialidases.

Dosages and Routes of Administration

[00100]As used herein, the term "pharmaceutically acceptable" refers to any formulation which is safe, and provides the appropriate delivery for the desired route of administration of an effective amount of at least one compound for use in the present invention. As such, all of the above-described formulations of the present invention are hereby referred to as "pharmaceutically acceptable." This term refers to the use of buffered formulations as well, wherein the pH is maintained at a particular desired value, ranging from pH 4.0 to pH 9.0, in accordance with the stability of the compounds and route of administration.

[00101]In one embodiment, a Lipid-conjugate used in the methods of this invention may be administered alone or within a composition comprising a Lipid-conjugate. In another embodiment, compositions comprising Lipid-conjugates in admixture with conventional excipients, i.e. pharmaceutically acceptable organic or inorganic carrier substances suitable for parenteral, enteral (e.g., oral) or topical application which do not deleteriously react with the active compounds may be used. Suitable pharmaceutically acceptable carriers include but are not limited to water, salt solutions, alcohols, gum arabic, vegetable oils, benzyl alcohols, polyethylene glycols, gelatine, carbohydrates such as lactose, amylose or starch, magnesium stearate, talc, silicic acid, viscous paraffin, white paraffin, glycerol, alginates, hyaluronic acid, collagen, perfume oil, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxy methylcellulose, polyvinyl pyrrolidone, etc. The pharmaceutical preparations can be sterilized and if desired mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, flavoring and/or aromatic substances and the like which do not deleteriously react with the active compounds. They can also be combined where desired with other active agents, e.g., vitamins.

[00102]In one embodiment, the therapeutic composition of the instant invention comprises a Lipid-conjugate and additional compounds effective in preventing or treating pathogenic infections. In one embodiment, the additional compounds comprise nucleotide analogs, interferons, or immunoglobulins. In another embodiment, the nucleotide analogs comprise acyclovir, ganciclovir, or ribavirin and interferons comprise

alpha-, beta-, or gamma-interferons. In one embodiment, any one of the abovementioned additional compounds is administered with one or more Lipid-conjugates to treat a viral infection, which in one embodiment is influenza, in another embodiment, it's poxvirus, in another embodiment, it's smallpox, while in another embodiment, it's vaccinia. In another embodiment, the additional compounds comprise nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, or fusion and attachment inhibitors. In one embodiment, any one of the abovementioned additional compounds is administered with one or more Lipid-conjugates to treat a viral infection. In another embodiment, the additional compounds comprise Zidovudine, Didanosine, Zalcitabine, Stavudine, Lamivudine, Abacavir, Tenofovir, Nevirapine, Delavirdine, Efavirenz, Saquinavir, Ritonavir, Indinavir, Nelfinavir, Amprenavir, Lopinavir, Atazanavir, Fosamprenavir, or Enfuvirtide. In one embodiment, any one of the abovementioned additional compounds is administered with one or more of the Lipid-conjugates to treat a viral infection.

[00103]In another embodiment, the additional compounds comprise Lactam Antibiotics, Aminoglycosides, Macrolides, Lincomycin, Clindamycin, Tetracyclines, Quinolones, Polypeptides, Sulfonamides, Trimethoprim-Sulfamethoxazole, or antimicrobial Chemoprophylaxis. In another embodiment, the additional compound is Erythromycin. In one embodiment, any one of the abovementioned additional compounds is administered with one or more of the Lipid-conjugates to treat a bacterial infection. In another embodiment, the additional compounds comprise Rifampicin, Pyrazinamid, Isoniazid, or Ethambutol. In one embodiment, any one of the abovementioned additional compounds is administered with one or more of the Lipid-conjugates to treat a bacterial infection, which is in one embodiment tuberculosis.

[00104]In another embodiment, the additional compounds comprise albendazole, mebendazole, pyrantel pamoate, thiabendazole, chloroquine, mefloquine, quinine, atovaquone-proguanil, quinidine, pyrimethamine, doxycycline, or a combination thereof. In one embodiment, any one of the abovementioned additional compounds is administered with one or more of the Lipid-conjugates to treat a parasitic infection.

[00105]In another embodiment, the additional compounds comprise analgesics, cytokines, growth factors, or a combination thereof. Compositions of the present invention may comprise any one of the compounds listed hereinabove or any combination thereof for use in the methods of this invention.

[00106]While the examples provided herein describe use of the phospholipid conjugates in subcutaneous, intraperitoneal or topical administration, the success described affords good evidence to suppose that other routes of administration, or combinations with other pharmaceutical preparations, would be at least as successful. In one embodiment, the route of administration may be parenteral, enteral, or a combination thereof. In another embodiment, the route may be subcutaneous, intraperitoneal, intravenous, intra-arterial, topical, transdermal, intradermal, vaginal, rectal, intra-ocular, conjunctival, inhalation, nasal aspiration (spray), sublingual, oral, or a combination thereof. In one embodiment, the dosage regimen will be determined by skilled clinicians, based on factors such as exact nature of the condition being treated, the severity of the condition, the age and general physical condition of the patient, etc.

[00107]For parenteral application, particularly suitable are injectable, sterile solutions, preferably oily or aqueous solutions, as well as suspensions, emulsions, or implants, including suppositories and enemas. Ampoules are convenient unit dosages. Such a suppository may comprise any agent described herein.

[00108]For application by inhalation, particularly for treatment of airway obstruction or congestion, solutions or suspensions of the compounds mixed and aerosolized or nebulized in the presence of the appropriate carrier suitable. Such an aerosol may comprise any agent described herein and, in one embodiment, may be used to treat diseases or conditions caused by airborne pathogens, which may be in one embodiment, influenza or tuberculosis.

[00109]For topical application, particularly for the treatment of skin diseases such as contact dermatitis or psoriasis, admixture of the compounds with conventional creams, lotions, or delayed release patches is acceptable. Such a cream or lotion may comprise

any agent described herein. In another embodiment, compounds for use in the present invention may be used to coat condoms, or any intravaginal or intraanal device. According to this embodiment, a compound of the invention may act as a lubricant, prevent infection by pathogens, or a combination thereof.

[00110]For enteral application, particularly suitable are tablets, dragees, liquids, drops, or capsules. A syrup, elixir, or the like can be used when a sweetened vehicle is employed.

[00111]Sustained or directed release compositions can be formulated, e.g., liposomes or those wherein the active compound is protected with differentially degradable coatings, e.g., by microencapsulation, multiple coatings, etc. It is also possible to freeze-dry the new compounds and use the lyophilisates obtained, for example, for the preparation of products for injection.

[00112]Thus, in one embodiment, the route of administration may be directed to an organ or system that is affected by the pathogenic infection. For example, compounds may be administered in aerosol form to treat infections by airborne pathogens. In another embodiment, the route of administration may be directed to a different organ or system than the one that is affected by the pathogenic infection. For example, compounds may be administered parenterally to treat infections by airborne pathogens.

[00113]Thus, the present invention provides for the use of Lipid-conjugates in various dosage forms suitable for administration using any of the routes listed hereinabove.

[00114]In general, the doses utilized for the above described purposes will vary, but will be in an effective amount to exert the desired anti-disease effect. As used herein, the term "pharmaceutically effective amount" refers to an amount of a compound of formulae A and I–XXI as described hereinbelow, which will produce the desired alleviation in symptoms or signs of disease in a patient. The doses utilized for any of the above-described purposes will generally be from 1 to about 1000 milligrams per kilogram of body weight (mg/kg), administered one to four times per day, or by continuous IV infusion. When the compositions are dosed topically, they will generally be in a concentration range of from 0.1 to about 10% w/v, administered 1-4 times per day.

[00115]In one embodiment of the invention, the concentrations of the compounds will depend on various factors, including the nature of the condition to be treated, the condition of the patient, the route of administration and the individual tolerability of the compositions.

[00116]It will be appreciated that the actual preferred amounts of active compound in a specific case will vary according to the specific compound being utilized, the particular compositions formulated, the mode of application, and the particular conditions and organism being treated. Dosages for a given host can be determined using conventional considerations, e.g., by customary comparison of the differential activities of the subject compounds and of a known agent, e.g., by means of an appropriate, conventional pharmacological protocol.

[00117]In one embodiment, the compounds of the invention may be administered acutely for acute treatment of temporary conditions, or may be administered chronically, especially in the case of progressive, recurrent, or degenerative disease. In one embodiment, one or more compounds of the invention may be administered simultaneously, or in another embodiment, they may administered in a staggered fashion. In one embodiment, the staggered fashion may be dictated by the stage or phase of the disease.

[00118]In one embodiment, the present invention offers methods for the treatment of disease based upon administration of lipids covalently conjugated through their polar head group to a physiologically acceptable chemical moiety, which may be of high or low molecular weight.

[00119]The present invention has been illustrated in terms of the anti-disease activity of Lipid-conjugates and methods of their use as pharmaceutical compositions in the treatment of disease. The following sections present some examples of the therapeutic Lipid-conjugate compounds for use in the present invention and their chemical preparation.

Compounds

[00120]In one embodiment, the compounds for use in the present invention comprise a lipid or phospholipid moiety bound to a physiologically acceptable monomer, dimer, oligomer, or polymer. In one embodiment, the lipid compounds (Lipid-conjugates) for use in the present invention are described by the general formula:

[phosphatidylethanolamine—Y]n—X

[phosphatidylserine—Y]n—X

[phosphatidylcholine—Y]n—X

[phosphatidylinositol—Y]n—X

[phosphatidylglycerol—Y]n—X

[phosphatidic acid—Y]n—X

[lyso-phospholipid-Y]n—X

[diacyl-glycerol-Y]n —X

[monoacyl-glycerol –Y]n—X

[sphingomyelin-Y]n—X

[sphingosine-Y]n—X

[ceramide-Y]n—X

wherein

Y is either nothing or a spacer group ranging in length from 2 to 30 atoms; and

X is a physiologically acceptable monomer, dimer, oligomer or polymer; and

n is the number of lipid molecules bound to a molecule of X, wherein ***n*** is a number from 1 to 1000.

[00121]In one embodiment, the invention provides low-molecular weight Lipid-conjugates, previously undisclosed and unknown to possess pharmacological activity, of the general formula described hereinabove. In another embodiment, wherein the general formula described hereinabove describes low-molecular weight Lipid-conjugates, X is a mono- or disaccharide, carboxylated disaccharide, mono- or dicarboxylic acids, a salicylate, salicylic acid, aspirin, lactobionic acid, maltose, an amino acid, glycine, acetic acid, butyric acid, dicarboxylic acid, glutaric acid, succinic acid, fatty acid, dodecanoic acid, didodecanoic acid, bile acid, cholic acid, cholesterylhemmisuccinate, a di- or tripeptide, an oligopeptide, a trisacharide, or a di- or trisaccharide monomer unit of heparin, heparan sulfate, keratin, keratan sulfate, chondroitin, chondroitin-6-sulfate, chondroitin-4-sulfate, dermatin, dermatan sulfate, dextran, or hyaluronic acid.

[00122]In one embodiment of this invention, X is salicylate, salicylic acid, aspirin, a monosaccharide, lactobionic acid, maltose, an amino acid, glycine, carboxylic acid, acetic acid, butyric acid, dicarboxylic acid, glutaric acid, succinic acid, fatty acid, dodecanoic acid, didodecanoic acid, bile acid, cholic acid, cholesterylhemmisuccinate, a dipeptide, a disaccharide, a trisaccharide, an oligosaccharide, an oligopeptide, or a di- or trisaccharide monomer unit of heparin, heparan sulfate, keratin, keratan sulfate, chondroitin, chondroitin-6-sulfate, chondroitin-4-sulfate, dermatin, dermatan sulfate, dextran, or hyaluronic acid, a glycosaminoglycan, polygeline ('haemaccel'), alginate, hydroxyethyl starch (hetastarch), polyethylene glycol, polycarboxylated polyethylene glycol, chondroitin-6-sulfate, chondroitin-4-sulfate, keratin, keratin sulfate, heparan sulfate, dermatin, dermatan sulfate, carboxymethylcellulose, heparin, dextran, or hyaluronic acid.

[00123]In one embodiment of this invention, n is a number from 1 to 1000. In another embodiment, n is a number from 1 to 500. In another embodiment, n is a number from 1 to 100. In another embodiment, n is a number from 2 to 100. In another embodiment, n is a number from 2 to 200. In another embodiment, n is a number from 3 to 300. In another

embodiment, n is a number from 10 to 400. In another embodiment, n is a number from 50 to 500. In another embodiment, n is a number from 100 to 300. In another embodiment, n is a number from 300 to 500. In another embodiment, n is a number from 500 to 800. In another embodiment, n is a number from 500 to 1000.

[00124]In one embodiment, the set of compounds comprising phosphatidylethanolamine covalently bound to a physiologically acceptable monomer or polymer, is referred to herein as the PE-conjugates. In another embodiment, related derivatives, in which either phosphatidylserine, phosphatidylcholine, phosphatidylinositol, phosphatidic acid or phosphatidylglycerol are employed in lieu of phosphatidylethanolamine as the lipid moiety provide equivalent therapeutic results, based upon the biological experiments described below for the Lipid-conjugates and the structural similarities shared by these compounds.

[00125]In another embodiment, the lipid or phospholipid moiety is phosphatidic acid, an acyl glycerol, monoacylglycerol, diacylglycerol, triacylglycerol, sphingosine, sphingomyelin, chondroitin-4-sulfate, chondroitin-6-sulfate, ceramide, phosphatidylethanolamine, phosphatidylserine, phosphatidylcholine, phosphatidylinositol, or phosphatidylglycerol, or an ether or alkyl phospholipid derivative thereof.

[00126]Other Lipid-conjugate derivatives relevant to this invention are Lipid-conjugates wherein at least one of the fatty acid groups of the lipid moieties at position C1 or C2 of the glycerol backbone are substituted by a long chain alkyl group attached by either ether or alkyl bonds, rather than ester linkages.

[00127]As defined by the structural formulae provided herein for the Lipid-conjugates, these compounds may contain between one to one thousand lipid moieties bound to a single physiologically acceptable polymer molecule.

[00128] In the methods, according to embodiments of the invention, the Lipid-conjugates administered to the subject are comprised from at least one lipid moiety covalently bound through an atom of the polar head group to a monomeric or polymeric moiety (referred to

herein as the conjugated moiety) of either low or high molecular weight. When desired, an optional bridging moiety can be used to link the Lipid-conjugates moiety to the monomer or polymeric moiety. The conjugated moiety may be a low molecular weight carboxylic acid, dicarboxylic acid, fatty acid, dicarboxylic fatty acid, acetyl salicylic acid, cholic acid, cholesterylhemisuccinate, or mono- or di-saccharide, an amino acid or dipeptide, an oligopeptide, a glycoprotein mixture, a di- or trisaccharide monomer unit of a glycosaminoglycan such as a repeating unit of heparin, heparan sulfate, hyaluronic acid, chondroitin-sulfate, dermatan, keratan sulfate, or a higher molecular weight peptide or oligopeptide, a polysaccharide, a hetero-polysaccharide, a homo-polysaccharide, a polypyranose, polyglycan, protein, glycosaminoglycan, or a glycoprotein mixture. The composition of phospholipid-conjugates of high molecular weight, and associated analogues, are the subject of US 5,064,817.

[00129]In one embodiment of the invention, when the conjugated carrier moiety is a polymer, the ratio of lipid moieties covalently bound may range from one to one thousand lipid residues per polymer molecule, depending upon the nature of the polymer and the reaction conditions employed. For example, the relative quantities of the starting materials, or the extent of the reaction time, may be modified in order to obtain Lipid-conjugate products with either high or low ratios of lipid residues per polymer, as desired.

[00130]In one embodiment, the term "moiety" means a chemical entity otherwise corresponding to a chemical compound, which has a valence satisfied by a covalent bond.

[00131]In one embodiment, examples of polymers which can be employed as the conjugated moiety for producing Lipid-conjugates for use in the methods of this invention may be physiologically acceptable polymers, including water-dispersible or -soluble polymers of various molecular weights and diverse chemical types, mainly natural and synthetic polymers, such as glycosaminoglycans, hyaluronic acids, heparin, heparin sulfates, chondroitin sulfates, chondroitin-6-sulfates, chondroitin-4-sulfates, keratins, keratin sulfates, dermatins, dermatan sulfates, dextrans, plasma expanders, including polygeline ("Haemaccel", degraded gelatin polypeptide cross-linked via urea

bridges, produced by "Behring"), "hydroxyethylstarch" (Hetastarch, HES) and extrans, food and drug additives, soluble cellulose derivatives (e.g., methylcellulose, carboxymethylcellulose), polyaminoacids, hydrocarbon polymers (e.g., polyethylene), polystyrenes, polyesters, polyamides, polyethylene oxides (e.g. polyethyleneglycols, polycarboxyethyleneglycols, polycarboxylated polyethyleneglycols), polyvinnylpyrrolidones, polysaccharides, hetero-polysaccharides, homo-polysaccharides, polypyranoses, alginates, assimilable gums (e.g., xanthan gum), peptides, injectable blood proteins (e.g., serum albumin), cyclodextrin, and derivatives thereof.

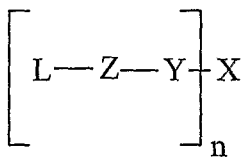
[00132]In one embodiment, examples of monomers, dimers, and oligomers which can be employed as the conjugated moiety for producing Lipid-conjugates for use in the methods of the invention may be mono- or disaccharides, trisaccharides, oligopeptides, carboxylic acids, dicarboxylic acids, fatty acids, dicarboxylic fatty acids, salicylates, slicyclic acids, acetyl salicylic acids, aspirins, lactobionic acids, maltoses, amino acids, glycines, glutaric acids, succinic acids, dodecanoic acids, didodecanoic acids, bile acids, cholic acids, cholesterylhemisuccinates, and di- and trisaccharide unit monomers of glycosaminoglycans including heparins, heparan sulfates, hyaluronic acids, chondroitins, chondroitin sulfates, chondroitin-6-sulfates, chondroitin-4-sulfates, dermatins, dermatan sulfates, keratins, keratan sulfates, or dextrans.

[00133]In some cases, according to embodiments of the invention, the monomer or polymer chosen for preparation of the Lipid-conjugate may in itself have select biological properties. For example, both heparin and hyaluronic acid are materials with known physiological functions. In the present invention, however, the Lipid-conjugates formed from these substances as starting materials display a new and wider set of pharmaceutical activities than would be predicted from administration of either heparin or hyaluronic acid which have not been bound by covalent linkage to a phospholipid. It can be shown, by standard comparative experiments as described below, that phosphatidylethanolamine (PE) linked to hyaluronic acid (Compound XXII), to heparin (Compound XXIV), to chondroitin sulfate A (Compound XXV), to carboxymethylcellulose (Compound XXVI), to Polygeline (haemaccel) (Compound XXVII), or to hydroxyethylstarch (Compound XXVIII), are far superior in terms of potency and range of useful pharmaceutical activity

to the free conjugates (the polymers above and the like). In fact, these latter substances are, in general, not considered useful in methods for treatment of most of the diseases described herein, including the treatment of pathogenic infections. Thus, the combination of a phospholipid such as phosphatidylethanolamine, or related phospholipids which differ with regard to the polar head group, such as phosphatidylserine (PS), phosphatidylcholine (PC), phosphatidylinositol (PI), and phosphatidylglycerol (PG), results in the formation of a compound which has novel pharmacological properties when compared to the starting materials alone.

[00134]The biologically active Lipid-conjugates described herein can have a wide range of molecular weight, e.g., above 50,000 (up to a few hundred thousands) when it is desirable to retain the Lipid conjugate in the vascular system and below 50,000 when targeting to extravascular systems is desirable. The sole limitation on the molecular weight and the chemical structure of the conjugated moiety is that it does not result in a Lipid-conjugate devoid of the desired biological activity, or lead to chemical or physiological instability to the extent that the Lipid-conjugate is rendered useless as a drug in the method of use described herein.

[00135]In one embodiment, the compound according to the invention is represented by the structure of the general formula (A):



(A)

wherein

L is a lipid or a phospholipid;

Z is either nothing, ethanolamine, serine, inositol, choline, or glycerol;

Y is either nothing or a spacer group ranging in length from 2 to 30 atoms;

X is a physiologically acceptable monomer, dimer, oligomer, or polymer; and

n is a number from 1 to 1000;

wherein any bond between L, Z, Y and X is either an amide or an esteric bond.

[00136]In one embodiment, X is a glycosaminoglycan.

[00137]In one embodiment, L is phosphatidyl, Z is ethanolamine, wherein L and Z are chemically bonded resulting in phosphatidylethanolamine, Y is nothing, and X is hyaluronic acid, wherein any bond between the phosphatidylethanolamine and the hyaluronic acid is an amide bond. In one embodiment, the phosphatidylethanolamine moiety is dipalmitoyl phosphatidylethanolamine. In another embodiment, the phosphatidylethanolamine moiety is dimyristoyl phosphatidylethanolamine.

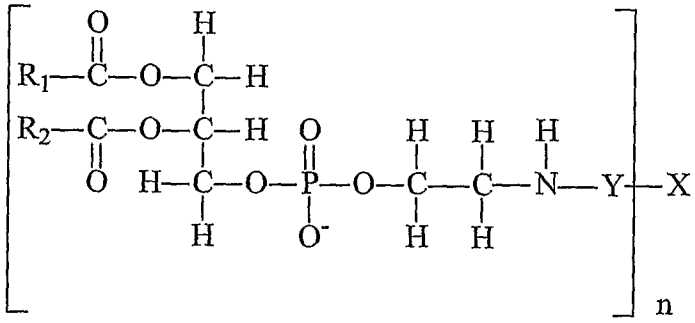
[00138]In another embodiment, L is phosphatidyl, Z is ethanolamine, wherein L and Z are chemically bonded resulting in phosphatidylethanolamine, Y is nothing, and X is chondroitin sulfate, wherein any bond between the phosphatidylethanolamine and the chondroitin sulfate is an amide bond. In one embodiment, the phosphatidylethanolamine moiety is dipalmitoyl-phosphatidyl-ethanolamine. In another embodiment, the phosphatidylethanolamine moiety is dimyristoyl-phosphatidyl-ethanolamine.

[00139]In another embodiment, L is phosphatidyl, Z is ethanolamine, wherein L and Z are chemically bonded resulting in phosphatidylethanolamine, Y is nothing, and X is heparin, wherein any bond between the phosphatidylethanolamine and the heparin is an amide bond. In one embodiment, the phosphatidylethanolamine moiety is dipalmitoyl-phosphatidyl-ethanolamine. In another embodiment, the phosphatidylethanolamine moiety is dimyristoyl-phosphatidyl-ethanolamine.

[00140]In another embodiment, L is phosphatidyl, Z is ethanolamine, wherein L and Z are chemically bonded resulting in phosphatidylethanolamine, Y is nothing, and X is polygeline, wherein any bond between the phosphatidylethanolamine and the polygeline is an amide bond. In one embodiment, the phosphatidylethanolamine moiety is

dipalmitoyl-phosphatidyl-ethanolamine. In another embodiment, the phosphatidylethanolamine moiety is dimyristoyl-phosphatidyl-ethanolamine.

[00141]In another embodiment, the compound according to the invention is represented by the structure of the general formula (I):



(I)

wherein

R_1 is a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

R_2 is a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

Y is either nothing or a spacer group ranging in length from 2 to 30 atoms; and

X is either a physiologically acceptable monomer, dimer, oligomer or a physiologically acceptable polymer; and

n is a number from 1 to 1,000;

wherein if Y is nothing the phosphatidylethanolamine is directly linked to X via an amide bond and if Y is a spacer, the spacer is directly linked to X via an amide or an esteric bond and to the phosphatidylethanolamine via an amide bond.

[00142]Preferred compounds for use in the methods of the invention comprise one of the following as the conjugated moiety **X**: acetate, butyrate, glutarate, succinate, dodecanoate, didodecanoate, maltose, lactobionic acid, dextran, alginate, aspirin, cholate,

cholesterylhemisuccinate, carboxymethyl-cellulose, heparin, hyaluronic acid, polygeline (haemaccel), polyethyleneglycol, and polycarboxylated polyethylene glycol. The polymers used as starting material to prepare the PE-conjugates may vary in molecular weight from 1 to 2,000 kDa.

[00143]Examples of phosphatidylethanolamine (PE) moieties are analogues of the phospholipid in which the chain length of the two fatty acid groups attached to the glycerol backbone of the phospholipid varies from 2 – 30 carbon atoms length, and in which these fatty acids chains contain saturated and/or unsaturated carbon atoms. In lieu of fatty acid chains, alkyl chains attached directly or via an ether linkage to the glycerol backbone of the phospholipid are included as analogues of PE. According to the present invention, a most preferred PE moiety is dipalmitoyl-phosphatidyl-ethanolamine. In another preferred embodiment of the present invention, the PE moiety is dimyristoyl-phosphatidyl-ethanolamine.

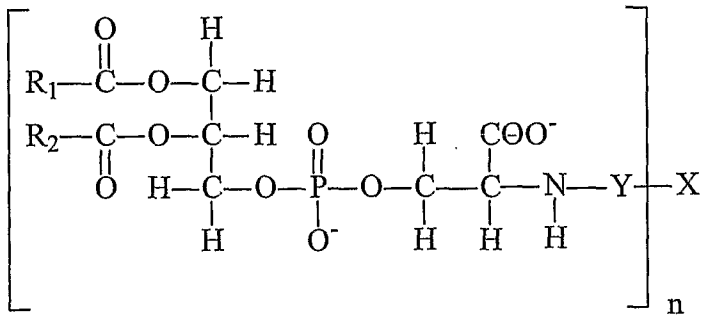
[00144]Phosphatidyl-ethanolamine and its analogues may be from various sources, including natural, synthetic, and semisynthetic derivatives and their isomers.

[00145]Phospholipids which can be employed in lieu of the PE moiety are N-methyl-PE derivatives and their analogues, linked through the amino group of the N-methyl-PE by a covalent bond; N,N-dimethyl-PE derivatives and their analogues linked through the amino group of the N,N-dimethyl-PE by a covalent bond, phosphatidylserine (PS) and its analogues, such as palmitoyl-stearoyl-PS, natural PS from various sources, semisynthetic PSs, synthetic, natural and artifactual PSs and their isomers. Other phospholipids useful as conjugated moieties in this invention are phosphatidylcholine (PC), phosphatidylinositol (PI), phosphatidic acid and phosphoatidylglycerol (PG), as well as derivatives thereof comprising either phospholipids, lysophospholipids, phosphatidyic acid, sphingomyelins, lysosphingomyelins, ceramide, and sphingosine.

[00146]For PE-conjugates and PS-conjugates, the phospholipid is linked to the conjugated monomer or polymer moiety through the nitrogen atom of the phospholipid polar head group, either directly or via a spacer group. For PC, PI, and PG conjugates, the

phospholipid is linked to the conjugated monomer or polymer moiety through either the nitrogen or one of the oxygen atoms of the polar head group, either directly or via a spacer group.

[00147]In another embodiment, the compound according to the invention is represented by the structure of the general formula (II):



(II)

wherein

R_1 is a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

R_2 is a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

Y is either nothing or a spacer group ranging in length from 2 to 30 atoms;

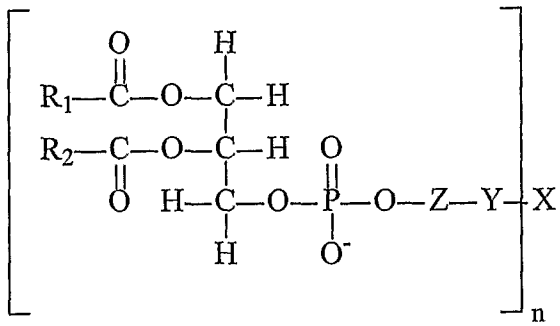
X is a physiologically acceptable monomer, dimer, oligomer or polymer; and

n is a number from 1 to 1000;

wherein if Y is nothing, the phosphatidylserine is directly linked to X via an amide bond and if Y is a spacer, the spacer is directly linked to X via an amide or an esteric bond and to the phosphatidylserine via an amide bond.

[00148]In one embodiment, the phosphatidylserine may be bonded to Y, or to X if Y is nothing, via the COO^- moiety of the phosphatidylserine.

[00149]In another embodiment, the compound according to the invention is represented by the structure of the general formula (III):



(III)

wherein

$\mathbf{R_1}$ is a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

$\mathbf{R_2}$ is a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

Z is either nothing, inositol, choline, or glycerol;

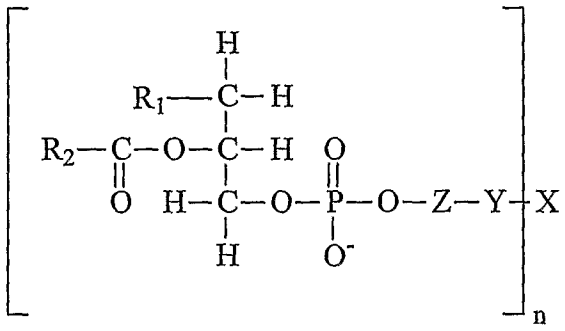
Y is either nothing or a spacer group ranging in length from 2 to 30 atoms;

X is a physiologically acceptable monomer, dimer, oligomer, or polymer; and

n is a number from 1 to 1000;

wherein any bond between the phosphatidyl, Z, Y and X is either an amide or an esteric bond.

[00150]In another embodiment, the compound according to the invention is represented by the structure of the general formula (IV):



(IV)

wherein

R_1 is either hydrogen or a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

R_2 is a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

Z is either nothing, inositol, choline, or glycerol;

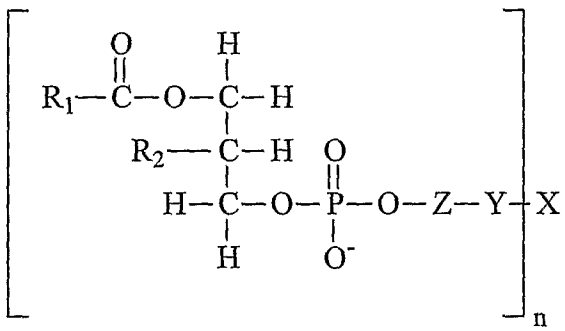
Y is either nothing or a spacer group ranging in length from 2 to 30 atoms;

X is a physiologically acceptable monomer, dimer, oligomer, or polymer; and

n is a number from 1 to 1000;

wherein any bond between the phospholipid, Z, Y and X is either an amide or an esteric bond.

[00151]In another embodiment, the compound according to the invention is represented by the structure of the general formula (V):



(V)

wherein

R_1 is a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

R_2 is either hydrogen or a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

Z is either nothing, inositol, choline, or glycerol;

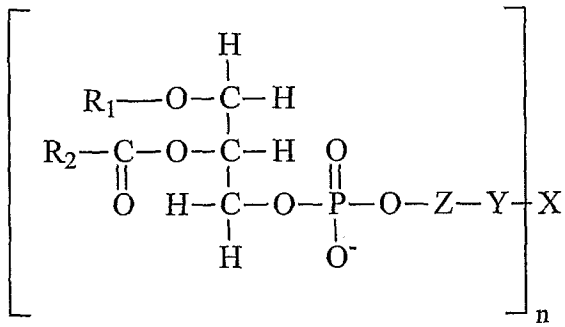
Y is either nothing or a spacer group ranging in length from 2 to 30 atoms;

X is a physiologically acceptable monomer, dimer, oligomer, or polymer; and

n is a number from 1 to 1000;

wherein any bond between the phospholipid, Z, Y and X is either an amide or an esteric bond.

[00152]In another embodiment, the compound according to the invention is represented by the structure of the general formula (VI):



(VI)

wherein

R_1 is either hydrogen or a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

R_2 is a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

Z is either nothing, inositol, choline, or glycerol;

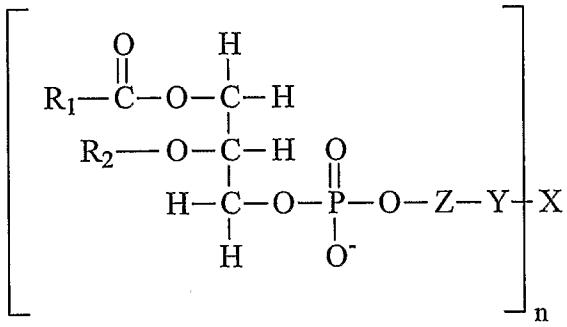
Y is either nothing or a spacer group ranging in length from 2 to 30 atoms;

X is a physiologically acceptable monomer, dimer, oligomer, or polymer; and

n is a number from 1 to 1000;

wherein any bond between the phospholipid, Z, Y and X is either an amide or an esteric bond.

[00153]In another embodiment, the compound according to the invention is represented by the structure of the general formula (VII):



(VII)

wherein

$\mathbf{R_1}$ is a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

$\mathbf{R_2}$ is either hydrogen or a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

Z is either nothing, inositol, choline, or glycerol;

Y is either nothing or a spacer group ranging in length from 2 to 30 atoms;

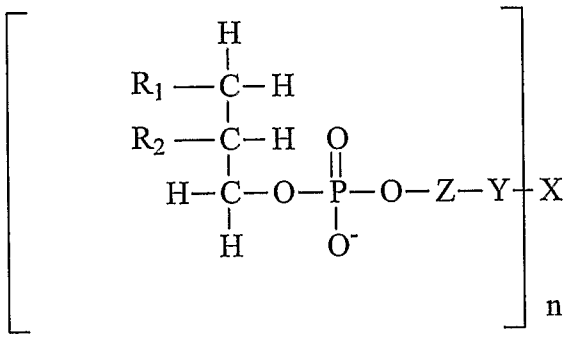
X is a physiologically acceptable monomer, dimer, oligomer, or polymer; and

n is a number from 1 to 1000;

wherein any bond between the phospholipid, Z, Y and X is either an amide or an esteric bond.

[00154]In one embodiment of the invention, phosphatidylcholine (PC), phosphatidylinositol (PI), phosphatidic acid (PA), wherein Z is nothing, and phosphatidylglycerol (PG) conjugates are herein defined as compounds of the general formula (III).

[00155]In another embodiment, the compound according to the invention is represented by the structure of the general formula (VIII):



(VIII)

wherein

R_1 is a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

R_2 is either hydrogen or a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

Z is either nothing, ethanolamine, serine, inositol, choline, or glycerol;

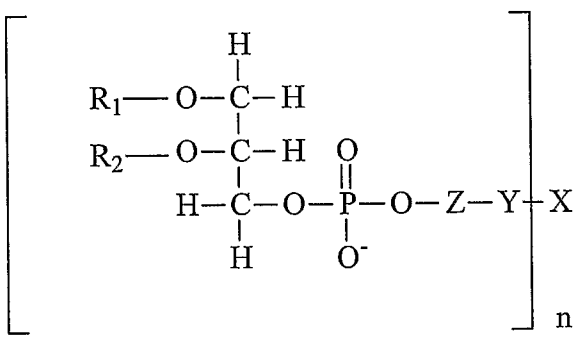
Y is either nothing or a spacer group ranging in length from 2 to 30 atoms;

X is a physiologically acceptable monomer, dimer, oligomer, or polymer; and

n is a number from 1 to 1000;

wherein any bond between the phospholipid, Z, Y and X is either an amide or an esteric bond.

[00156]In another embodiment, the compound according to the invention is represented by the structure of the general formula (IX):



(IX)

wherein

R_1 is either hydrogen or a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

R_2 is either hydrogen or a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

Z is either nothing, ethanolamine, serine, inositol, choline, or glycerol;

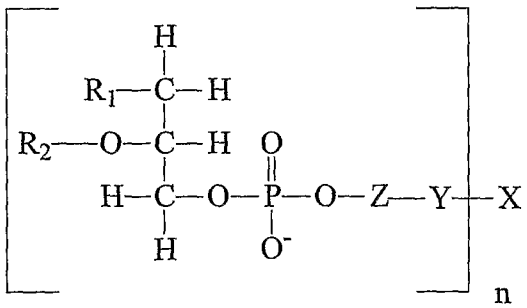
Y is either nothing or a spacer group ranging in length from 2 to 30 atoms;

X is a physiologically acceptable monomer, dimer, oligomer, or polymer; and

n is a number from 1 to 1000;

wherein any bond between the phospholipid, Z, Y and X is either an amide or an esteric bond.

[00157]In another embodiment, the compound according to the invention is represented by the structure of the general formula (IXa):



(IXa)

wherein

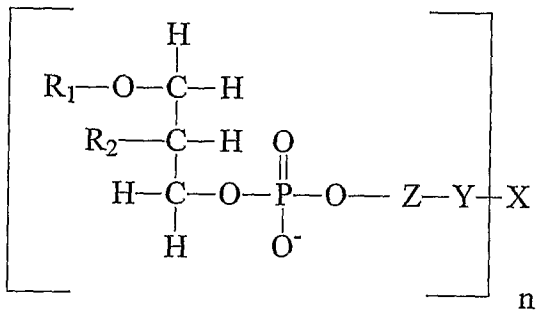
R_1 is either hydrogen or a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

R_2 is either hydrogen or a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

Z is either nothing, ethanolamine, serine, inositol, choline, or glycerol;

Y is either nothing or a spacer group ranging in length from 2 to 30 atoms;
X is a physiologically acceptable monomer, dimer, oligomer, or polymer; and
n is a number from 1 to 1000;
wherein any bond between the phospholipid, Z, Y and X is either an amide or an esteric bond.

[00158]In another embodiment, the compound according to the invention is represented by the structure of the general formula (IXb):

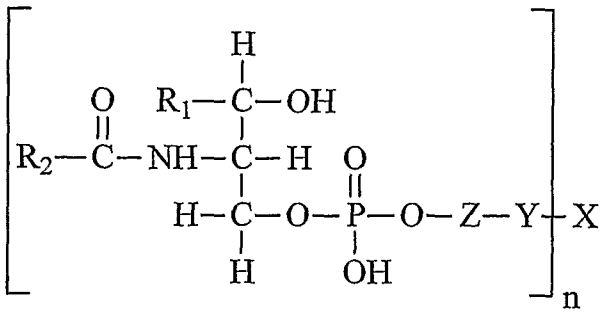


(IXb)

wherein

R_1 is either hydrogen or a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;
R_2 is either hydrogen or a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;
Z is either nothing, ethanolamine, serine, inositol, choline, or glycerol;
Y is either nothing or a spacer group ranging in length from 2 to 30 atoms;
X is a physiologically acceptable monomer, dimer, oligomer, or polymer; and
n is a number from 1 to 1000;
wherein any bond between the phospholipid, Z, Y and X is either an amide or an esteric bond.

[00159]In another embodiment, the compound according to the invention is represented by the structure of the general formula (X):



(X)

wherein

R_1 is either hydrogen or a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

R_2 is a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

Z is either nothing, ethanolamine, serine, inositol, choline, or glycerol;

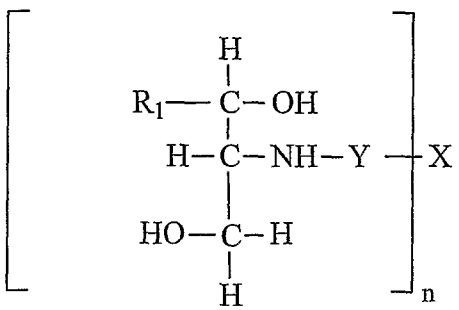
Y is either nothing or a spacer group ranging in length from 2 to 30 atoms;

X is a physiologically acceptable monomer, dimer, oligomer, or polymer; and

n is a number from 1 to 1000;

wherein any bond between the ceramide phosphoryl, Z, Y and X is either an amide or an esteric bond.

[00160]In another embodiment, the compound according to the invention is represented by the structure of the general formula (XI):



(XI)

wherein

R_1 is a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

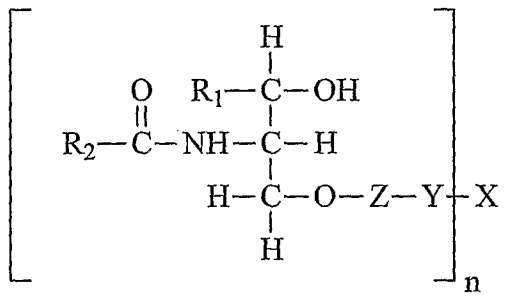
Y is either nothing or a spacer group ranging in length from 2 to 30 atoms;

X is a physiologically acceptable monomer, dimer, oligomer or polymer; and

n is a number from 1 to 1000;

wherein if Y is nothing the sphingosyl is directly linked to X via an amide bond and if Y is a spacer, the spacer is directly linked to X and to the sphingosyl via an amide bond and to X via an amide or an esteric bond.

[00161]In another embodiment, the compound according to the invention is represented by the structure of the general formula (XII):



(XII)

wherein

R_1 is a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

R_2 is a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

Z is either nothing, ethanolamine, serine, inositol, choline, or glycerol;

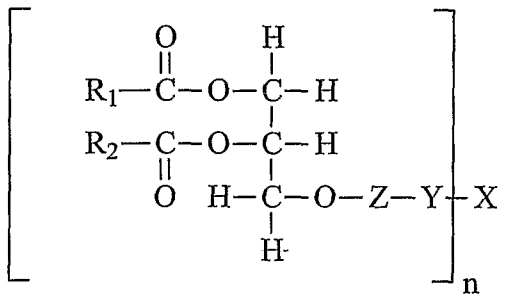
Y is either nothing or a spacer group ranging in length from 2 to 30 atoms;

X is a physiologically acceptable monomer, dimer, oligomer or polymer; and

n is a number from 1 to 1000;

wherein any bond between the ceramide, Z, Y and X is either an amide or an esteric bond.

[00162]In another embodiment, the compound according to the invention is represented by the structure of the general formula (XIII):



(XIII)

wherein

$\mathbf{R_1}$ is a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

$\mathbf{R_2}$ is a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

Z is either nothing, choline, phosphate, inositol, or glycerol;

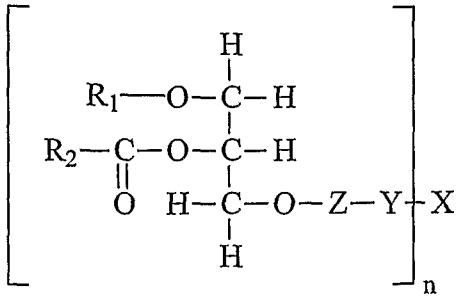
Y is either nothing or a spacer group ranging in length from 2 to 30 atoms;

X is a physiologically acceptable monomer, dimer, oligomer or polymer; and

n is a number from 1 to 1000;

wherein any bond between the diglyceryl, Z, Y and X is either an amide or an esteric bond.

[00163]In another embodiment, the compound according to the invention is represented by the structure of the general formula (XIV):



(XIV)

wherein

R_1 is either hydrogen or a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

R_2 is a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

Z is either nothing, choline, phosphate, inositol, or glycerol;

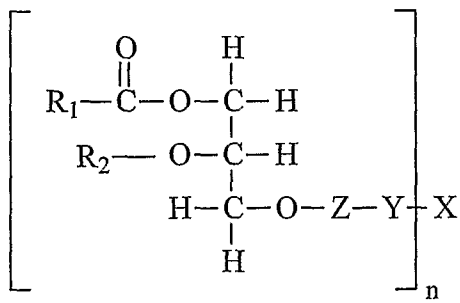
Y is either nothing or a spacer group ranging in length from 2 to 30 atoms;

X is a physiologically acceptable monomer, dimer, oligomer or polymer; and

n is a number from 1 to 1000;

wherein any bond between the glycerolipid, Z, Y and X is either an amide or an esteric bond.

[00164]In another embodiment, the compound according to the invention is represented by the structure of the general formula (XV):



(XV)

wherein

R_1 is a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

R_2 is either hydrogen or a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

Z is either nothing, choline, phosphate, inositol, or glycerol;

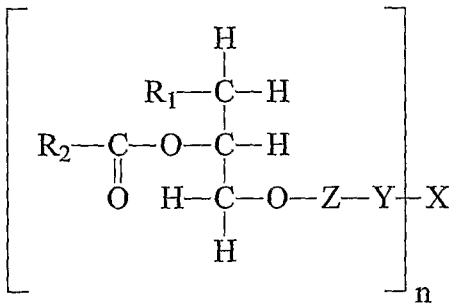
Y is either nothing or a spacer group ranging in length from 2 to 30 atoms;

X is a physiologically acceptable monomer, dimer, oligomer or polymer; and

n is a number from 1 to 1000;

wherein any bond between the glycerolipid, Z, Y and X is either an amide or an esteric bond.

[00165]In another embodiment, the compound according to the invention is represented by the structure of the general formula (XVI):



(XVI)

wherein

R_1 is either hydrogen or a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

R_2 is a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

Z is either nothing, choline, phosphate, inositol, or glycerol;

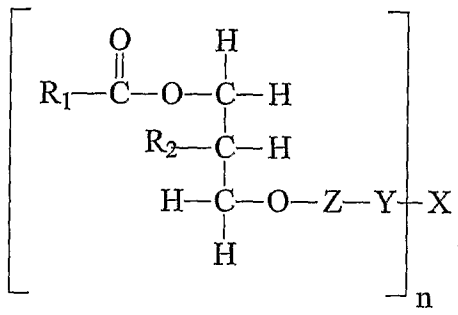
Y is either nothing or a spacer group ranging in length from 2 to 30 atoms;

X is a physiologically acceptable monomer, dimer, oligomer or polymer; and

n is a number from 1 to 1000;

wherein any bond between the lipid, Z, Y and X is either an amide or an esteric bond.

[00166]In another embodiment, the compound according to the invention is represented by the structure of the general formula (XVII):



(XVII)

wherein

R_1 is either hydrogen or a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

R_2 is a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

Z is either nothing, choline, phosphate, inositol, or glycerol;

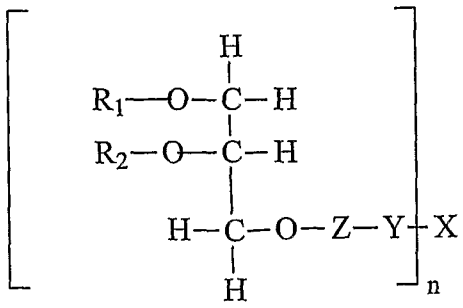
Y is either nothing or a spacer group ranging in length from 2 to 30 atoms;

X is a physiologically acceptable monomer, dimer, oligomer or polymer; and

n is a number from 1 to 1000;

wherein any bond between the lipid, Z, Y and X is either an amide or an esteric bond.

[00167]In another embodiment, the compound according to the invention is represented by the structure of the general formula (XVIII):



(XVIII)

wherein

R_1 is either hydrogen or a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

R_2 is either hydrogen or a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

Z is either nothing, choline, phosphate, inositol, or glycerol;

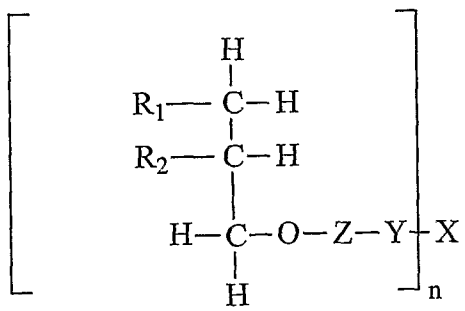
Y is either nothing or a spacer group ranging in length from 2 to 30 atoms;

X is a physiologically acceptable monomer, dimer, oligomer or polymer; and

n is a number from 1 to 1000;

wherein any bond between the lipid, Z, Y and X is either an amide or an esteric bond.

[00168]In another embodiment, the compound according to the invention is represented by the structure of the general formula (XIX):



(XIX)

wherein

R_1 is either hydrogen or a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

R_2 is either hydrogen or a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

Z is either nothing, choline, phosphate, inositol, or glycerol;

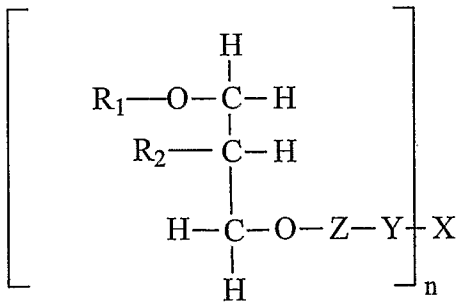
Y is either nothing or a spacer group ranging in length from 2 to 30 atoms;

X is a physiologically acceptable monomer, dimer, oligomer or polymer; and

n is a number from 1 to 1000;

wherein any bond between the lipid, Z, Y and X is either an amide or an esteric bond.

[00169]In another embodiment, the compound according to the invention is represented by the structure of the general formula (XX):



(XX)

wherein

R_1 is either hydrogen or a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

R_2 is either hydrogen or a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

Z is either nothing, choline, phosphate, inositol, or glycerol;

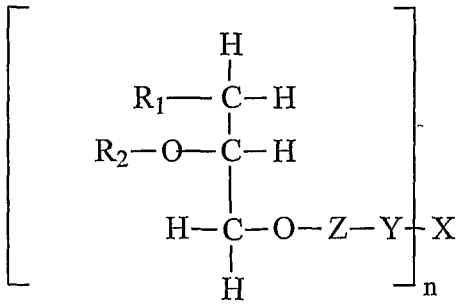
Y is either nothing or a spacer group ranging in length from 2 to 30 atoms;

X is a physiologically acceptable monomer, dimer, oligomer or polymer; and

n is a number from 1 to 1000;

wherein any bond between the lipid, Z, Y and X is either an amide or an esteric bond.

[00170]In another embodiment, the compound according to the invention is represented by the structure of the general formula (XXI):



(XXI)

wherein

$\mathbf{R_1}$ is either hydrogen or a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

$\mathbf{R_2}$ is either hydrogen or a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

Z is either nothing, choline, phosphate, inositol, or glycerol;

Y is either nothing or a spacer group ranging in length from 2 to 30 atoms;

X is a physiologically acceptable monomer, dimer, oligomer or polymer; and

n is a number from 1 to 1000;

wherein any bond between the lipid, Z, Y and X is either an amide or an esteric bond.

[00171]For any or all of the compounds represented by the structures of the general formulae: (A), (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (IXa), (IXb), (X), (XI), (XII), (XIII), (XIV), (XV), (XVI), (XVII), (XVIII), (XIX), (XX), (XXI), and (XXII) hereinabove: In one embodiment, X is a glycosaminoglycan.

[00172]In one embodiment of the invention, the glycosaminoglycan may be, *inter alia*, hyaluronic acid, heparin, heparan sulfate, chondroitin sulfate, keratin, keratan sulfate, dermatan sulfate or a derivative thereof.

[00173]In another embodiment, the glycosaminoglycan is a polymer of disaccharide units. In another embodiment, the number of the disaccharide units in the polymer is m. In another embodiment, m is a number from 2-10,000. In another embodiment, m is a number from 2-500. In another embodiment, m is a number from 2-1000. In another embodiment, m is a number from 50-500. In another embodiment, m is a number from 2-2000. In another embodiment, m is a number from 500-2000. In another embodiment, m is a number from 1000-2000. In another embodiment, m is a number from 2000-5000. In another embodiment, m is a number from 3000-7000. In another embodiment, m is a number from 5000-10,000. In another embodiment, a disaccharide unit of a glycosaminoglycan may be bound to one lipid or phospholipid moiety. In another embodiment, each disaccharide unit of the glycosaminoglycan may be bound to zero or one lipid or phospholipid moieties. In another embodiment, the lipid or phospholipid moieties are bound to the -COOH group of the disaccharide unit. In another embodiment, the bond between the lipid or phospholipid moiety and the disaccharide unit is an amide bond.

[00174]In another embodiment, the chondroitin sulfate may be, *inter alia*, chondroitin-6-sulfate, chondroitin-4-sulfate or a derivative thereof.

[00175]In one embodiment of the invention **Y** is nothing. Non limiting examples of suitable divalent groups forming the optional bridging group (spacer) **Y**, according to embodiments of the invention, are straight or branched chain alkylene, e.g., of 2 or more, preferably 4 to 30 carbon atoms, —CO—alkylene—CO, —NH—alkylene—NH—, —CO—alkylene—NH—, —NH—alkylene—NHCO—alkylene—NH—, an amino acid, cycloalkylene, wherein alkylene in each instance, is straight or branched chain and contains 2 or more, preferably 2 to 30 atoms in the chain, -(-O-$CH(CH_3)CH_2$-)$_x$- wherein ***x*** is an integer of 1 or more.

[00176]According to embodiments of the invention, in addition to the traditional phospholipid structure, related derivatives for use in this invention are phospholipids modified at the C1 or C2 position to contain an ether or alkyl bond instead of an ester bond. In one embodiment of the invention, the alkyl phospholipid derivatives and ether phospholipid derivatives are exemplified herein.

[00177]In one embodiment of the invention, the sugar rings of the glycosaminoglycan are intact. In another embodiment, intact refers to closed. In another embodiment, intact refers to natural. In another embodiment, intact refers to unbroken.

[00178]In one embodiment of the invention, the structure of the lipid or phospholipid in any compound according to the invention is intact. In another embodiment, the natural structure of the lipid or phospholipids in any compound according to the invention is maintained.

[00179]In one embodiment, the compounds for use in the present invention are biodegradable.

[00180]In one embodiment, the compound according to the invention is phosphatidylethanolamine bound to aspirin. In one embodiment, the compound according to the invention is phosphatidylethanolamine bound to glutarate.

[00181]In some embodiments, the compounds for use are as listed in Table 1 below.

Table 1.

Phospholipid	**Spacer**	**Polymer (m.w.)**	**Compound**
PE	None	Hyaluronic acid (2-2000 kDa)	XXII
Dimyristoyl-PE	None	Hyaluronic acid	XXIII
PE	None	Heparin (0.5-110 kDa)	XXIV

PE	None	Chondroitin sulfate A	XXV
PE	None	Carboxymethylcellulose (20-500 kDa)	XXVI
PE	Dicarboxylic acid + Diamine	Polygeline (haemaccel) (4-40 kDa)	XXVII
PE	None	Hydroxyethylstarch	XXVIII
PE	Dicarboxylic acid + Diamine	Dextran (1-2,000 kDa)	XXIX
PE	None	Aspirin	XXX
PE	Carboxyl amino group	Hyaluronic acid (2-2000 kDa)	XXXI
PE	Dicarboxyl group	Hyaluronic acid (2-2000 kDa)	XXXII
PE	Dipalmitoic acid	Hyaluronic acid (2-2000 kDa)	XXXIII
PE	Carboxyl amino group	Heparin (0.5-110 kDa)	XXXIV
PE	Dicarboxyl group	Heparin (0.5-110 kDa)	XXXV
PE	Carboxyl amino group	Chondroitin sulfate A	XXXVI
PE	Dicarboxyl group	Chondroitin sulfate A	XXXVII
PE	Carboxyl amino group	Carboxymethylcellulose (20-500 kDa)	XXXVIII
PE	Dicarboxyl group	Carboxymethylcellulose (20-500 kDa)	XXXIX
PE	None	Polygeline (haemaccel) (4-40 kDa)	XL

PE	Carboxyl amino group	Polygeline (haemaccel) (4-40 kDa)	XLI
PE	Dicarboxyl group	Polygeline (haemaccel) (4-40 kDa)	XLII
PE	Carboxyl amino group	Hydroxyethylstarch	XLIII
PE	Dicarboxyl group	Hydroxyethylstarch	XLIV
PE	None	Dextran (1-2,000 kDa)	XLV
PE	Carboxyl amino group	Dextran (1-2,000 kDa)	XLVI
PE	Dicarboxyl group	Dextran (1-2,000 kDa)	XLVII
PE	Carboxyl amino group	Aspirin	XLVIII
PE	Dicarboxyl group	Aspirin	XLIX
PE	None	Albumin	L
PE	None	Alginate (2-2000kDa)	LI
PE	None	Polyaminoacid	LII
PE	None	Polyethylene glycol	LIII
PE	None	Lactobionic acid	LIV
PE	None	Acetylsalicylate	LV
PE	None	Cholesteryl-hemmisuccinate	LVI
PE	None	Maltose	LVII
PE	None	Cholic acid	LVIII
PE	None	Chondroitin sulfates	LIX

PE	None	Polycarboxylated polyethylene glycol	LX
Dipalmitoyl-PE	None	Hyaluronic acid	LXI
Dipalmitoyl-PE	None	Heparin	LXII
Dipalmitoyl-PE	None	Chondroitin sulfate A	LXIII
Dipalmitoyl-PE	None	Carboxymethylcellulose	LXIV
Dipalmitoyl-PE	None	Polygeline (haemaccel)	LXV
Dipalmitoyl-PE	None	Hydroxyethylstarch	LXVI
Dipalmitoyl-PE	None	Dextran	LXVII
Dipalmitoyl-PE	None	Aspirin	LXVIII
Dimyristoyl-PE	None	Heparin	LXVIX
Dimyristoyl-PE	None	Chondroitin sulfate A	LXX
Dimyristoyl-PE	None	Carboxymethylcellulose	LXXI
Dimyristoyl-PE	None	Polygeline (haemaccel)	LXXII
Dimyristoyl-PE	None	Hydroxyethylstarch	LXXIII
Dimyristoyl-PE	None	Dextran	LXXIV
Dimyristoyl-PE	None	Aspirin	LXXV
PS	None	Hyaluronic acid	LXXVI
PS	None	Heparin	LXXVII
PS	None	Polygeline (haemaccel)	LXXVIII
PC	None	Hyaluronic acid	LXXIX
PC	None	Heparin	LXXX
PC	None	Polygeline (haemaccel)	LXXXI
PI	None	Hyaluronic acid	LXXXII
PI	None	Heparin	LXXXIII
PI	None	Polygeline (haemaccel)	LXXXIV
PG	None	Hyaluronic acid	LXXXV
PG	None	Heparin	LXXXVI
PG	None	Polygeline (haemaccel)	LXXXVII

[00182]In one embodiment of the invention, the compounds administered are Compound XXII, Compound XXIII, Compound XXIV, Compound XXV, Compound XXVI, Compound XXVII, Compound XXVIII, Compound XXIX and Compound XXX, or pharmaceutically acceptable salts thereof, in combination with a physiologically acceptable carrier or solvent. According to embodiments of the invention, these polymers, when chosen as the conjugated moiety, may vary in molecular weights from 200 to 2,000,000 Daltons. In one embodiment of the invention, the molecular weight of the polymer as referred to herein is from 200 to 1000 Daltons. In another embodiment, the molecular weight of the polymer as referred to herein is from 200 to 1000 Daltons. In another embodiment, the molecular weight of the polymer as referred to herein is from 1000 to 5000 Daltons. In another embodiment, the molecular weight of the polymer as referred to herein is from 5000 to 10,000 Daltons. In another embodiment, the molecular weight of the polymer as referred to herein is from 10,000 to 20,000 Daltons. In another embodiment, the molecular weight of the polymer as referred to herein is from 10,000 to 50,000 Daltons. In another embodiment, the molecular weight of the polymer as referred to herein is from 20,000 to 70,000 Daltons. In another embodiment, the molecular weight of the polymer as referred to herein is from 50,000 to 100,000 Daltons. In another embodiment, the molecular weight of the polymer as referred to herein is from 100,000 to 200,000 Daltons. In another embodiment, the molecular weight of the polymer as referred to herein is from 200,000 to 500,000 Daltons. In another embodiment, the molecular weight of the polymer as referred to herein is from 200,000 to 1,000,000 Daltons. In another embodiment, the molecular weight of the polymer as referred to herein is from 500,000 to 1,000,000 Daltons. In another embodiment, the molecular weight of the polymer as referred to herein is from 1,000,000 to 2,000,000 Daltons. Various molecular weight species have been shown to have the desired biological efficacy, as shown in the section below.

[00183]In one embodiment of this invention, low molecular weight phosphatidylethanolamine (PE)-conjugates are defined hereinabove as the compounds of formula (I) wherein:

R_1 is a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

R_2 is a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

Y is either nothing or a spacer group ranging in length from 2 to 30 atoms;

X is a mono- or disaccharide, carboxylated disaccharide, mono- or dicarboxylic acids, a salicylate, salicylic acid, aspirin, lactobionic acid, maltose, an amino acid, glycine, acetic acid, butyric acid, dicarboxylic acid, glutaric acid, succinic acid, fatty acid, dodecanoic acid, didodecanoic acid, bile acid, cholic acid, cholesterylhemmisuccinate, a di- or tripeptide, an oligopeptide, a trisachariде, or a di- or trisaccharide monomer unit of heparin, heparan sulfate, keratin, keratan sulfate, chondroitin, chondroitin-6-sulfate, chondroitin-4-sulfate, dermatin, dermatan sulfate, dextran, or hyaluronic acid; and

n is the number of lipid moiety molecules bound to a molecule of X wherein n is a number from 1 to 1000.

[00184]In one embodiment of this invention, low molecular weight phosphatidylserine (PS)-conjugates are defined hereinabove as the compounds of formula (II) wherein:

R_1 is a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

R_2 is a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

Y is either nothing or a spacer group ranging in length from 2 to 30 atoms;

X is a mono- or disaccharide, carboxylated disaccharide, mono- or dicarboxylic acids, a salicylate, salicylic acid, aspirin, lactobionic acid, maltose, an amino acid, glycine, acetic acid, butyric acid, dicarboxylic acid, glutaric acid, succinic acid, fatty acid, dodecanoic acid, didodecanoic acid, bile acid, cholic acid, cholesterylhemmisuccinate, a di- or

tripeptide, an oligopeptide, a trisaccharide, or a di- or trisaccharide monomer unit of heparin, heparan sulfate, keratin, keratan sulfate, chondroitin, chondroitin-6-sulfate, chondroitin-4-sulfate, dermatin, dermatan sulfate, dextran, or hyaluronic acid; and

n is the number of lipid moiety molecules bound to a molecule of X wherein n is a number from 1 to 1000.

[00185]In one embodiment of this invention, Phosphatidylcholine (PC), Phosphatidylinositol (PI), and Phosphatidylglycerol (PG) conjugates are hereinabove defined as the compounds of formula (III) wherein:

$\mathbf{R_1}$ is a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

$\mathbf{R_2}$ is a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

Z is either nothing, inositol, choline, or glycerol;

Y is either nothing or a spacer group ranging in length from 2 to 30 atoms;

X is a mono- or disaccharide, carboxylated disaccharide, mono- or dicarboxylic acids, a salicylate, salicylic acid, aspirin, lactobionic acid, maltose, an amino acid, glycine, acetic acid, butyric acid, dicarboxylic acid, glutaric acid, succinic acid, fatty acid, dodecanoic acid, didodecanoic acid, bile acid, cholic acid, cholesterylhemmisuccinate, a di- or tripeptide, an oligopeptide, a trisaccharide, or a di- or trisaccharide monomer unit of heparin, heparan sulfate, keratin, keratan sulfate, chondroitin, chondroitin-6-sulfate, chondroitin-4-sulfate, dermatin, dermatan sulfate, dextran, or hyaluronic acid; and

n is the number of lipid moiety molecules bound to a molecule of X wherein n is a number from 1 to 1000.

[00186]Examples of suitable divalent groups forming the optional bridging group **Y** are straight- or branched –chain alkylene, e.g., of 2 or more, preferably 4 to 18 carbon atoms,

—CO—alkylene—CO, —NH—alkylene—NH—, —CO—alkylene—NH—, cycloalkylene, wherein alkylene in each instance, is straight or branched chain and contains 2 or more, preferably 2 to 18 carbon atoms in the chain, —(—O—$CH(CH_3)CH_2$—)$_x$— wherein ***x*** is an integer of 1 or more.

[00187]In another embodiment, in addition to the traditional phospholipid structure, related derivatives for use in this invention are phospholipids modified at the C1 or C2 position to contain an ether or alkyl bond instead of an ester bond. These derivatives are exemplified hereinabove by the general formulae (VIII) and (IX) wherein:

R_1 is a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

R_2 is a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

Z is either nothing, ethanolamine, serine, inositol, choline, or glycerol;

Y is either nothing or a spacer group ranging in length from 2 to 30 atoms;

X is a mono- or disaccharide, carboxylated disaccharide, mono- or dicarboxylic acids, a salicylate, salicylic acid, aspirin, lactobionic acid, maltose, an amino acid, glycine, acetic acid, butyric acid, dicarboxylic acid, glutaric acid, succinic acid, fatty acid, dodecanoic acid, didodecanoic acid, bile acid, cholic acid, cholesterylhemmisuccinate, a di- or tripeptide, an oligopeptide, a trisaccharide, or a di- or trisaccharide monomer unit of heparin, heparan sulfate, keratin, keratan sulfate, chondroitin, chondroitin-6-sulfate, chondroitin-4-sulfate, dermatin, dermatan sulfate, dextran, or hyaluronic acid; and

n is the number of lipid moiety molecules bound to a molecule of X wherein n is a number from 1 to 1000.

[00188]In another embodiment, related low molecular weight derivatives for use in this invention are exemplified hereinabove by the general formulae (X), (XI) and (XII) wherein:

R_1 is a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

R_2 is a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

Z is either nothing, ethanolamine, serine, inositol, choline, or glycerol;

Y is either nothing or a spacer group ranging in length from 2 to 30 atoms;

X is a mono- or disaccharide, carboxylated disaccharide, mono- or dicarboxylic acids, a salicylate, salicylic acid, aspirin, lactobionic acid, maltose, an amino acid, glycine, acetic acid, butyric acid, dicarboxylic acid, glutaric acid, succinic acid, fatty acid, dodecanoic acid, didodecanoic acid, bile acid, cholic acid, cholesterylhemmisuccinate, a di- or tripeptide, an oligopeptide, a trisaccharide, or a di- or trisaccharide monomer unit of heparin, heparan sulfate, keratin, keratan sulfate, chondroitin, chondroitin-6-sulfate, chondroitin-4-sulfate, dermatin, dermatan sulfate, dextran, or hyaluronic acid; and

n is the number of lipid moiety molecules bound to a molecule of X wherein n is a number from 1 to 1000.

[00189]In another embodiment, related low molecular weight derivatives for use in this invention are exemplified hereinabove by the general formulae (XIII) wherein:

R_1 is a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

R_2 is a linear, saturated, mono-unsaturated, or poly-unsaturated, alkyl chain ranging in length from 2 to 30 carbon atoms;

Z is either nothing, choline, phosphate, inositol, or glycerol;

Y is either nothing or a spacer group ranging in length from 2 to 30 atoms;

X is a mono- or disaccharide, carboxylated disaccharide, mono- or dicarboxylic acids, a salicylate, salicylic acid, aspirin, lactobionic acid, maltose, an amino acid, glycine, acetic acid, butyric acid, dicarboxylic acid, glutaric acid, succinic acid, fatty acid, dodecanoic acid, didodecanoic acid, bile acid, cholic acid, cholesterylhemmisuccinate, a di- or tripeptide, an oligopeptide, a trisaccharide, or a di- or trisaccharide monomer unit of heparin, heparan sulfate, keratin, keratan sulfate, chondroitin, chondroitin-6-sulfate, chondroitin-4-sulfate, dermatin, dermatan sulfate, dextran, or hyaluronic acid; and

n is the number of lipid moiety molecules bound to a molecule of X wherein n is a number from 1 to 1000.

[00190]In one embodiment of the invention, x is covalently conjugated to a lipid. In another embodiment, x is covalently conjugated to a lipid via an amide bond. In another embodiment, x is covalently conjugated to a lipid via an esteric bond. In another embodiment, the lipid is phosphatidylethanolamine. In another embodiment, the GAG may be, *inter alia*, chondroitin sulfate. In another embodiment, the GAG may be, *inter alia*, heparin. In another embodiment, the GAG may be, *inter alia*, hyaluronic acid. In another embodiment, the conjugate is biodegradable.

[00191]In one embodiment, the invention provides glycosaminoglycan (GAG) compounds covalently conjugated to a lipid to obtain a compound having preferred therapeutic properties. In another embodiment, the GAG compound is covalently conjugated to a lipid via an amide bond. In another embodiment, the GAG compound is covalently conjugated to a lipid via an esteric bond. In another embodiment, the lipid may be, *inter alia*, phosphatidylethanolamine. In another embodiment, the GAG may be, *inter alia*, chondroitin sulfate. In another embodiment, the GAG may be, *inter alia*, heparin. In another embodiment, the GAG may be, *inter alia*, hyaluronic acid. In another embodiment, the conjugate is biodegradable.

[00192] Cell surface GAGs play a key role in protecting cells from diverse damaging agents and processes, such as reactive oxygen species and free radicals, endotoxins, cytokines, invasion promoting enzymes, and agents that induce and/or facilitate

degradation of extracellular matrix and basal membrane, cell invasiveness, white cell extravasation and infiltration, chemotaxis, and others. In addition, cell surface GAGs protect cells from bacterial, viral and parasitic infection, and their stripping exposes the cell to interaction and subsequent internalization of the microorganism. Enrichment of cell surface GAGs would thus assist in protection of the cell from injurious processes. Thus, in one embodiment of the invention, PLA2 inhibitors are conjugated to GAGs or GAG-mimicking molecules. In another embodiment, these Lipid-conjugates provide wide-range protection from diverse injurious processes, and are effective in amelioration of diseases that requires cell protection from injurious biochemical mediators.

[00193]In another embodiment, a GAG-mimicking molecule may be, *inter alia*, a negatively charged molecule. In another embodiment, a GAG-mimicking molecule may be, *inter alia*, a salicylate derivative. In another embodiment, a GAG-mimicking molecule may be, *inter alia*, a dicarboxylic acid.

[00194]In another embodiment, the invention provides a pharmaceutical composition for treating a subject suffering from a pathogenic effect, including a lipid or phospholipid moiety bonded to a physiologically acceptable monomer, dimer, oligomer, or polymer; and a pharmaceutically acceptable carrier or excipient.

[00195]In another embodiment, the invention provides a pharmaceutical composition for treating a subject suffering from a viral infection, including a lipid or phospholipid moiety bonded to a physiologically acceptable monomer, dimer, oligomer, or polymer; and a pharmaceutically acceptable carrier or excipient.

[00196]In another embodiment, the invention provides a pharmaceutical composition for treating a subject suffering from an influenza infection, including a lipid or phospholipid moiety bonded to a physiologically acceptable monomer, dimer, oligomer, or polymer; and a pharmaceutically acceptable carrier or excipient.

[00197]In another embodiment, the invention provides a pharmaceutical composition for treating a subject suffering from a poxvirus infection, including a lipid or phospholipid

moiety bonded to a physiologically acceptable monomer, dimer, oligomer, or polymer; and a pharmaceutically acceptable carrier or excipient.

[00198]In another embodiment, the invention provides a pharmaceutical composition for treating a subject suffering from a chordopoxvirinae infection, including a lipid or phospholipid moiety bonded to a physiologically acceptable monomer, dimer, oligomer, or polymer; and a pharmaceutically acceptable carrier or excipient.

[00199]In another embodiment, the invention provides a pharmaceutical composition for treating a subject suffering from a vaccinia infection, including a lipid or phospholipid moiety bonded to a physiologically acceptable monomer, dimer, oligomer, or polymer; and a pharmaceutically acceptable carrier or excipient.

[00200]In another embodiment, the invention provides a pharmaceutical composition for treating a subject suffering from a smallpox infection, including a lipid or phospholipid moiety bonded to a physiologically acceptable monomer, dimer, oligomer, or polymer; and a pharmaceutically acceptable carrier or excipient.

[00201]In another embodiment, the invention provides a pharmaceutical composition for treating a subject suffering from a bacterial infection, including a lipid or phospholipid moiety bonded to a physiologically acceptable monomer, dimer, oligomer, or polymer; and a pharmaceutically acceptable carrier or excipient.

[00202]In another embodiment, the invention provides a pharmaceutical composition for treating a subject suffering from a pathogenic effect, including any one of the compounds for use in the present invention or any combination thereof; and a pharmaceutically acceptable carrier or excipient. In another embodiment, the compounds for use in the present invention include, *inter alia*, the compounds represented by the structures of the general formulae as described hereinbelow: (A), (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (IXa), (IXb), (X), (XI), (XII), (XIII), (XIV), (XV), (XVI), (XVII), (XVIII), (XIX), (XX), (XXI), (XXII), or any combination thereof.

[00203]In another embodiment, the invention provides a pharmaceutical composition for treating a subject suffering from a viral infection, including any one of the compounds for use in the present invention or any combination thereof; and a pharmaceutically acceptable carrier or excipient. In another embodiment, the compounds for use in the present invention include, *inter alia*, the compounds represented by the structures of the general formulae as described hereinbelow: (A), (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (IXa), (IXb), (X), (XI), (XII), (XIII), (XIV), (XV), (XVI), (XVII), (XVIII), (XIX), (XX), (XXI), (XXII) or any combination thereof.

[00204]In another embodiment, the invention provides a pharmaceutical composition for treating a subject suffering from an influenza infection, including any one of the compounds for use in the present invention or any combination thereof; and a pharmaceutically acceptable carrier or excipient. In another embodiment, the compounds for use in the present invention include, *inter alia*, the compounds represented by the structures of the general formulae as described hereinbelow: (A), (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (IXa), (IXb), (X), (XI), (XII), (XIII), (XIV), (XV), (XVI), (XVII), (XVIII), (XIX), (XX), (XXI), (XXII) or any combination thereof.

[00205]In another embodiment, the invention provides a pharmaceutical composition for treating a subject suffering from a poxvirus infection, including any one of the compounds for use in the present invention or any combination thereof; and a pharmaceutically acceptable carrier or excipient. In another embodiment, the compounds for use in the present invention include, *inter alia*, the compounds represented by the structures of the general formulae as described hereinbelow: (A), (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (IXa), (IXb), (X), (XI), (XII), (XIII), (XIV), (XV), (XVI), (XVII), (XVIII), (XIX), (XX), (XXI), (XXII) or any combination thereof.

[00206]In another embodiment, the invention provides a pharmaceutical composition for treating a subject suffering from a chordopoxvirinae infection, including any one of the compounds for use in the present invention or any combination thereof; and a pharmaceutically acceptable carrier or excipient. In another embodiment, the compounds for use in the present invention include, *inter alia*, the compounds represented by the

structures of the general formulae: as described hereinbelow (A), (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (IXa), (IXb), (X), (XI), (XII), (XIII), (XIV), (XV), (XVI), (XVII), (XVIII), (XIX), (XX), (XXI), (XXII) or any combination thereof.

[00207]In another embodiment, the invention provides a pharmaceutical composition for treating a subject suffering from a vaccinia infection, including any one of the compounds for use in the present invention or any combination thereof; and a pharmaceutically acceptable carrier or excipient. In another embodiment, the compounds for use in the present invention include, *inter alia*, the compounds represented by the structures of the general formulae as described hereinbelow: (A), (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (IXa), (IXb), (X), (XI), (XII), (XIII), (XIV), (XV), (XVI), (XVII), (XVIII), (XIX), (XX), (XXI), (XXII) or any combination thereof.

[00208]In another embodiment, the invention provides a pharmaceutical composition for treating a subject suffering from a smallpox infection, including any one of the compounds for use in the present invention or any combination thereof; and a pharmaceutically acceptable carrier or excipient. In another embodiment, the compounds for use in the present invention include, *inter alia*, the compounds represented by the structures of the general formulae as described hereinbelow: (A), (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (IXa), (IXb), (X), (XI), (XII), (XIII), (XIV), (XV), (XVI), (XVII), (XVIII), (XIX), (XX), (XXI), (XXII) or any combination thereof.

[00209]In another embodiment, the invention provides a pharmaceutical composition for treating a subject suffering from a bacterial infection, including any one of the compounds for use in the present invention or any combination thereof; and a pharmaceutically acceptable carrier or excipient. In another embodiment, the compounds for use in the present invention include, *inter alia*, the compounds represented by the structures of the general formulae as described hereinbelow: (A), (I), (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (IXa), (IXb), (X), (XI), (XII), (XIII), (XIV), (XV), (XVI), (XVII), (XVIII), (XIX), (XX), (XXI), (XXII) or any combination thereof.

Preparation of Compounds for Use in the Present Invention

[00210]The preparation of some high molecular weight Lipid-conjugates is the subject of United States Patent 5,064,817, which is incorporated herein by reference. These synthetic methods are considered to be applicable as well to the preparation of low molecular weight Lipid-conjugates, i.e. Lipid-conjugates comprising monomers and dimers as the conjugated moiety, with appropriate modifications in the procedure as would be readily evident to one skilled in the art. The preparation of some low molecular weight Lipid-conjugates may be conducted using methods well known in the art or as described in United States Patent Application 10/952,496, which is incorporated herein by reference.

[00211]Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limiting the remainder of the disclosure in any way whatsoever.

EXAMPLES

The abbreviations used in the examples below are:

PE = phosphatidyl-ethanolamine

HA= hyaluronic acid

Cpd = Compound

Compound XXII = dipalmitoyl-PE conjugated to HA

Compound XXIII = dimyristoyl-phosphatidyl-ethanolamine linked to HA

Compound XXIV = PE conjugated to heparin

CSA = chondroitin sulfate A

Compound XXV = PE conjugated to CSA

CMC = carboxymethyl cellulose

Compound XXVI = PE conjugated to CMC

Compound XXVII = PE conjugated to Polygeline (haemaccel)

The compounds used in the examples below were prepared as described in United States Patent Application 10/952,496, which is incorporated herein by reference.

EXAMPLE 1: Viral Infection

[00212]The Lipid-conjugates are effective in the prophylaxis and treatment of viral infection, particularly infections due to human influenza virus and vaccinia virus. This is demonstrated for human influenza virus in Experiment 1.1-1.2, and for vaccinia in Experiment 1.3 below.

[00213]Viral infection is the cause of a number of human and animal diseases throughout the world. The process of viral infection comprises several stages, including attachment, penetration, uncoating, replication, maturation, release and reinfection. In order to assess the ability of Lipid-conjugates to prevent viral infection, human cell lines were incubated with a preparation of a viral agent, and the ability of the virus to infect cells is compared in the presence and absence of Lipid-conjugate.

[00214]Experiment 1.1: The effect of Lipid-conjugate treatment on human influenza virus infection *in vitro*.

[00215]**Virus and cell lines.** Each virus was obtained from the source described in Table 1.1. Kidney cell lines were obtained from American Type Culture Collection (ATCC). The cells were grown in minimal essential medium (Gibco-BRL, Gaithersburg, Md.) supplemented with 0.1% $NaHCO_3$ and 5 to 9% fetal bovine serum (HyClone Laboratories, Logan, Utah). When performing antiviral assays, serum was reduced to 2%

and 50 μg gentamicin (Sigma Chemical Company, St. Louis, MO) per ml was added to the medium

Table 1.1: Description of viruses used in a screen of some Lipid-conjugates

Virus	*Strain*	*Source*	*Cell line*
Influenza type A	A/New Caledonia/20/99 (H1N1)	Center for Disease Control and Prevention [CDC]	Madin Darby canine kidney (MDCK) cells
	A/Panama/2007/99 (H3N2)	CDC	Madin Darby canine kidney (MDCK) cells
Influenza type B	B/Hong Kong/330/02	CDC	Madin Darby canine kidney (MDCK) cells
Pichinde virus	An 4763	Dr. J. D. Gangemi, Univ. of South Carolina School of Medicine, Columbia, SC	African green monkey kidney (BS-C-1) cells
Punta Toro virus	Adames	U. S. Army Medical Research Institute for Infectious Diseases, Fort	Rhesus monkey kidney (LLC-MK2) cells

		Detrick, Frederick, MD	
Respiratory syncytial virus	A2	ATCC	African green monkey kidney (MA-104) cells

1. Inhibition of Viral Cytopathic Effect (CPE)

[00216] *A. Visual Observation*

[00217]A viral CPE assay was performed as described (Barnard DL et al. Antivir Chem Chemother. 2001 Jul;12(4):241-250).

[00218]Compounds were evaluated using four log10 dilutions of each test compound (e.g., 1000, 100, 10, 1 μg/ml) (Tables 1.2 and 1.3) with an additional concentration of 2000 μg/ml for some experiments (Tables 1.4 and 1.5). Viruses (Influenza type A Strain H1N1, Influenza type A Strain H3N2, Influenza type B, Pichinde virus, Punta Toro virus, and Respiratory syncytial virus) were used at a multiplicity of infection (MOI) of 0.001 to 0.010. The MOIs used were virus dependent and chosen for each strain such that 100% of the cells in the virus controls showed cytopathic effects (CPE) within 5 to 7 days. Cell were grown to an 18 h monolayer (80-100% confluent) in 96-well tissue culture plates and were incubated with various concentrations of each compound as described above. Within 5 minutes of compound incubation, a volume of virus equal to that of the compound was added to the cells. The plates were then sealed and incubated at 37°C for approximately 72 to 120 hr until the cells in the virus control wells showed complete viral CPE as observed by light microscopy.

[00219]Each concentration of drug was assayed for virus inhibition in triplicate. Three wells were set aside as uninfected, untreated cell controls per test and three wells per test compound receive untreated, virus-infected cells and represented positive controls for

virus replication. Ribavirin, used as a positive control drug, was evaluated in parallel with compounds for each virus.

[00220]The 50% effective concentrations (EC_{50}) were calculated by regression analysis of the means of the CPE ratings as compared to untreated, uninfected controls for each concentration. Cells were rated based on changes in enlargement, granularity, ragged edges, filmy appearance, rounding, detachment from the surface of the well, and other changes. Morphological changes results from cytotoxicity of a compound were graded on a scale of 0-5; 0 = no toxicity, 1 = partial toxicity–slight, 2 = partial toxicity, 3 = partial toxicity–heavy, 4 = partial toxicity–very heavy, and 5 = complete cytotoxicity, based on the degree of cytotoxicity observed. The CPE results were then quantified spectrophotometrically by neutral red (NR) uptake assay (see below).

[00221] *B. Increase in Neutral Red (NR) Dye Uptake*

[00222]A Neutral Red Dye Uptake assay was performed as described previously (McManus, NH, Appl. Environment. Microbiol. 31:35-38, 1976) to verify the inhibitory activity and cytotoxicity that was observed in the CPE inhibition assay. Briefly, medium was removed from each well of a plate scored for CPE from a CPE inhibition assay, 0.034% NR in Sörenson's citrate buffer (pH 4.0) was added to each well of the plate and the plate incubated for 2 h at 37°C in the dark. The NR solution was removed from the wells. After rinsing and aspirating to dryness, the remaining dye was extracted for 30 min, at room temperature in the dark, from the cells using absolute ethanol buffered with Sörenson's citrate buffer. The percentage of NR uptake, indicating viable cells, was read on a microplate autoreader (Bio-Tek EL 1309; Bio-Tek Instruments,Winooski, Vt., USA) at dual wavelengths of 405 and 540 nm. The difference between the two readings were calculated to eliminate background. Absorbance values were expressed as percentages of untreated controls, and EC50 values were calculated as described above.

2. Cytotoxicity Assay

[00223] *A. Visual Observation*

[00224]Uninfected cells were treated with each concentration of test compound in duplicate and run in parallel with the infected, treated wells in the CPE inhibition tests described above. The toxicity control cells (uninfected and treated) were examined under a light microscope for changes in cell appearance compared to control cells (uninfected, untreated) on the same plate as described above. The 50% cell inhibitory (cytotoxic) concentrations (IC_{50}) were calculated by regression analysis.

[00225] *B. Neutral Red Uptake*

[00226]The toxicity control cells (uninfected and treated) described in the previous section were further examined for neutral red dye uptake compared to control cells (uninfected, untreated) on the same plate. Neutral red was added to the toxicity control wells, and the degree of color intensity was determined spectrophotometrically as described above. A neutral red IC50 (NR IC50) was subsequently determined. Absorbance values were expressed as percentages of uninfected, untreated controls, and IC_{50} values were calculated as described above.

3. Data analysis

[00227]Each test compound's antiviral activity was expressed as a selectivity index (SI), which is the IC_{50} divided by the EC_{50}. Generally, an SI of 10 or greater is indicative of positive antiviral activity, although other factors, such as a low SI for the positive control, are also taken into consideration.

[00228]Tables 1.2 and 1.3 demonstrate the capacity of the Lipid-conjugates evaluated at low concentration to prevent infection of target cells by influenza virus.

[00229]Nine compounds were evaluated for *in vitro* antiviral testing against influenza A (H1N1 strain) virus, influenza A (H3N2 strain) virus, influenza B virus, respiratory syncitial virus (RSV), Punta Toro virus, and Pichinde virus using various kidney cell lines described in Table 1.1. Two series of Lipid-conjugate dosages were used as described in the methods hereinabove.

[00230]Using a lower range of doses, Compound XXIV had significant anti-viral activity against influenza A (H1N1 strain) virus (Table 1.2). The EC50 vs this virus was 5 μg/ml by visual assay and 2.5 μg/ml by neutral red assay, with an IC50 (cytotoxicity) >100 μg/ml. Against the influenza A (H3N2 strain) virus, the EC50 was 35 μg/ml by visual assay and 45 μg/ml by neutral red assay with the same IC50 as above. Compound XXIV was also efficacious vs RSV, with an EC50 of 4 μg/ml using visual assay only, but was not active by neutral red assay. Compound XXIV did not display a virus inhibitory effect against Punta Toro virus at the concentrations tested.

[00231]Compound XXV was less active, with EC50 values vs the influenza A (H1N1 strain) virus of 50 μg/ml by visual assay and 35 μg/ml by neutral red assay and an IC50 >100 μg/ml (Table 1.3). This compound did not demonstrate a virus inhibitory effect against influenza A (H3N2 strain), influenza B, or RSV at the concentrations tested. Compound XXV did not display a virus inhibitory effect against Punta Toro virus.

TABLE 1.2: Antiviral activity of Compound XXIV (dipalmitoyl-phosphatidyl-ethanolamine conjugated to heparin) at low concentrations

Virus	**EC_{50} (?g/ml)**	**SI (IC_{50}/ EC_{50})**
Visual Observation Assay		
Punta Toro A	>100	0
Respiratory Syncytial A	4	**25**
Influenza A (H1N1 strain)	5	**20**
Influenza A (H3N2 strain)	35	2.9
Neutral Red Uptake Assay		

Punta Toro A	>100	0
Respiratory Syncytial A	>100	0
Influenza A (H1N1 strain)	2.5	**40**
Influenza A (H3N2 strain)	45	2.2

SI – selectivity index. Generally, an SI ≥ 10 is indicative of positive antiviral activity, although other factors such as a low SI for the positive control are also taken into consideration. IC_{50} for Compound XXIV was >100 ? g/ml for all viruses.

TABLE 1.3: Antiviral activity of Compound XXV (dipalmitoyl-phosphatidyl-ethanolamine (PE) conjugated to chondroitin-sulfate A) at low concentrations

Virus	**EC_{50} (? g/ml)**	**SI (IC_{50}/ EC_{50})**
Visual Observation Assay		
Punta Toro A	>100	0
Influenza A (H1N1 strain)	50	2
Neutral Red Uptake Assay		
Punta Toro A	>100	0
Influenza A (H1N1 strain)	35	2.9

SI – selectivity index. IC_{50} for Compound XXV was >100 ? g/ml for all viruses.

[00232]Using higher concentrations of Lipid-conjugates, the results demonstrate a strong effect of Compound XXIV (100) against infection with Influenza A virus H1N1 strain (Tables 1.4 and 1.5). In addition, Compound XXIII (170) and Compound XXIII (80)

showed antiviral activity against the H3N2 strain of Influenza A virus in the visual test but not the neutral red assay (Table 1.5).

[00233]**TABLE 1.4. Antiviral activity of Compound XXIV (dipalmitoyl-phosphatidyl-ethanolamine conjugated to heparin; MK-610) at high concentration**

Virus	**IC_{50} (?g/ml)**	**EC_{50} (?g/ml)**	**SI (IC_{50}/ EC_{50})**
Visual Observation Assay			
Influenza A (H1N1 strain)	35	400	**11**
Influenza A (H3N2 strain)	100	200	2
Influenza B	90	350	**3.9**
Neutral Red Uptake Assay			
Influenza A (H1N1 strain)	64	1000	**15.6**
Influenza A (H3N2 strain)	110	900	**8.2**
Influenza B	220	450	2

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TABLE 1.5. Antiviral activity of Lipid-Conjugates against Influenza A (H1N1 and H3N2 strains) and Influenza B viruses at high concentration.

	Influenza A (H1N1 strain)		**Influenza A (H3N2 strain)**		**Influenza B**	
Compound (phosphate content)	Visual	NR	Visual	NR	Visual	NR
Name						
Ribavirin	**22**	**25**	**56**	**36**	**22**	**19**
Compound XXIV (100)	**11**	**15.6**	2	8.2	3.9	2
Compound XXII (170)	3.6	0	**25**	0	10	0
Compound XXV (60)	2.5	0	0	0	0	0
Compound XXIII (80)	0	0	**10**	6.5	0	0
Compound XXV (230)	0	0	6.7	7.2	0	0
Compound XXII (85)	0	0	2.5	0	0	0
Compound XXIV (50)	0	0	0	0	0	0
Compound XXII (40)	0	0	0	0	0	0
Compound XXV (100)	0	0	0	0	0	0

SI – selectivity index (IC_{50}/ EC_{50}); Visual = *Visual Observation Assay*; NR = *Neutral Red Uptake Assay*

[00234]Experiment 1.2 demonstrates the effect of Lipid-conjugate treatment on human influenza virus infection *in vivo*. We use young adult (18-21 g) female BALB/c mice infected intranasally with either influenza A/NWS/33 (H1N1), A/PR8/34 (H1N1), A/New Caledonia/20/99 (H1N1), A/Victoria/3/75 (H3N2), A/Port Chalmers/1/73 (H3N2), B/Hong Kong/5/72, B/Lee/40, B/Sichuan/379/99, or A/Duck/MN/1525/81 (H5N1) virus at sufficient dose to render death in approximately 90% of the mice, with the mean day to death being 6-10 days. The animals are monitored for arterial oxygen saturation levels using a pulse oximeter on days 3 through 11 (the infection usually induces major declines in these levels by about day 9-10 due to lung consolidation). We also sacrifice mice on days 1, 3, 6, and 9 for assay of lung score, lung weight increase, and lung virus titer. We usually use 22 infected mice for each dosage of test compound, and 35 infected mice treated with placebo. Three uninfected mice are included as toxicity controls, these are treated in parallel to the above, and weight loss or gain is determined during the period of treatment. A group of normal controls are also run in parallel to ascertain their weight gain during the study as well as the normal arterial oxygen saturation levels. Some of these animals are also killed to determine normal lung parameters.

[00235]If the test compound is considered to be an immunomodulator, we would inject mice with the compound intraperitoneally every other day for a total of 4 treatments beginning 24 h prior to virus exposure. If the material is considered to be antiviral, a twice daily for 5 days treatment schedule is recommended, with therapy beginning 4 h pre-virus exposure. We generally try to select three dosages varying 2-fold or 1/2 log10 from each other, with the high dose being approximately the maximum tolerated dose.

[00236]Ribavirin is usually included at a single dose as a known positive control.

[00237]Experiment 1.3 demonstrates the effect of Lipid-conjugate treatment on vaccinia virus infection *in vitro*.

[00238]BS-C-1 cell monolayers ($3x10^6$ cells), in 3 cm diameter plastic dishes, were infected with a dilution of a crude stock of vaccinia virus (WR strain), to give a m.o.i. of

1 PFU per 10 cells. After adsorption for 1 hr, the cells were washed and 2 ml of Dulbecco's MEM, supplemented with 2% fetal calf serum, containing 1:10 dilution of the compound to be tested, were added. The cultures were incubated for 2 days at 37°C and then harvested. Control infected cultures that were not treated with the compounds, were harvested at 0 time and at 48 hr. The virus titer in all cultures was determined, after three cycles of freezing and thawing, by plaque assay in BS-C-1 cells.

[00239]Table 1.6 demonstrates the capacity of the Lipid-conjugates to prevent infection of target cells by vaccinia virus. Compounds XXII, XXIII, and XXV inhibited viral infection in culture by 62-99%.

TABLE 1.6: Antiviral activity of Lipid-Conjugates against Vaccinia virus

Time (PFU/culture) (hr)	Compound tested	Virus titer	% inhibition
0	-	less than 10^4	
48	-	$8.6x10^7$	0%
48	Compound XXII-40*	$3.3x10^6$	96.2%
48	Compound XXII-80*	$2.3x10^7$	73.3%
48	Compound XXIII	$7.7x10^4$	99.9%
48	Compound XXV	$3.2x10^7$	62.8%

*The number expresses the amount of nmoles lipid conjugated to 1 mg of polymer

[00240]These experiments demonstrate that administration of Lipid-conjugates is effective therapy in the prevention and treatment of viral infection, including influenza and vaccinia viruses.

[00241]It will be appreciated by persons skilled in the art that the present invention is not limited by what has been particularly shown and described herein above and that numerous modifications, all of which fall within the scope of the present invention, exist. Rather, the scope of the invention is defined by the claims which follow:

What we claim is:

1. Use of a lipid or phospholipid moiety bonded to a physiologically acceptable monomer, dimer, oligomer, or polymer, in the preparation of a pharmaceutical composition for suppressing, inhibiting, preventing, or treating infection with an influenza virus in a subject.

2. The use according to claim 1, wherein said phospholipid moiety is phosphatidylethanolamine and said physiologically acceptable monomer, dimer, oligomer, or polymer is a glycosaminoglycan.

3. The use according to claim 2, wherein said phosphatidylethanolamine is dipalmitoyl phosphatidylethanolamine and said glycosaminoglycan is heparin.

4. The use according to claim 2, wherein said phosphatidylethanolamine is dipalmitoyl phosphatidylethanolamine and said glycosaminoglycan is chondroitin sulfate.

5. The use according to claim 2, wherein said phosphatidylethanolamine is dipalmitoyl phosphatidylethanolamine and said glycosaminoglycan is hyaluronic acid.

6. The use according to claim 2, wherein said phosphatidylethanolamine is dimyristoyl phosphatidylethanolamine and said glycosaminoglycan is hyaluronic acid.

7. Use of a lipid or phospholipid moiety bonded to a physiologically acceptable monomer, dimer, oligomer, or polymer, in the preparation of a pharmaceutical composition for suppressing, inhibiting, preventing, or treating poxvirus infection in a subject.

8. The use according to claim 7, wherein said phospholipid moiety is phosphatidylethanolamine and said physiologically acceptable monomer, dimer, oligomer, or polymer is a glycosaminoglycan.

9. The use according to claim 8, wherein said phosphatidylethanolamine is dipalmitoyl phosphatidylethanolamine and said glycosaminoglycan is heparin.

10. The use according to claim 8, wherein said phosphatidylethanolamine is dipalmitoyl phosphatidylethanolamine and said glycosaminoglycan is chondroitin sulfate.

11. The use according to claim 8, wherein said phosphatidylethanolamine is dipalmitoyl phosphatidylethanolamine and said glycosaminoglycan is hyaluronic acid.

12. The use according to claim 8, wherein said phosphatidylethanolamine is dimyristoyl phosphatidylethanolamine and said glycosaminoglycan is hyaluronic acid.