The invention relates to glucan-comprising formulations as anti-viral compositions.
ANTIVIRAL APPLICATION OF COMPOSITIONS COMPRISING GLUCAN

FIELD OF THE INVENTION

This invention relates to methods and uses of oxidized cellulose as well as other glucans (polysaccharides) for antiviral applications.

BACKGROUND OF THE INVENTION

Contagious respiratory illnesses that are transmitted by airborne pathogen, such as viruses, are a major health risk because of their efficient and rapid ability to spread from one individual to another. The main way airborne respiratory pathogens are spread from person to person is in respiratory droplets of coughs and sneezes that are deposited in the respiratory system of a nearby individual. Thus, breathing infected air in a closed environment or coming in contact with infected surfaces are sufficient to cause pathogen infection. Airborne viral threats include, *inter alia*, the influenza infection (commonly known as "the flu") that causes mild to severe illness and only rarely leads to death on one hand, and the threat of an eruption of a deadly pandemic that can be caused by more lethal viruses such as H5N1 avian influenza and severe acute respiratory syndrome (SARS) on the other. Although less deadly, between 5% to 20% of the population in the United States are infected by influenza annually, of which more than 200,000 people are hospitalized and about 36,000 die. The most famous and lethal outbreak of a viral pandemic was called the Spanish flu pandemic (caused by type A influenza, H1N1 subtype), which lasted between 1918 and 1919. This violent viral subtype had an infection rate of 50% of the population that lead to the death of 2-20% of the infected individuals, killing in total between 50-100 million people. New violent strains of influenza are known to develop every couple of decades, as well as other kind of viruses that may develop violent strains that can infect humans. Thus, the threat of a lethal viral pandemic that can affect millions of individuals worldwide is an ongoing threat.

The most effective way of preventing an airway infection by airborne pathogen such as viruses is vaccination against a specific virus which allows the immune system to inhibit pathogen invasion into the body and significantly reduce the initiation of disease. However, as viruses evolve and change rapidly (especially influenza) and as
different viruses can mutate into lethal strains, this approach is only partially effective and only against a limited selection of virus-induced diseases.

Additional protective measures include preventing infected fluids from reaching the airway or any other sensitive mucosa, either by maintaining personal hygiene (hand wash, eliminating pathogen from surfaces, etc.) or by wearing protective equipment such as face masks, various respirators and other protective clothing (e.g. gloves and gowns).

Although these protective measures are effective to some extent, once dealing with a lethal pathogen there is a need to develop protective measures that are as efficient as possible in order to eliminate or minimize any danger of infection. Such protective measures should be as inexpensive as possible, comfortable and easy to use in order to allow use by the entire population in a case of a pandemic.

Oxidized cellulose has been shown to inactivate bacteria and fungi and inhibit their growth mainly due to its acidic pH [1-5], however there is still a need to provide an effective means to reduce and inactivate viral pathogens.

REFERENCES

SUMMARY OF THE INVENTION
The present invention is based on the finding the glucans, such as oxidized cellulose (OC), are able to entrap viruses, such as air-borne viruses, and prevent (or at least minimize) their entry into the body, *inter alia* through the airways; such is achieved by coating the airways by OC, and in particular in the form of microparticles.

Powder inhalation of OC microparticles results in coating of pharynx and lower airways, while protection against infections through the nasal route can be achieved by
administering a nasal spray or nasal gel. A virus reaching the airways encounters OC particles that bind to it and prevent its further binding and invasion through epithelia. Additionally, binding of pathogen to the insoluble OC particle increases the pathogen's clearance from the airways by the muco-ciliary pathway.

Thus, by one of its aspects, the invention provides a composition comprising at least one glucan, salt or a derivative thereof, for use in reducing a concentration of at least one viral pathogen in or on a target environment, said at least one glucan is not cellulose or any non-oxidized form thereof.

The term "glucan" refers to a polysaccharide of sugar monomers linked together by glycosidic bonds. The glucan may be α- or β-glucan and may be of natural, synthetic or semi-synthetic origin. The glucan may also be a combination of two or more glucans. Within the scope of the present invention, the term does not encompass cellulose or any non-oxidized form thereof (i.e., cellulose ethers, cellulose esters, etc.), unless specifically disclosed. Excluded from the scope of the present invention are, therefore, any non-oxidized cellulose derivatives including ethers, esters and alkyls thereof.

In some embodiments, the glucan is selected amongst polysaccharides having a plurality of D-glucose monomers linked together by glycosidic bonds.

In other embodiments, the at least one glucan is selected from P-1,4-glucans, β-1,3-glucans, β-1,6-glucans, a-1,4-glucans, a-1,6-glucans, P-1,3/p-1,6-glucans and a-1,4/a-1,6-glucans.

In some other embodiments, said glucan is selected from oxidized cellulose, pullulan, starch, glycogen, dextran, lichenin, mannan, galactomannan, arabinogalactan, galacton, chitosan, chinin, barely beta-glucan, oat beta-glucan galacton, pullulan, carob galactomannan, xylolucan, guar galactomannan, pectic galactan, rhamnogalacturonan-galacturonic acid, pachyman, curdlan and any derivative thereof.

In such embodiments, the at least one glucan may be oxidized cellulose.

As known to a person skilled in the art, "oxidized cellulose" is a rigid, long chain polymer, consisting of 3,000 to 5,000 glucose residues in β-(1,4) linkage, having at least part or all of the hydroxymethylene (exocyclic -CH₂OH) groups oxidized to carboxylic acid (-COOH) groups or charged carboxylate groups (-COO⁻). The oxidized cellulose employed in the present invention may be synthetic, semi-synthetic or commercially attained. The oxidized cellulose may also be in crystalline form, amorphous form or may be partially crystalline and partially amorphous.
Oxidation of cellulose may be achieved by various synthetic pathways as may be known to the artisan. Such oxidation, preferably does not substantially affect the glucose ring structure, although a certain degree of ring opening may occur depending on the oxidative conditions employed. The degree of oxidation of the hydroxymethylene groups may be quantified (for example by titration) and the percent weight of the -COOH groups from the total weight of the polymer (or percent oxidation) may be calculated [6]. In some embodiments, the percent weight of the -COOH groups is at least 3% of the total weight of the oxidized cellulose. In other embodiments, the percent weight of the -COOH groups of the total weight of the oxidized cellulose is between 3 and 25%.

It is of note that cellulose and oxidized cellulose are different compounds, having vastly different chemical and physical properties, despite the fact that the latter may be produced from the former, in terms of their respective chemical structure, reactivity and toxicity. A person skilled in the art would appreciate that when searching for an alternative active agent to commonly used agent, particularly for human and animal use, one needs to take into account that the alternative substance used in the pharmaceutical product must be toxicologically acceptable, well tolerated by the tissue to which it is applied, (e.g., skin, mucosa, etc.) stable and inexpensive to produce.

The oxidized cellulose may be used in the composition of the invention in one or more of the following forms:

(a) acidic form- having substantially all carboxylic groups protonated, namely in the form of -COOH;

(b) salt form- having some or all of the oxidized groups in the charged carboxylate form, namely in the form of -COOX, wherein X is a monovalent, divalent or multivalent metal ion selected for example amongst alkali and alkaline metal ions; wherein in cases where only some of the oxidized groups are in the form of salts, the remaining oxidized groups may be in the acidic form, or a derivatized form; or

(c) derivatized form (i.e. "derivative")- having some or all of the oxidized groups in the form -COOR, wherein R is an organic radical selected amongst substituted or unsubstituted C1-C20 alkyl, cycloalkyl, alkylene or cycloalkylene; substituted or unsubstituted C6-C12 aryl or arylene; substituted or unsubstituted C5-C12 heteroaryl or heteroarylene (having at least one heteroatom selected from N, O, S), C2-C20 alkenyl, alkenylene, cycloalkenyl or cycloalkenylene; wherein each of said groups may be
substituted by one or more organic or inorganic atom or groups such as halogens (Br, Cl, I, F), nitro, amines (primary, secondary or tertiary), alkyls, aryls and others as may be known to a person skilled in the art. The chemical transformation to the derivatized form, from the acid or salt forms, may be achieved by any transformation known to the person skilled in the art.

The bond between the O atom of the carboxylic moiety of the oxidized cellulose and the atom of the R group may be an ionic bond (such as in the case of a salt of metal or non-metal ions such as ammoniums) a covalent bond, a coordination bond or any other interaction which is capable of holding the two moieties (the oxidized cellulose and the R moiety) in close proximity. In some embodiments, the bond is a covalent bond. In other embodiments, the covalent bond is a hydrolysable bond.

The compositions of the invention may comprise any combination of glucans, or oxidized celluloses. In some embodiments, the composition comprises a single form of glucan, e.g., only amorphous oxidized cellulose. In other embodiments, the composition comprises at least two forms of glucans, for example oxidized cellulose and an oxidized cellulose derivative.

In some embodiments, the oxidized cellulose is selected from amorphous oxidized cellulose, crystalline oxidized cellulose and mixtures thereof. In other embodiments, the oxidized cellulose may be amorphous.

The composition of the invention may be used to reduce the concentration of at least one viral pathogen in a target environment.

The term "viral pathogen" refers to a viral infectious agent that can replicate inside the living cells of an organism, typically ranging between 20-300 nanometers in length. Virus particles (known as virions) consist of two or three parts: i) the genetic material made from either DNA or RNA; ii) a protein coat that protects these genes; and in some cases iii) an envelope of lipids that surrounds the protein coat when they are outside a cell.

In some embodiments, the viral pathogen is selected from double-stranded (ds) DNA viruses, single-stranded (ss) DNA viruses, dsRNA virusrs (+)/(-) ssRNA viruses, retroviruses, pararetroviruses (dsDNA-RT) and prions.

Exemplary dsDNA viruses are Caudovirales, such as those of family Myoviridae, family Podoviridae, or family Siphoviridae; Herpesvirales, such as those of family Alloherpesviridae, family Herpesviridae, or family Malacoherpesviridae;
Ligamenvirales, such as family Lipothrixviridae or family Rudiviridae; family Adenoviridae; family Ampullariviridae; family Ascoviridae; family Asfarviridae; family Baculoviridae; family Bicaudaviridae; family Clavaviridae; family Corticoviridae; family Feuselloviridae; family Globuloviridae; family Gutaviridae; family Hytrosaviridae; family Iridoviridae; family Mimiviridae; family Nimaviridae; family Papillomaviridae; family Phycodnaviridae; family Plasmaviridae; family Polydnaviridae; family Polomaviridae; family Poxviridae; family Tectiviridae; Dinodavirus; Nudivirus; Salterprovirus; Rhizidovirus; Abalone shrivelling syndrome-associated virus; Bandicoot papillomatosis carcinoma virus; Kls-V; Haloarcula hispanica pleomorphic virus 1; Marseille virus; Mavivirus virophage; Megavirus; Organic Lake virophage; Sputnik virophage; Sputnik virophage 2; Sulfolobus turreted isocahedral virus; Thremus aquaticus virus IN93; Thremus thermophilus virus P23-77; and others.

Exemplary ssDNA viruses are those of family Anelloviridae, family Bacillariodnaviridae, family Bidnaviridae, family Ciroviridae, family Geminiviridae, family Inoviridae, family Microviridae, family Nanoviridae, family Parvoviridae, and others.

Exemplary dsDNA viruses are those of family Alternaviridae, family Alternaviridae, family Birnaviridae, family Chrysoviridae, family Cystoviridae, family Endornaviridae, family Hypoviridae, family Partitiviridae, family Picobirnaviridae, family Reoviridae, family Totiviridae, Varicosavirus, La France isometric virus, Sclerotinia sclerotiorum debilitation associated virus, Sclerotinia sclerotiorum mitovirus 1, Sclerotinia sclerotiorum mitovirus 2, and others.

Exemplary (+)ssRNA viruses include viruses selected from the order Nidovirales, including the virus families Arteriviridae, Coronavirus, SARS, Mesoniviridae and Roniviridae; the order Picornavirales, including the families Dicistroviridae, Iflaviridae, Marnaviridae, Picornaviridae, Poliovirus, the common cold virus, Hepatitis A virus, Secoviridae includes subfamily Comovirinae, Bacillariornavirus and Labyrnavirus; the order Tymovirales, including the families Alphaflexiviridae, Betaflexiviridae, Gammaflexiviridae and Tymoviridae; Alphatetraviridae, Alvernaviridae, Astroviridae, Barnaviridae, Bromoviridae, Caliciviridae, Carmotetraviridae, Closteroviridae, Flaviviridae including Yellow fever virus, West Nile virus, Hepatitis C virus and Dengue fever virus, Leviviridae,
Exemplary (-)ssRNA viruses include viruses of the order Mononegavirales, including the family Bornaviridae such as the Borna disease virus, family Filoviridae such as the Ebola virus and the Marburg virus, family Paramyxoviridae including Measles virus, Mumps virus, Nipah virus and Hendra virus, family Rhabdoviridae including Rabies virus, family Arenaviridae such as Lassa virus, family Bunyaviridae including Hantavirus and Crimean-Congo hemorrhagic fever, family Ophioviridae, family Orthomyxoviridae including the Influenza viruses.

Exemplary ssRNA retroviruses include viruses of the genus Alpharetrovirus; including Avian leukosis virus and Rous sarcoma virus, genus Betaretrovirus such as the Mouse mammary tumor virus, genus Gamaretrovirus including the Murine leukemia virus and the Feline leukemia virus, genus Deltaretrovirus including the Bovine leukemia virus and the cancer-causing Human T-lymphotropic virus, genus Epsilonretrovirus such as the Walleye dermal sarcoma virus, genus Lentivirus including the Human immunodeficiency virus 1, Simian, and Feline immunodeficiency viruses.

In some embodiments, the viral pathogen is H1N1 influenza virus.

"Reducing the concentration" (or any lingual variant thereof) of the viral pathogen is meant to encompass the reduction of the number of viral microorganisms or viral colonies, or elimination thereof, in a target environment comprising such pathogens as a result of contact between the pathogen and the composition of the invention. In some embodiments, the glucan reduces the concentration of said viral pathogen in the target environment by at least 10%. In some other embodiments, the glucan reduces the concentration of the viral pathogen by at least 10%, 20%, 30%, 40% or even 50%.

The "target environment" may refer, in some embodiments, to biological samples, tissues, or generally surfaces and in other embodiments to non-biological surfaces.

Non-biological surfaces may include, in some embodiments, protective equipment (i.e. respirators and protective clothing), countertops, sanitary equipment, utensils, clothing, or any other non-biological surface which may be suspected of carrying viral pathogens.
For example, glucan, e.g. oxidized cellulose, can be added to protective equipment such as respirators and protective clothing in order to enhance their virus filtering/neutralizing ability. Most of the respirators do not trap particles in a sieve-like mechanism only, but rather particles are trapped (i.e. particles stick to a fiber) by one of four mechanisms: filtering interception, filtering by inertial impaction, filtration by Brownian diffusion and filtration by sieving. Since in all the mechanisms but sieving particles have to adhere to the filter's surface or fibers, the inventors of the present invention have found that increasing the affinity of a surface or a fiber to pathogens increases its ability to bind to such pathogens.

Thus, target environments of the invention may be either made of the glucan (e.g. knitted or woven fibrous products made from oxidized cellulose fibers) or treated (e.g. associated with or at least partially coated) with the glucan to possess strong affinity towards a viral pathogen.

In addition to its ability to intercept the pathogens, protective wear must be comfortable to wear and non-irritating to the skin and/or respiratory system in order to allow its use for long periods of time. In this connection, oxidized cellulose, as well as other glucans of the invention, are known to be biocompatible and do not cause any hazardous or irritating reaction to either the respiratory system or to the skin.

In some embodiments, the composition of the invention is a pharmaceutical composition, thereby making the composition suitable for contacting with biological surfaces (i.e. biological target environments).

Biological surfaces may include, in some embodiments, epithelia tissues or endothelia tissues. For example, the pharmaceutical composition of the invention may be administered to internal body tissues (such as nasal cavities, air-tract tissues, ear canals, vaginal tissues, etc), or administered onto external tissues such as skin and ocular tissues.

In some embodiments, where the composition is a pharmaceutical composition, it may further comprise a "pharmaceutically acceptable carrier", such as a vehicle, an adjuvant, an excipient, or a diluent. Such carriers are well known to those who are skilled in the art. It is preferred that the pharmaceutically acceptable carrier be one which is chemically inert to the glucan or oxidized cellulose or any other component of the composition and one which has no detrimental side effects or toxicity under the conditions of use.
The choice of carrier will be determined in part by the particular pharmaceutical composition, as well as by the particular method used to administer the composition. Accordingly, there is a wide variety of suitable formulations of the pharmaceutical composition of the present invention. In some embodiments, though exemplary and non-limiting, the composition of the invention may be in a form suitable for administration in an administration form selected from topical, oral, aerosol, intranasal, intraocular, parenteral, subcutaneous, intravenous, intramuscular, interperitoneal, rectal, and vaginal administrations.

Pharmaceutical formulations for topical application on the skin of the subject or on the subject's hair may be in the form of a gel, ointment, emulsion, thick cream, liniment, balsam, lotion, foam, mask, shampoo, tonic means, cleaner, spray, hair spray, (or it may be in the form of a means for the hair treatment such as rinsing, coloring, discoloring, hairdressing, hair straighting, hair waving, or hair fixing), powder including liquid powder, compact powder, cosmetic pencil, or in any other traditional form used in the field of cosmetology or dermatology.

Pharmaceutical formulations suitable for oral administration can consist of (a) liquid solutions, such as an effective amount of the glucan (e.g. oxidized cellulose) dissolved in diluents, such as water, saline, or orange juice; (b) capsules, sachets, tablets, lozenges, and troches, each containing a predetermined amount of the oxidized cellulose, as solids or granules; (c) powders; (d) suspensions in an appropriate liquid; and (e) suitable emulsions. Liquid formulations may include diluents, such as water and alcohols, for example, ethanol, benzyl alcohol, and the polyethylene alcohols, either with or without the addition of a pharmaceutically acceptable surfactant, suspending agent, or emulsifying agent. Capsule forms can be of the ordinary hard- or soft-shelled gelatin type containing, for example, surfactants, lubricants, and inert fillers, such as lactose, sucrose, calcium phosphate, and starch. Tablet forms can include one or more of lactose, sucrose, mannitol, corn starch, potato starch, alginic acid, acacia, gelatin, guar gum, colloidal silicon dioxide, magnesium stearate, calcium stearate, zinc stearate, stearic acid, and other excipients, colorants, diluents, buffering agents, disintegrating agents, moistening agents, preservatives, flavoring agents, and pharmaceutically compatible carriers. Lozenge forms can comprise the oxidized cellulose in a flavor, usually sucrose and acacia, as well as pastilles comprising the active ingredient in an inert base, such as gelatin and glycerin, or sucrose and acacia, emulsions, gels, and the
like containing, in addition to the oxidized cellulose, such carriers as are known in the art.

The pharmaceutical composition of the present invention, alone or in combination with other suitable components, can be made into aerosol formulations to be administered via inhalation or intranasal. These aerosol formulations can be placed into pressurized acceptable propellants, such as dichlorodifluoromethane, propane, nitrogen, and the like. They also may be formulated as pharmaceuticals for non-pressured preparations, such as in a nebulizer or an atomizer.

Pharmaceutical formulations for intranasal or mucosal delivery may comprise enhancing agents such as solubilization agents; charge modifying agents; pH control agents; degradative enzyme inhibitors; mucolytic or mucus clearing agents; ciliostatic agents; membrane penetration-enhancing agents such as surfactants, bile salts, phospholipid or fatty acid additives, mixed micelle, liposome, or carrier, alcohols, enamines, NO donor compounds, long-chain amphipathic molecules, small hydrophobic penetration enhancers; sodium or a salicylic acid derivatives; glycerol ester of acetoacetatic acids, cyclodextrin or beta-cyclodextrin derivatives, medium-chain fatty acids, chelating agents, amino acids or salts thereof, N-acetylamino acids or salts thereof, enzyme degradatives to a selected membrane component, inhibitors of fatty acid synthesis, inhibitors of cholesterol synthesis; or any combination of these membrane penetration enhancing agents; modulatory agents of epithelial junction physiology, such as nitric oxide (NO) stimulators, chitosan, and chitosan derivatives; vasodilator agents; selective transport-enhancing agents; and stabilizing delivery vehicles, carriers, supports or complex-forming species which is/are effectively combined, associated, contained, encapsulated or bound to stabilize the glucan for enhanced mucosal delivery.

In some embodiments of the invention, the mucosal pharmaceutical compositions of the invention may be supplemented with any suitable penetration-promoting agent that facilitates absorption, diffusion, or penetration of the composition or any component thereof across mucosal barriers.

Certain pharmaceutical formulations for intranasal applications as for aerosol applications are specifically adapted for a selected target cell, tissue or organ, which are at a remote target site or even a particular disease state. Efficiently loaded formulations at effective concentration levels in a carrier or other delivery vehicle, may be delivered
and maintained in a stabilized form, e.g., at the nasal mucosa and/or during passage through intracellular compartments and membranes, to a remote target site for action (e.g., a defined tissue, organ, or extracellular compartment).

Pharmaceutical formulations for intraocular administration may be administered topically to the eye or eye lid, for example, using drops, an ointment, a cream, a gel, a suspension, etc. The glucan (e.g. oxidized cellulose) may be formulated with excipients such as methylcellulose, hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyvinyl pyrrolidine, neutral poly (meth) acrylate esters, and other viscosity-enhancing agents.

Pharmaceutical formulations suitable for parenteral administration include aqueous and non-aqueous, isotonic sterile injection solutions, which can contain antioxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and non-aqueous sterile suspensions that include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives. The oxidized cellulose can be administered in a physiologically acceptable diluent in a pharmaceutical carrier, such as a sterile liquid or mixture of liquids, including water, saline, aqueous dextrose and related sugar solutions, an alcohol, such as ethanol, isopropanol, or hexadecyl alcohol, glycols, such as propylene glycol or polyethylene glycol, glycerol ketals, such as 2,2-dimethyl-1,3-dioxolane-4-methanol, ethers, such as poly(ethyleneglycol) 400, an oil, a fatty acid, a fatty acid ester or glyceride, or an acetylated fatty acid glyceride with or without the addition of a pharmaceutically acceptable surfactant, such as a soap or a detergent, suspending agent, such as pectin, caromers, methylcellulose, hydroxypropylmethylcellulose, or carboxymethylcellulose, or emulsifying agents and other pharmaceutical adjuvants.

Oils, which can be used in parenteral pharmaceutical formulations, include petroleum, animal, vegetable, or synthetic oils. Specific examples of oils include peanut, soybean, sesame, cottonseed, corn, olive, petrolatum, and mineral. Suitable fatty acids for use in parenteral formulations include oleic acid, stearic acid, and isostearic acid. Ethyl oleate and isopropyl myristate are examples of suitable fatty acid esters. Suitable soaps for use in parenteral formulations include fatty alkali metal, ammonium, and triethanolamine salts, and suitable detergents include (a) cationic detergents such as, for example, dimethyl dialkyl ammonium halides, and alkyl pyridinium halides, (b) anionic detergents such as, for example, alkyl, aryl, and olefin
sulfonates, alkyl, olefin, ether, and monoglyceride sulfates, and sulfosuccinates, (c)
nonionic detergents such as, for example, fatty amine oxides, fatty acid alkanoamides, 
and polyoxy-ethylenepolypropylene copolymers, (d) amphoteric detergents such as, for 
example, alkyl -P-aminopropionates, and 2-alkyl-imidazoline quaternary ammonium 
salts, and (3) mixtures thereof.

The parenteral pharmaceutical formulations will typically contain from about 
0.05 to about 25% by weight of a glucan, such as oxidized cellulose, in solution.
Suitable preservatives and buffers can be used in such formulations. In order to 
minimize or eliminate irritation at the site of injection, such compositions may contain 
one or more nonionic surfactants having a hydrophile-lipophile balance (HLB) of from 
about 12 to about 17. The quantity of surfactant in such formulations ranges from about 
5 to about 15% by weight. Suitable surfactants include polyethylene sorbitan fatty acid 
esters, such as sorbitan monooleate and the high molecular weight adducts of ethylene 
oxide with a hydrophobic base, formed by the condensation of propylene oxide with 
propylene glycol. The parenteral formulations can be presented in unit-dose or multi-
dose sealed containers, such as ampoules and vials, and can be stored in a freeze-dried 
(lyophilized) condition requiring only the addition of the sterile liquid carrier, for 
example, water, for injections, immediately prior to use. Extemporaneous injection 
solutions and suspensions can be prepared from sterile powders, granules, and tablets of 
the kind previously described.

The pharmaceutical compositions of the present invention may be made into 
injectable formulations. The requirements for effective pharmaceutical carriers for 
injectable compositions are well known to those of ordinary skill in the art. See for 
example Pharmaceutics and Pharmacy Practice, J.B. Lippincott Co., Philadelphia, Pa., 
Banker and Chalmers, eds., pages 238-250 (1982), and ASHP Handbook on Injectable 

Additionally, the pharmaceutical compositions of the present invention may be 
made into suppositories by mixing with a variety of bases, such as emulsifying bases or 
water-soluble bases. Formulations suitable for vaginal administration may be presented 
as pessaries, tampons, creams, gels, pastes, foams, or spray formulas containing, in 
addition to the active ingredient, such carriers as are known in the art to be appropriate.

In some embodiments, the pharmaceutical composition is a topical formulation.
In other embodiments, the pharmaceutical composition is an intranasal formulation. In
yet other embodiments, the pharmaceutical composition is an intraocular formulation. In yet other embodiments, the composition is formulated for mucosal application. In other embodiments, the composition is formulated for inhalation.

In some embodiments, the glucan is present in the composition in a form selected from a fiber, a particle, a microparticle, and a nanoparticle. In other embodiments, the glucan may be present in the composition in an insoluble form.

In some embodiments, the glucan, e.g., oxidized cellulose, is in a nanoparticle, e.g., nanocrystalline form.

The term "particle" or any variation thereof is meant to encompass glucan in solid particulate form. Without being limited thereto, the particles may be symmetrical or unsymmetrical, may be elongated having a rod-like shape, round (spherical), elliptical, pyramidal, disk-like, branch, network or any irregular shape.

It should be noted that the averaged diameter of the glucan (typically oxidized cellulose) particles may be measured by any method known to a person skilled in the art. The term "averaged diameter" refers to the arithmetic mean of measured diameters, wherein the diameters range ±25% of the mean. For example, the expression "averaged diameter of between about 0.01 and about 100 microns" encompasses particles having diameters 25% smaller than 0.01 microns and 25% larger than 100 microns, namely from 0.0075 microns to 125 microns. An averaged diameter of 30 microns thus refers to an actual average of between 22.5 and 37.5 microns.

In some embodiments, the particle has an average diameter of between about 0.01 and about 100 microns. In other embodiments, the particle has an average diameter of between about 0.1 and about 100 microns, between about 1 and about 100 microns, between about 10 and about 100 microns, between about 25 and about 100 microns, between about 50 and about 100 microns, or between about 75 and about 100 microns.

In some other embodiments, the particle has an average diameter of between about 0.01 and about 75 microns, between about 0.01 and about 50 microns, between about 0.01 and about 25 microns, between about 0.01 and about 10 microns, between about 0.01 and about 1 micron, or between about 0.01 and about 0.1 microns.

In some other embodiments, the particle has an average diameter of between about 0.1 and about 75 microns, between about 0.1 and about 50 microns, between about 0.1 and about 25 microns, between about 0.1 and about 10 microns, or between about 0.01 and about 1 micron.
In further embodiments, the particles have an averaged diameter of between about 0.01 and about 30 microns. In yet further embodiments, the particles have an averaged diameter of between about 0.1 and about 10 microns.

The term "fiber" relates to particles having an elongated shape, having one dimension (length) which is significantly larger than its other dimensions (i.e. width or diameter).

In other embodiments, the composition of the invention further comprises a "film-forming agent", being an agent capable of forming a film on the surface of the target environment once the composition is applied thereon. Non-limiting examples of such film-forming agents may be, for example, nano crystalline cellulose (NCC).

In another aspect, a pharmaceutical composition comprising at least one glucan, salt or a derivative thereof, may be used in reducing exposure of a subject's tissues to at least one air-borne viral pathogen by capturing said air-borne viral pathogen, said at least one glucan is not cellulose or any non-oxidized form thereof.

The term "subject" relates to mammals, which may be human or non-human mammals. In some embodiments, the subject is a human.

The term "air-borne" is meant to encompass viral pathogens which are transmitted through air, for example during coughing and sneezing.

In some embodiments, the air-borne viral pathogen is selected from double-stranded (ds) DNA viruses, single-stranded (ss) DNA viruses, dsRNA viruses (+)/(-) ssRNA viruses, retroviruses and pararetroviruses (dsDNA-RT).

In other embodiments, the air-borne viral pathogen is H1N1 influenza virus.

In this aspect, the pharmaceutical composition induces at least one effect associated with "reducing exposure", namely limiting, arresting or diminishing exposure, of the subject's tissues (such as airways) to air-borne viral pathogens, thereby reducing, ameliorating or preventing unwanted conditions or diseases associated with these pathogens in the subject. The term also encompasses preventing the manifestation of such symptoms before they occur, to slow down the progression of the disease, slow down the deterioration of symptoms, to enhance the onset of remission period, slow down or delay the onset of progressive chronic stage of the disease, to lessen the severity of the disease, to improve survival rate or more rapid recovery, prevent the disease from occurring or a combination of two or more of the above.
The reduction in exposure is obtained by "capturing" of the air-borne viral pathogen by the glucan, thereby reducing or eliminating the passage of the pathogen through the composition or a substrate carrying the composition. It should be noted that the compositions of the invention, comprising at least one glucan (typically oxidized cellulose), are used to create a barrier between the pathogen and the target environment (such as a body tissue). The capturing may be physical capturing, i.e., mechanical entrapment or physical absorption of the viral pathogen onto the glucan. The physical entrapment may result from physical forces, such as charge-induced absorption, polarity-induced absorption, etc., residing between the pathogen and the glucan. Alternatively, the capturing may be chemical capturing, in which the glucan chemically binds to the pathogen. In some embodiments, the capturing is chemical capturing.

In some embodiments, the composition captures at least 10% of said viral pathogen in the target environment. In some other embodiments, the composition captures at least 10%, 20%, 30%, 40% or even 50% of the viral pathogen in the target environment.

In some embodiments, the pharmaceutical composition may be in a form suitable for administration in an administration form selected from topical, oral, aerosol, intranasal, and intraocular administration.

In other embodiments, the pharmaceutical composition may be in a form of a coating onto a non-biological surface, such as fibers.

In some other embodiments, the tissue is a part of the subject's respiratory system.

In further embodiments, the pharmaceutical composition further comprises a film-forming agent.

In accordance with some embodiments, the glucan derivative is a drug derivative. In such embodiments, the drug derivative may be selected from antibiotics, anti-inflammatory agent, anti-allergy agents, and anti-cancer agents.

The pharmaceutical composition of the invention may be used in the treatment of diseases or disorders. Therefore, in another aspect, there is provided a pharmaceutical composition of the invention, for the treatment and/or prophylaxis of at least one disease or disorder associated with or mediated by at least one air-borne viral pathogen.

The term "treatment" or any lingual variation thereof refers within the scope of the present invention to a clinical endpoint characterized by an improvement in the
subjects condition; a reduction in the severity, frequency, duration or progression of one or more adverse symptoms or complications associated with the disease or disorder; and/or an inhibition, reduction, elimination, prevention or reversal of one or more of the physiological, biochemical or cellular manifestations or characteristics of the disorder or disease, including complete prevention of the disease or disorder.

As may be known to the person skilled in the art, when the viral pathogen enters the subject's body, via for example the respiratory system, it induces an array of diseases or disorders which may be caused, directly or indirectly, by the pathogen, and thus is referred to as a "disease or disorder associated with or mediated by at least one (air-borne) viral pathogen". In its broadest definition, this expression is used to mean that there exists a relationship between an exposure to an pathogen and the induction of a symptom, a condition, a disorder or a disease, or that there exists a secondary effect of the exposure to the pathogen which exacerbates a condition, a disorder or a disease that may have been initially caused by another factor.

In other embodiments, the disease is influenza.

Another aspect of the invention provides a method for the treatment or prophylaxis of at least one disease or disorder associated with or mediated by at least one air-borne viral pathogen, the method comprising administering to a subject an effective amount of at least one glucan, wherein said at least one glucan is not cellulose or any non-oxidized form thereof.

A further aspect provided by the invention is a method for delaying the onset or lessening the severity of at least one disease or disorder associated with or mediated by at least one air-borne viral pathogen, the method comprising administering to a subject an effective amount of at least one glucan, wherein said at least one glucan is not cellulose or any non-oxidized form thereof.

In order to achieve any one of the therapeutic benefits of the compositions and methods of the invention, the active component, namely the at least one glucan, being preferably an oxidized cellulose, a salt or a derivative thereof, should be administered therapeutically or prophylactically in an efficient amount which may vary according to the status of the condition, the type of treatment sought (i.e., therapeutic or preventive), the general condition of the subject, use of other drugs or agents and any other factor as may be known to a medical practitioner. The dose amount, frequency or duration of administration may be proportionally increased or reduced. The term "effective
"amount" or any lingual variation thereof, refers generally to a therapeutic or prophylactic amount which is, when administered to a subject, sufficient to reduce, prevent, delay and/or inhibit the onset or progression or worsening of a disease or disorder; to reduce, relieve, and/or alleviate the severity, frequency, duration, susceptibility or probability of one or more undesirable symptom or condition associated with the disease or disorder; to hasten the recovery from one or more symptoms associated with the disease or disorder.

The treatment or prophylactic regimens may be short term or long term and may depend on such factors as discussed hereinabove. The compositions or methods of the invention may employ a single administration of any one composition or multiple administrations, wherein the composition is administered alone or in combination with other therapeutics or treatments.

Without wishing to be bound to specific dosages and particular regimes, as the therapeutic or prophylactic efficacy of the compositions and methods of the invention may vary between one subject to another, a subject may be administered a composition of the invention once, twice, three, four, five or more times daily, weekly, monthly or annually. Depending on the therapeutic effect sought, therapeutic or a prophylactic, and the type of formulation, e.g., for oral, nasal or topical administration, the dose size may vary between about 0.1 mg/kg, to about 100 mg/kg.

The composition of the invention may be administered by a medical practitioner or by the subject being treated prior to an expected contact with a viral pathogen, immediately after such a contact, or within a short period after the onset of at least one symptom associated with a disease or disorder.

In some embodiments, the at least one glucan is oxidized cellulose, a salt or derivative thereof.

In other embodiments, the subject is one suffering from said disease or disorder.

In some other embodiments, the disease is influenza.

A further aspect of the invention provides a product for use in reducing concentration of a viral pathogen in or on a target environment, the product comprising the composition of the invention as herein described.

In some embodiments, the product may be a woven or non-woven fiber-based product comprising fibers which are either (i) produced from the composition or (ii) at least partially coated by the composition of the invention. Such products may be, in
some embodiments, selected from an artificial respiratory system, a face mask, an air
filter, a glove, a sanitary wipe, a paper product, a sanitary curtain, protective clothing, or
bedclothes.

In other embodiments, the product comprises a substrate that is at least partially
coated by the composition of the invention. The substrate may be selected, in some
embodiments, from a rigid substrate and a flexible substrate.

In some embodiments, the rigid substrate may be made of at least one of metal,
ceramic, wood, plastics, and glass. In other embodiments, the flexible substrate may be
made of at least one material selected from paper, plastic, and metal.

The “substrate” may be substantially two-dimensional (a thin flat substrate) or a
three-dimensional curved (non-flat) surface. The substrate can be of any smoothness.
The substrate onto which a coating of the composition of the invention is at least
partially applied may not necessarily be of the same material as the bulk of the object
carrying the substrate.

The composition of the invention is said to "at least partially coat" (or any
lingual variation thereof) the substrate. The portion (region) of the substrate to be coated
may be of any size and structure, the portion may be continuous or comprise of several
non-continuous sub-regions on the substrate's surface. In some embodiments, the at
least one portion of the substrate is its entire surface.

In another aspect, the invention provides a method of reducing a concentration
of a viral pathogen in or on a target environment comprising contacting the target
environment with at least one glucan, wherein said at least one glucan is not cellulose or
any non-oxidized form thereof.

In some embodiments, said at least one glucan is selected from P-1,4-glucans, β-
1,3-glucans, β-1,6-glucans, a-1,4-glucans, a-1,6-glucans, P-1,3/p-1,6-glucans, and a-
1,4/a-1,6-glucans. In such embodiments, said glucan may be selected from amorphous
oxidized cellulose, crystalline oxidized cellulose, and a salt or derivative thereof.

The term "contacting" refers to bringing of the viral pathogen and the at least
one glucan into physical contact. Therefore, in some embodiments, the contacting is
carried out by applying said at least one glucan, or a composition comprising it, in or
onto the target environment.

In some embodiments, applying said at least one glucan in the target
environment is carried out by embedding the glucan in the target environment. In other
embodiments, application of the glucan may be carried out by coating, dipping, wiping, spreading, smearing or spraying the composition of the invention onto the target environment.

**DETAILED DESCRIPTION OF THE INVENTION**

At first, the pattern of proteins of the tested viral sample was established in order to evaluate the efficiency of the staining method used. For this purpose, virus inactivation was carried out using the following protocol.

Influenza virus samples were defrosted and 1.2 ml of virus samples were placed in a 3 cm Petri dish placed on ice. 2 ml of 0.45 μM filtered PBS (phosphate buffered saline) was added to each Petri dish and then mixed by swirling. The plates were placed on ice under a 254 nm UV lamp at a distanced of about 10 cm from the plate and left under the UV light for 10 min.

The virus samples were used for SDS (sodium dodecyl sulfate polyacrylamide gel electrophoresis) page study as follows. The viruses were diluted in PBS to the following dilution ratios: 1/2, 1/4, 1/8, 1/16, 1/32 and 1/64. Each diluted sample was then mixed with SAB X4 (12μl SAB with 36μl sample) and maintained at boiling temperature for 3 min. Samples were loaded on two 15% acryl amide SDS gels and stained with imperial protein stain (Peirce).

Results of the SDS study demonstrate that lysed viral particles gave a distinct proteins pattern that was detectable using coomassie stain. It is postulated, that following the binding of the viral particles to oxidized cellulose and the precipitation of the bound complex by centrifugation, a reduction in the viral proteins that are available in the supernatant would be observed.

The ability of oxidized cellulose to bind and precipitate influenza viruses was assessed by incubation of influenza viruses (strain Influenza A/WSN/33 - H1N1) with OC or Avicel (microcrystalline cellulose) suspensions followed by centrifugation. The control (total) included centrifugated virus particles at the same concentration.

The binding assay of influenza viruses to oxidized cellulose (OC) was performed in the samples detailed in Table 1.
The tubes were rolled for 30 minutes at room temperature, and then centrifuged for 1 min at 10000 RPM at room temperature. The supernatant was removed from the solid pellet to a new tube (termed hereinafter as unbound, or UB). 45µL of the UB samples were mixed with 15µL SABX4 and the pH was adjusted with 2µL of 3M Tris pH=8.45.

The OC solid pellet of sample 1 was washed and incubated with 1 ml of PBS, vortexed and centrifuged again for 1 minute at 10000 RPM. The OC and Avicel pellets of samples 2 and 3, respectively, were washed with saline and incubated in 0.5 ml of saline, vortexed and centrifuged as mentioned before.

Following centrifugation, the supernatant was removed, and the pellet was resuspended in 60µL of SABX4. The OC samples (termed hereinafter as bound, or B) were pH adjusted with 5µL of 3M Tris buffer at pH=8.45.

Control sample of the virus (termed hereinafter as Total) was prepared by adding 0.2 ml of inactivated viruses to 0.1 ml PBS, centrifugating for 1 minute at 10000 RPM, and mixing 45µL of the supernatant with 15µL SABX4.

All samples were then boiled for 4 minutes, and then placed on a 15% SDS gel (10µL from the B and 22 µL from UB).

From a comparative SDS study it was evident that OC binds viruses much more efficiently than Avicel. Since small amounts of OC (5mg) were used, one wash with PBS was able to change the pH dramatically and reduce the binding while in the saline washes that did not affect the pH and the viruses remained bound to OC.
CLAIMS:
1. A composition comprising at least one glucan, salt or a derivative thereof, for use in reducing a concentration of at least one viral pathogen in or on a target environment, said at least one glucan is not cellulose or any non-oxidized form thereof.
2. The composition of claim 1, wherein said at least one glucan is selected from β-1,4-glucans, P-1,3-glucans, β-1,6-glucans, α-1,4-glucans, α-1,6-glucans, β-1,3/β-1,6-glucans, and α-1,4/α-1,6-glucans.
3. The composition of claim 2, wherein said glucan is selected from oxidized cellulose, pullulan, starch, glycogen, dextran, lichenin, mannan, galactomannan, arabinobioxytan, galacton, chitosan, chitin, barely beta-glucan, oat beta-glucan galacton, pullulan, carob galactomannan, xyloglucan, guar galactomannan, pectic galactan, rhamnogalacturonan-galacturonic acid, pachymann, curdlan, and any derivative thereof.
4. The composition of claim 2, wherein said at least one glucan is at least partially oxidized cellulose or fully oxidized cellulose.
5. The composition of claim 4, wherein said oxidized cellulose is selected from amorphous oxidized cellulose, crystalline oxidized cellulose, and mixtures thereof.
6. The composition of claim 5, wherein said oxidized cellulose is amorphous.
7. The composition of any one of claims 1 to 6, wherein the viral pathogen at least one pathogen selected from double-stranded (ds) DNA viruses, single-stranded (ss) DNA viruses, dsRNA viruses (+)/(-) ssRNA viruses, retroviruses and pararetroviruses (dsDNA-RT).
8. The composition of claim 7, wherein the viral pathogen is H1N1 influenza virus.
9. The composition of any one of claims 1 to 8, wherein the target environment a non-biological surface.
10. The composition of claim 9, wherein said non-biological surface is selected from protective equipment, respirators, protective clothing, countertops, sanitary equipment, and utensils.
11. The composition of any one of claims 1 to 8 being a pharmaceutical composition.
12. The composition of claim 11, further comprising a pharmaceutically acceptable carrier.
13. The composition of claim 11 or 12, wherein the target environment a biological surface.
14. The composition of claim 13, wherein said biological surface is selected from epithelia tissues or endothelia tissues.

15. The composition of any one of claims 11 to 14, being in a form suitable for administration in an administration form selected from topical, oral, aerosol, intranasal, intraocular, parenteral, subcutaneous, intravenous, intramuscular, interperitoneal, rectal, and vaginal administration.

16. The composition of any one of claims 1 to 15, wherein said glucan is in a form selected from a fiber, a particle, a microparticle, and a nanoparticle.

17. The composition of claim 16, wherein the particle has an average diameter of between about 0.01 and about 100 microns.

18. The composition of any one of claims 1 to 17, wherein said glucan reduces the concentration of said viral pathogen in said target environment by at least 10%.

19. The composition of any one of claims 1 to 18, further comprising a film-forming agent.

20. A pharmaceutical composition comprising at least one glucan, salt or a derivative thereof, for use in reducing exposure of a subject's tissue to at least one airborne viral pathogen by capturing said airborne viral pathogen, said at least one glucan is not cellulose or any non-oxidized form thereof.

21. The pharmaceutical composition of claim 20, wherein said at least one glucan is selected from P-1,4-glucans, P-1,3-glucans, β-1,6-glucans, a-1,4-glucans, a-1,6-glucans, β-1,3/β-1,6-glucans, and a-1,4/a-1,6-glucans.

22. The pharmaceutical composition of claim 21, wherein said glucan is selected from amorphous oxidized cellulose, crystalline oxidized cellulose, and mixtures thereof.

23. The pharmaceutical composition of any one of claims 20 to 22, wherein said glucan is in a form selected from a fiber, a particle, a microparticle, and a nanoparticle.

24. The pharmaceutical composition of claim 23, wherein the particle has an average diameter of between about 0.01 and about 100 microns.

25. The pharmaceutical composition of any one of claims 20 to 24, being in a form suitable for administration in an administration form selected from topical, oral, aerosol, intranasal, and intraocular administration.

26. The pharmaceutical composition of any one of claims 20 to 24, being in a form of a coating onto a non-biological surface or a biological surface.
27. The pharmaceutical composition of any one of claims 20 to 26, wherein the tissue is a part of the subject's respiratory system.

28. The composition of any one of claims 20 to 27, further comprising a film-forming agent.

29. The pharmaceutical composition of any one of claims 20 to 28, wherein the airborne viral pathogen is selected from double-stranded (ds) DNA viruses, single-stranded (ss) DNA viruses, dsRNA viruses (+)/(-) ssRNA viruses, retroviruses and pararetroviruses (dsDNA-RT).

30. The pharmaceutical composition of claim 29, wherein the airborne viral pathogen is H1N1 influenza virus.

31. The pharmaceutical composition of any one of claims 20 to 30, wherein said composition captures at least 10% of said viral pathogen in the target environment.

32. The pharmaceutical composition of any one of claims 20 to 31, wherein said glucan derivative is a drug derivative.

33. The pharmaceutical composition of claim 32, wherein said drug is selected from antibiotics, anti-inflammatory agent, anti-allergy agents, and anti-cancer agents.

34. A pharmaceutical composition according to any one of claims 20 to 33, for the treatment and/or prophylaxis of at least one disease or disorder associated with or mediated by at least one airborne viral pathogen.

35. The pharmaceutical composition of claim 34, wherein said disease is influenza.

36. The pharmaceutical composition of any one of claims 34 to 35 being a topical formulation.

37. The pharmaceutical composition of any one of claims 34 to 35 being an intranasal formulation.

38. The pharmaceutical composition of any one of claims 34 to 35 being an intraocular formulation.

39. The pharmaceutical composition of any one of claims 34 to 35 being formulated for mucosal application.

40. The pharmaceutical composition of any one of claims 34 to 35 being formulated for inhalation.

41. A product for use in reducing concentration of a viral pathogen in or on a target environment comprising the composition of claim 1.
42. The product of claim 41, being a woven or non-woven fiber-based product comprising fibers which are either (i) produced from the composition of claim 1 or (ii) at least partially coated by the composition of claim 1.

43. The product of claim 42, selected from an artificial respiratory system, a face mask, an air filter, a glove, a sanitary wipe, a paper product, a sanitary curtain, protective clothing, and bedclothes.

44. The product of claim 41, comprising a substrate at least partially coated by the composition of claim 1.

45. The product of claim 43, wherein said substrate is selected from a rigid substrate and a flexible substrate.

46. The product of claim 45, wherein said rigid substrate is made of at least one of metal, ceramic, wood, plastics, and glass.

47. The product of claim 46, wherein said flexible substrate is made of at least one paper, plastic and metal.

48. A method of reducing a concentration of a viral pathogen in or on a target environment comprising contacting the target environment with at least one glucan, salt or a derivative thereof, said at least one glucan is not cellulose or any non-oxidized form thereof.

49. The method of claim 48, wherein said at least one glucan is selected from β-1,4-glucans, P-1,3-glucans, β-1,6-glucans, a-1,4-glucans, a-1,6-glucans, β-1,3/β-1,6-glucans, and a-1,4/a-1,6-glucans.

50. The method of claim 49, wherein said glucan is selected from amorphous oxidized cellulose, crystalline oxidized cellulose, and mixtures thereof.

51. The method of any one of claims 48 to 50, wherein said contacting is carried out by applying said at least one glucan in or onto the target environment.

52. The method of claim 51, wherein applying said at least one glucan in the target environment is carried out by embedding the glucan in the target environment.

53. The method of claim 51, wherein applying said at least one glucan onto the target environment is carried out by coating, dipping, wiping, spreading, smearing or spraying

54. A method for the treatment or prophylaxis of at least one disease or disorder associated with or mediated by at least one air-borne viral pathogen, the method
comprising administering to a subject an effective amount of at least one glucan, wherein said at least one glucan is not cellulose or any non-oxidized form thereof.

55. A method for delaying the onset or lessening the severity of at least one disease or disorder associated with or mediated by at least one air-borne viral pathogen, the method comprising administering to a subject an effective amount of at least one glucan, wherein said at least one glucan is not cellulose or any non-oxidized form thereof.

56. The method according to claim 54 or 55, wherein said at least one glucan is oxidized cellulose, a salt or derivative thereof.

57. The method according to claim 54 or 55, wherein said subject is one suffering from said disease or disorder.

58. The method of any one of claims 54 to 55, wherein said disease is influenza.
A. CLASSIFICATION OF SUBJECT MATTER
INV. A01N43/16 A61K31/716 A01P1/00
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
A01N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>wo 2009/137831 A2 (UNIVERSITY OF FLORIDA RESEARCH FOUNDATION, INC.) 12 November 2009 (2009-11-12) claims 1, 25; figure 14; example 6; table 4</td>
<td>1-58</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:
  *A* document defining the general state of the art which is not considered to be of particular relevance
  *E* earlier application or patent but published on or after the international filing date
  *L* document which may throw doubts on priority claim(s) in which a later document is cited to establish the publication date of another citation or of other special reason (as specified)
  *O* document referring to an oral disclosure, use, exhibition or other means
  *P* document published prior to the international filing date but later than the priority date claimed

T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is taken alone

Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

A* document member of the same patent family

Date of the actual completion of the international search: 4 September 2013

Date of mailing of the international search report: 08/10/2013

Name and mailing address of the ISA:
European Patent Office P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016

Authorized officer: Breimai er, Wal traud
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td><strong>US 2012/114724</strong> AI (UNIVERSITY OF FLORIDA RESEARCH FOUNDATION, INC.) 10 May 2012 (2012-05-10) paragraphs [0006, 14, 43, 90]; claims 1, 9, 25, 30; examples 4, 6</td>
<td>1-58</td>
</tr>
<tr>
<td>X</td>
<td><strong>WO 2009/129585</strong> AI (SUNNYWISPE P LTD) 29 October 2009 (2009-10-29) the whole document</td>
<td>1-58</td>
</tr>
<tr>
<td>X</td>
<td><strong>US 7 019 191 B2</strong> (ETHIC0N, INC.) 28 March 2006 (2006-03-28) the whole document</td>
<td>1-58</td>
</tr>
</tbody>
</table>

Form PCT/ISA/210 (continuation of second sheet) (April 2005)

page 2 of 4
<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHI LADELPHIA, PA, US; 1976, &quot;BIOLOGICAL ACTIVITY OF POLY SACCHARIDES AS A FUNCTION OF THEIR STRUCTURAL PROPERTIES&quot;, XP002712239, Database access on no. prev97865021655 abstract</td>
<td>1-58</td>
</tr>
<tr>
<td>X</td>
<td>GB 1 313 373 A (AJINOMOTO CO., INC.) 11 April 1973 (1973-04-11) the whole document</td>
<td>1-58</td>
</tr>
</tbody>
</table>

Form PCT/ISA/210 (continuation of second sheet) (April 2008)
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>US 6 541 014 B2 (ADVANCIS PHARMACEUTICAL CORP.) 1 April 1 2003 (2003-04-01) column 5, line 7 - line 12; claims 1, 17 column 6, line 8 - line 26</td>
<td>1-3</td>
</tr>
<tr>
<td>Patent document cited in search report</td>
<td>Publication date</td>
<td>Patent family member(s)</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>-----------------</td>
<td>-------------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2723414 AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CN 102083310 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 2276343 A2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2011524338 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 2009137831 A2</td>
</tr>
<tr>
<td>US 2012114724 AI</td>
<td>10-05-2012</td>
<td>NONE</td>
</tr>
<tr>
<td>WO 2009129585 AI</td>
<td>29-10-2009</td>
<td>AU 2009240797 AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2726196 AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CN 102036691 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 2296713 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NZ 589519 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2012276217 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WO 2009129585 AI</td>
</tr>
<tr>
<td>US 7019191 B2</td>
<td>28-03-2006</td>
<td>AR 040297 AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU 2003204947 AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BR 0304169 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA 2433976 AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CN 1531910 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 1462123 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 2004290649 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>KR 20040086071 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2004193088 AI</td>
</tr>
<tr>
<td>GB 1313373 A</td>
<td>11-04-1973</td>
<td>CA 965782 AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FR 2059511 AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GB 1313373 A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2003099706 AI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US 2006110455 AI</td>
</tr>
</tbody>
</table>