

NOVEL COMPOSITION FOR TREATMENT OF INFLAMMATORY RELATED DISORDERS

CROSS-REFERENCE TO RELATED APPLICATION

5 This application claims the benefit of US Provisional Application no. 63/468,018, filed on May 22, 2023. The entire disclosure of the application identified in this paragraph is incorporated herein by reference.

FIELD OF THE INVENTION

10 Disclosed herein are novel compositions comprising the complexes of deferoxamine B with zinc or gallium and hydrophilic non-ionic surfactant formulation, allowing administration of said complexes via the oral route, and its uses thereof in at least one of modulating pro-and anti-inflammatory cytokines, acting as an antibiotic and chelating of labile and redox-active iron, within and out of cells. More specifically, the
15 compositions are useful for treating conditions associated with inflammation, infection and iron overload.

BACKGROUND REFERENCES

References considered to be relevant as background to the presently disclosed subject matter are listed below:

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Acknowledgement of the above references herein is not to be inferred as meaning that these are in any way relevant to the patentability of the presently disclosed subject matter.

BACKGROUND OF THE INVENTION

Diabetes is a very widespread illness – globally, 537 million adults (20-79 years) are living with diabetes - 1 in 10. This number is predicted to rise to 643 million by 2030 and 783 million by 2045. Currently, (according to a recent CDC publication) an estimated
5 50% of people in the USA have either Diabetes or have Pre-Diabetes - 37.3 million people have diabetes (11.3% of the US population) and 96 million people aged 18 years or older have prediabetes (38.0% of the adult US population). The incidence of diabetes is increasing because of more advanced aging of populations and the alarming increase in the prevalence of obesity in adults as well as children and young adults. It is expected
10 that the prevalence of diabetes will reach 783 million by 2045 (1). The economic burden of diabetes in 2012 alone was estimated at US\$245B, including US\$176B in direct medical costs and US\$69B in reduced productivity (2). In 2021 Diabetes caused at least USD 966 Billion dollars in health expenditure – a 316% increase over the last 15 years (3).

15 Clinical care of Type 2 Diabetes (T2D), (mainly its symptoms) and its complications is clearly improving. Nevertheless, complications are still very common and usually the disease worsens over time. Diabetes is among the leading causes of death, vision loss, amputation, and end-stage renal disease, in the USA. In addition, it is a substantial risk factor for atherosclerotic disease - the leading cause of morbidity,
20 mortality, and expenditures in diabetic persons. Generally, classic risk factors for T2D include increased body-mass-index (BMI) to ≥ 30 kg/m², HbA1c levels of $\geq 6\%$ and the metabolic syndrome (4). Current standard of care for T2D initially comprises lifestyle and diet management, followed by anti-hyperglycemic mono-therapy with Metformin in mild cases (HbA1c $\leq 9\%$), or with dual therapy (Metformin combined with another medication).
25 If the HbA1C reduction target is not reached in ~3 months of triple therapy, or the disease had a more severe form initially, the treatment steps up to include a combination of injectable therapy, e.g., rapid acting insulin injections at different regimens with or without GLP-1 receptor agonists. Yet, the use of medications is often followed by serious limitations, including adverse side effects and, more importantly, the risk of life-
30 threatening hypoglycemia (5). A recent study about Metformin, the first line of defense against T2D has reached a conclusion that preconception paternal metformin treatment is associated with major birth defects, particularly genital birth defects in boys. Therefore, even this treatment, until recently believed to be adverse effect free, is now implicated as problematic (3).

A line of publications has disclosed incriminating evidence, demonstrating a causal relationship between the accumulation of labile redox-active iron within various tissues, such as pancreatic cells and hepatocytes, and T2D development (6-11). Iron affects glucose metabolism (12-14), which in turn, impinges on iron metabolic pathways. Briefly, accumulation of labile and redox-active iron within various tissues contributes to formation of reactive oxygen-derived species (ROS) via Fenton reaction, that promote the initiation of an inflammatory response, which in turn, underlies insulin resistance (IR) and metabolic syndrome, and plays a pivotal role in the pathophysiology of T2D (15). Still, iron was suggested to be functionally important for normal insulin secretion and pancreatic beta-cells metabolism (9,16,17). Exposure of pancreatic islets to high glucose concentrations stimulates production of ferritin (18), serving as a mechanism for the beta-cells to facilitate and maintain the critical iron stores during insulin secretion (9). Accordingly, hepcidin, iron-regulating hormone, produced by the liver and pancreas to facilitate intracellular iron accumulation by binding the iron exporter ferroportin (Fpn) and mediating its internalization and degradation (17-20), is located within the insulin secretory vesicles islets, and secreted after stimulation with high glucose. Since Fpn is expressed by beta-cells, hepcidin thus exerts an autocrine inhibitory action on beta-cells iron export (9,20,21).

Specifically in the liver, excessively accumulated iron interferes with glucose metabolism via both decreased insulin clearance and impaired insulin signaling, causing, as a result, hyperinsulinemia (22). Hyperinsulinemia, in turn, promotes the intra-hepatic buildup of iron, acting as mutually enhancing processes (8,22). Insulin was reported to directly enhance the uptake of extracellular iron, inducing the redistribution of transferrin receptor on the cell surface (23). Thus, it was shown that “iron and insulin are synergistic in promoting oxidative stress with release of ROS and inflammatory cytokines in the sub-endothelial space” (24). These inflammatory cytokines, in turn, promote ferritin synthesis in Kupffer cells and macrophages (8). These processes result in liver steatosis and, most important, in insulin resistance (25).

The porosity of liver sinusoidal endothelial cells (LSEC) – their key feature, ensures bidirectional passive transport of lipoproteins, drugs and solutes and insulin, between the liver capillaries and the liver parenchyma. This porosity is realized via fenestrations – transcellular pores with diameters in the range of 50–300 nm – typically grouped together in sieve plates. Several liver disorders as well as, most important, aging, severely reduce LSEC porosity, decreasing their filtration properties (26).

Fenestration loss during aging manifests as changes in the liver microcirculation, in particular within LSEC, which is a cause of dyslipidemia (26-27) and insulin resistance (26-27). At the morphological level, LSEC in old age have markedly reduced porosity (percent of the cell surface area covered in fenestrations) by about 50% – in other words, older LSEC become “defenestrated”. This defenestration results in hampered bi-directional traffic of substrates between the blood and the hepatocytes. Biomolecules such as lipoproteins, or hormones, or bioactive molecules (such as insulin) pass less easily through aged LSEC to reach the hepatocytes to be processed and/or exert their effects. Therefore, older rats showed a significant reduction in the hepatic volume of insulin distribution, illustrating that fenestrations facilitate insulin transfer to hepatocytes, while “defenestration” is linked to impaired insulin signaling followed by insulin resistance (26-28). On the other hand, recent findings demonstrate a clear causative link between the accumulation of the redox-active iron and LSEC defenestration (26-28). In other words, a direct mechanism binding iron accumulation in the specific organ (liver) and the pivotal feature of Type 2 Diabetes (insulin resistance), was established.

For years, increased iron stores were hypothesized to predict the development of T2D, while iron depletion was protective (29). Intracellular labile and redox-active iron often induces damage and modulates the development of various T2D complications (29). Attempts have been made in the past to treat diabetes with iron chelators, including Desferal® (where the active component is deferoxamine B - DFO). These treatments yielded controversial results that did not justify using Desferal® as an anti-T2D drug (31-33). Although iron chelating medications demonstrated minor efficacy against diabetes, caused by primary or secondary hemochromatosis (HFE hereditary hemochromatosis, beta-thalassemia) (34,35), in other subjects the success was even more limited. The main drawback of Desferal® is that its active component (DFO) does not penetrate membranes and, therefore, cannot scavenge the intracellular labile iron from within cells. DFO is a long-linear polar molecule; this specific structure explains its lack of infiltrability into cells.

Binding of a zinc ion to DFO and forming the newly developed zinc-DFO complex renders the molecule less polar, characterized by a relatively tight globular structure. This globular structure readily passes through cellular membranes. Within cells (as well as outside of cells), the zinc ion of the Zn-DFO complex readily exchanges “its” zinc ion with cellular labile iron. The process was suggested by Chevion M in 1991 and the term “push-pull mechanism” was then coined (36). Thus, the main obstacle of iron chelation by

Desferal® (alone) is overcome by the use of the Zn-DFO complex (36,37), so that intracellular toxic iron is sequestered and removed. This exchange reaction is explained by the affinity constants of DFO to ferric iron (46), which is markedly higher than that of DFO to zinc (log stability constants are 10^{31} & 10^{11} , respectively) (38). When zinc-DFO enters a cell, in the presence of intra-cellular labile iron, a rapid exchange of the zinc ion by iron occurs, forming the Fe-DFO complex. Zinc ion/s remain within the cell, and the Fe-DFO complex is mobilized into the circulation system and subsequently removed from the body (36).

The anti-diabetic effect of the Zn-DFO complex was tested on animal models of the disease (T2D). In this model, the drug was administered by intraperitoneal injections. The drug demonstrated high efficacy, normalizing blood glucose level, improving lipid profile, noticeably reducing serum insulin and bringing insulin resistance, expressed as HOMA-IR (Homeostatic Model Assessment for Insulin Resistance) almost to normal values (>93%). The effect on hepatic markers, e.g., ALT and AST, was limited, therefore the need for a more potent effect, specifically and effect targeting the liver was now clear.

Further, the Zn-DFO complex was tested on human subjects. In this trial, the drug was injected subcutaneously using multiple escalating doses. The study was prematurely terminated due to local pains at the injection site. This early termination meant that the participants did not reach the dose, that was expected to be optimal (because the dose reached using the escalating dose regimen was a lower dose than planned). Yet, in all three participants, a significant reduction in blood glucose level was observed. In addition, two patients demonstrated reduction in serum insulin and in HbA1c levels, having certain effect even on insulin resistance, expressed as HOMA-IR. No systemic adverse effects were observed. These outcomes emphasized a need for oral formulation of the Zn-DFO complex.

Poloxamers are a class of hydrophilic non-ionic surfactant of the more general class of copolymers known as poloxamers. Poloxamer 407 is a triblock copolymer consisting of a central hydrophobic block of polypropylene glycol flanked by two hydrophilic blocks of polyethylene glycol (PEG). The approximate lengths of the two PEG blocks are 101 repeat units, while the approximate length of the propylene glycol block is 56 repeat units. Most of the common uses of Poloxamer 407 are due to its surfactant properties. Yet, pharmacological studies revealed limitations in using Poloxamer 407 in medicine, such as an effect on plasma levels of cholesterol and triglycerides (39,40), alterations in lipid composition of serum lipoproteins (41), and lipases inhibition, followed

by eventual formation of aortic atherosclerotic lesions (42). Poloxamer 407 was described (43) as a compound with specific effect in liver, acting as a “defenestrating agent” in LSEC.

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SUMMARY OF THE INVENTION

Disclosed herein are compositions comprising (1) the complexes of deferoxamine B (DFO B) with at least one metal, such as zinc, gallium, silver, gold, molybdenum, vanadium, or any ionic forms thereof and (2) a hydrophilic non-ionic surfactant formulation comprising polyethylene glycol (PEG) and nonionic triblock copolymers composed of a central hydrophobic chain of polyoxypropylene (poly(propylene oxide)) flanked by two hydrophilic chains of polyoxyethylene (poly(ethylene oxide)), and diluent. Zinc may be present in the Zn-DFO complex as Zn^{2+} or gallium may be present in the Ga-DFO complex as Ga^{3+} . The hydrophilic non-ionic surfactant may be a poloxamer, such as poloxamer 407.

The concentration of the components of the hydrophilic formulation polyethylene glycol in a range of 17-23%, nonionic triblock copolymers composed of a central hydrophobic chain of polyoxypropylene (poly(propylene oxide)) flanked by two hydrophilic chains of polyoxyethylene (poly(ethylene oxide)) in a range of 8-12%, and diluent. The metal-DFO complex may be in pharmaceutical compositions comprising said metal-deferoxamine complexes and pharmaceutically acceptable inactive ingredients.

By one embodiment, either the metal ion or deferoxamine B are in the form of a salt with an acid, and the complex comprises an acid, in addition to the deferoxamine B and the metal ion. The acid is selected from the following non-limiting examples, including: 1-hydroxy-2-naphthoic acid, 2,2-dichloroacetic acid, 2-oxoglutaric acid, 4-acetamidobenzoic acid, 4-aminosalicylic acid, acetic acid, alkanesulphonic acid, alkenesulphonic acid, alkynesulphonic acid with any substitutions, adipic acid, ascorbic acid, aspartic acid, benzoic acid, camphoric acid, camphor-10-sulfonic acid, decanoic acid, hexanoic acid, octanoic acid, carbonic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, gluconic acid, glucuronic acid, glutamic acid, glutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, hydrobromic acid, hydrochloric acid, isobutyric acid, lactic acid, lactobionic acid, lauric acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid or its derivatives, or a substituted hydrocarbyl sulphonic acid, for example a hydroxy-, alkoxy-, acyloxy-, alkoxycarbonyl-, halogen-,

aromatic- or amino- substituted alkylsulphonic acid, nicotinic acid, nitric acid, oleic acid, oxalic acid, palmitic acid, pantoic acid, phosphoric acid, propionic acid, pyroglutamic acid, salicylic acid, sebacic acid, seleninic acid, selenonic acid, or any seleninic or selenonic analogue of the previously mentioned sulfonic compounds, stearic acid, succinic acid, 5 sulfuric acid, tartaric acid, thiocyanic acid, undecylenic acid.

The pharmaceutical composition may be administered alone or in combination with other pharmaceutically acceptable drug products. The pharmaceutical composition may be adapted to any mode of administration to the subject in need, including: oral, gavage, topical, ocular, nasal, administration to the ear, administration by inhalation, by 10 eye drops, systemic administration including parenteral, by injection, by suppositories, by patches, or by any other clinically accepted method and means. The pharmaceutical composition can be administered topically and/or systemically by any pharmaceutically acceptable method, including tablets, mini-tablets, pills, lozenges, pastilles, capsules, drinkable preparations, oral suspensions, soluble films, powders, ointments, creams, 15 pastes, encapsulated gel, patches, liposomes or sprayable aerosol or vapors containing the composition, when applied in an acceptable carrier. Alternatively, to any pulmonary delivery as by oral inhalation such as by using liquid nebulizers, aerosol-based metered dose inhalers (MDI's), or dry powder dispersion devices. Alternatively, the administration may be systemic such as by per os, i/v, i/m, s/c or any other modes of administration.

20 Metal-deferoxamine complexes can be applied as is, or conjugated with sugars, starches, amino acids, polyethylene-glycol, or polyglycerol-based compounds. Metal-deferoxamine complexes can be applied as is, or conjugated with hydrazines, hydroxylamines, amines, halides, aliphatics, aromatics, heterocyclic compounds, or any other pharmaceutically acceptable groups.

25 The clinical applications of the composition include the treatment, prophylaxis, and/or prevention of: Type 2 diabetes, metabolic syndrome and any other diabetes-related conditions and complications, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), Wilson's disease; Type 1 diabetes and its complications; neoplastic diseases with inflammatory component in pathophysiology; 30 diseases of the blood and blood-forming organs, involving the immune mechanism; metabolic disorders involving the inflammatory component; neurodegenerative and demyelinating disorders, such as multiple sclerosis, amyotrophic lateral sclerosis, age-related macular degeneration, Parkinson's disease, Alzheimer disease; inflammatory diseases of the central nervous system; immune-related disorders of circulatory and

cardiovascular system; inflammatory diseases of respiratory system, especially asthma, cystic fibrosis, allergic rhinitis, nasal polyposis and COPD; skin inflammatory disorders, especially, psoriasis, rheumatic arthritis, psoriatic arthritis, wound healing, injury due to exposure to chemical agents, heat or cold; ischemia and reperfusion injury; stroke;
5 immune-related diseases of digestive system, especially inflammatory bowel disease; thalassemia; hemochromatosis; autoimmune disorders; inflammatory diseases of oral cavity and salivary glands; infectious diseases, especially caused by *Escherichia coli*, *Staphylococcus aureus*, *Alcaligenes faecalis*, *Neisseria meningitidis*, *Prevotella intermedia*, *Porphyromonas gingivalis*, and species of *Salmonella*, *Shigella*, *Proteus*,
10 *Providencia*, *Enterobacter*, *Morganella* and *Pseudomonas*.

BRIEF DESCRIPTION OF THE DRAWINGS

In order to better understand the subject matter that is disclosed herein and to exemplify how it may be carried out in practice, embodiments will now be described, by
15 way of non-limiting example only, with reference to the accompanying drawings, in which:

Figure 1 depicts a comparative dissolution profile of Zn-DFO release from capsules.

Figure 2A depicts the AUC of DFO following intravenous administration. Figure 2B depicts the AUC of Fe-DFO after intravenous administration.

Figure 3 depicts the dynamics Fe-DFO using oral administration of Zn-DFO, diluted in
20 water.

Figure 4A depicts the dynamics Fe-DFO formulated in poloxamer in serum following oral administration. Figure 4B depicts the dynamics Fe-DFO formulated in gelucire in serum following oral administration. Figure 4C depicts the dynamics Fe-DFO formulated in labrasol/labrafac in serum following oral administration.

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DETAILED DESCRIPTION

Deferoxamine (DFO) is a siderophore (CAS# 70-51-9) that is synthesized by several microorganisms, including the generally recognized as safe (GRAS) bacterium *Streptomyces pilosus*. As detailed herein, DFO is a chelating agent. It comprises several
30 hydroxamic acid groups, which deprotonate to hydroxamates that bind to metal ion to form a complex. In a particular embodiment, the DFO is DFO-B

The term "*chelation*" relates to a particular way, by which ions and molecules bind metal ions. According to the International Union of Pure and Applied Chemistry (IUPAC), chelation involves the formation or presence of two or more separate coordinate bonds between a polydentate (multiple bonded) ligand and a single central atom. Usually these
5 ligands are organic compounds, and are called *chelants*, *chelators*, *chelating agents*, or *sequestering agents*. The chelate effect describes the enhanced affinity of chelating ligands for a metal ion compared to the affinity of a collection of similar nonchelating (monodentate) ligands for the same metal.

As used herein the term "*complex*" (also known as *complex ion* or *coordination
10 complexes*) refers to a chemical compound composed of a ligand having multiple binding sites (multidentate ligand) and a metal ion. The ligand being a chelating agent is in association with at least one metal ion.

As used herein, the term "*association*" refers to the chemical or physical force which holds two entities together (i.e. the ligand and the metal ion). Such force may be
15 any type of chemical or physical bonding interaction known to a person skilled in the art. Non-limiting examples of such association interactions are ionic bonding, covalent bonding, coordination bonding, complexation, hydrogen bonding, van der Waals bonding, hydrophobicity-hydrophilicity interactions, etc.

In some embodiments, the association may be via covalent bonding. In other
20 specific embodiments, the association may be via coordinative bonding. As used herein the term *coordinative bonding* or *coordinate bond* refers to a type of covalent bond in which two shared electrons originate from the same atom (known as dative bond). In the context of the present disclosure, the association between the ligand and the metal comprises association via multiple atoms in the ligand to several sites on the metal. Thus,
25 the association may be viewed as comprising more than one bond, at times two covalent bonds, at times one covalent bond and one coordinate bond, at times two coordinate bonds. The number of bonds is known as the complex's coordination number. The bonds may include single (sigma bond) and/or double (pi) bond and may be dipolar bonds.

It should be understood to a person skilled in the art that in some cases the
30 associative interactions between two atoms or two chemical entities may involve more than one type of chemical and/or physical interactions.

When referring to a *metal* it is to be understood as including any one or more of the elements commonly known as transition metals or post transition metals. In some

embodiments, the metal may act as a Lewis acid by accepting electron pairs from a donor Lewis bases (i.e. a chelating agent), thus forming a complex or complex ions. It should be noted that the donating electrons may be viewed as an electron pair donated into an empty metal orbital. In the context of the present disclosure, the metal may be referred to as a "*central metal*".

In some embodiments, at least one metal is selected from the group consisting of zinc, gallium, silver, gold, molybdenum, or any ionic forms thereof. In some embodiments, the metal may be found in the human body, namely may be an endogenous, non-toxic metal. In accordance with the present disclosure, at least one metal is a metal ion. In some embodiments, at least one metal ion may be selected from the group consisting of Zn^{2+} , Ga^{3+} , Ag^{1+} , Au^{3+} , Au^{1+} , V^{4+} , V^{5+} , Mo^{4+} , and Mo^{6+} .

As detailed herein, upon administration of the complex into a tissue or an organism, since the association between the ligand and the metal is reversible, the metal ion may be replaced by a different metal ion from an endogenous source and in turn may bind to another cellular component or could be released into the circulation in a ligand-free/unbound form. When referring to a *ligand-free/unbound form* it should be noted that the metal ion is free from or unbound to the ligand (i.e. DFO).

It was suggested that the release of the metal ion from the complex and the concomitant replacement by a different metal ion is derived from the differences in the dissociation constant of each one of the two metal ions from the ligand (i.e. DFO). In other words, replacement will be favorable in case the differences in the dissociation constants are such that dissociation of the complex and release of the metal ion is thermodynamically favorable as the association constant of the 'new' metal with the ligand (i.e., DFO) is higher than for the original metal ion. Without being bound by theory, it was suggested that a complex of deferoxamine B (DFO-B) and Zn^{2+} will have the tendency to release the metal ion (i.e. Zn^{2+}) and to bind Fe^{3+} . In some embodiments, the free unbound form of the metal ion may have a physiological effect, for example an antioxidant effect.

In some other embodiments, the metal ion is a redox inert metal. In other words, the metal ion does not participate in oxidation-reduction reactions in the body.

In some embodiments the at least one metal ion is Zn^{2+} . In yet some further embodiments the at least one metal ion is Ga^{3+} . In some embodiments, the composition described herein may comprise at least one complex of DFO with Zn^{2+} . In yet some other

embodiments, the composition described herein may comprise at least one complex of DFO with Ga^{3+} .

It should be appreciated that the composition described herein may comprise at least one complex of metal-DFO. In yet some other embodiments, the compositions may
5 comprise at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100 or more complexes. Still further, it must be appreciated that these complexes or any combinations thereof may be presented in the compositions at any ratio, for example, 1:1, to 0,0001:100,000 or more.

In yet some further embodiments, the compositions described herein may
10 comprise at least one complex of DFO with Ga^{3+} and at least one complex of DFO with Zn^{2+} . It should be noted that in certain embodiments such combinations may exist in said composition in any ratio, for example a ratio ranging between about 1:1 to 0.0001:100,000 to 100,000:0.0001. More specifically, 0.1:1, 0.2:1, 0.3:1, 0.4:1, 0.5:1, 0.6:1, 0.7:1, 0.8:1, 0.9:1, 1:1, 1:2, 1:3, 1:4, 1:5, 1:6, 1:7, 1:8, 1:9, 1:10, or more.

By one embodiment either the metal ion or the DFO are in the form of a salt with
15 an acid, and/or the complex comprises an acid, in addition to the siderophores and the metal ion. The acid may be selected from non-limiting examples, being 1-hydroxy-2-naphthoic acid, 2,2-dichloroacetic acid, 2-oxoglutaric acid, 4-acetamidobenzoic acid, 4-aminosalicylic acid, acetic acid, alkanesulphonic acid, alkenesulphonic acid,
20 alkynesulphonic acid with any substitutions, adipic acid, ascorbic acid, aspartic acid, benzoic acid, camphoric acid, camphor-10-sulfonic acid, decanoic acid, hexanoic acid, octanoic acid, carbonic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, gluconic acid, glucuronic acid, glutamic acid, glutaric acid, glycerophosphoric acid, glycolic acid,
25 hippuric acid, hydrobromic acid, hydrochloric acid, isobutyric acid, lactic acid, lactobionic acid, lauric acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid or its derivatives, or a substituted hydrocarbyl sulphonic acid, for example a hydroxy-,
alkoxy-, acyloxy-, alkoxycarbonyl-, halogen-, aromatic- or amino- substituted
alkylsulphonic acid, nicotinic acid, nitric acid, oleic acid, oxalic acid, palmitic acid, pantoic
30 acid, phosphoric acid, propionic acid, pyroglutamic acid, salicylic acid, sebacic acid, seleninic acid, selenonic acid, or any seleninic or selenonic analogue of the previously mentioned sulfonic compounds, stearic acid, succinic acid, sulfuric acid, tartaric acid, thiocyanic acid, undecylenic acid.

Metal-DFO complexes can be applied as is, or conjugated with sugars, starches, amino-acids, polyethylene-glycol, or polyglycerol-based compounds. Metal-DFO complexes can be applied as is, or conjugated with hydrazines, hydroxylamines, amines, halides, aliphatic, aromatic, heterocyclic compounds or any other pharmaceutically acceptable groups.

In another embodiment, the composition disclosed herein may be formulated in a pharmaceutical composition. More specifically, the composition described herein comprises as an active ingredient at least one of the metal-DFO complexes as described above, or any combinations thereof, and at least one pharmaceutically acceptable carriers, diluents, and/or excipients.

As used herein "*pharmaceutically acceptable carrier*" includes any and all solvents, dispersion media, coatings and the like. The use of such media and agents for pharmaceutical active substances is well known in the art. Except as any conventional media or agent is incompatible with the active ingredient, its use in the therapeutic composition is contemplated. In some embodiments the disclosed pharmaceutical composition of is suitable for systemic administration. The pharmaceutical composition can be administered and dosed by the methods described herein, in accordance with good medical practice. More specifically, the compositions used in the methods and kits, described herein after, may be adapted for administration by systemic, parenteral, intraperitoneal, transdermal, oral (including buccal or sublingual), rectal, topical (including buccal or sublingual), vaginal, intranasal and any other appropriate routes. Such formulations may be prepared by any method known in the art of pharmacy, for example by bringing into association the active ingredient with the carrier(s) or excipient(s).

The phrases "*systemic administration*", "*administered systemically*" as used herein mean the administration of a compound, drug or other material other than directly into the central blood system, such that it enters the patient's system and, thus, is subject to metabolism and other like processes. The phrases "*parenteral administration*" and "*administered parenterally*" as used herein means modes of administration other than enteral and topical administration, usually by injection, and includes, without limitation, intravenous, intramuscular, intraarterial, intrathecal, intracapsular, intraorbital, intracardiac, intradermal, intraperitoneal, transtracheal, subcutaneous, subcuticular, intraarticular, subcapsular, subarachnoid, intraspinal and intrasternal injection and infusion.

Systemic administration includes parenteral injection by intravenous bolus injection, by intravenous infusion, by sub-cutaneous, intramuscular, intraperitoneal injections or by suppositories, by patches, or by any other clinically accepted method, including tablets, pills, lozenges, pastilles, capsules, drinkable preparations, ointment, cream, paste, encapsulated gel, patches, boluses, or sprayable aerosol or vapors containing these complexes and combinations thereof, when applied in an acceptable carrier. Alternatively, to any pulmonary delivery as by oral inhalation such as by using liquid nebulizers, aerosol-based metered dose inhalers (MDI's), or dry powder dispersion devices.

In other embodiments the pharmaceutical composition described herein is adapted for topical administration. By "*topical administration*" it is meant that the pharmaceutical composition and the carrier may be adapted to any mode of topical administration including: epicutaneous, oral, bronchoalveolar lavage, ophthalmic administration, enema, nasal administration, administration to the ear, administration by inhalation.

Regardless of the route of administration selected, the compounds described herein, which may be used in a suitable hydrated form, and/or the pharmaceutical compositions, are formulated into pharmaceutically-acceptable dosage forms by conventional methods known to those of skill in the art.

Pharmaceutical compositions used to treat subjects in need thereof generally comprise a buffering agent, an agent who adjusts the osmolarity thereof, and optionally, one or more pharmaceutically acceptable carriers, excipients and/or additives as known in the art. Supplementary active ingredients can also be incorporated into the compositions. The carrier can be solvent or dispersion medium containing, for example, water, ethanol, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the use of a coating, such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants.

In some embodiments the pharmaceutical composition comprising DFO with a metal, as the active ingredient, can be administered either alone or in combination with other metal-DFO complexes. Of particular relevance are formulations of the complexes or any compositions described herein adapted for use as nano- or micro-particles. Nanoscale drug delivery systems using liposomes and nanoparticles are emerging technologies for the rational drug delivery, which offers improved pharmacokinetic

properties, controlled and sustained release of drugs and, more importantly, lower systemic toxicity. A particularly desired solution allows for externally triggered release of encapsulated compounds. Externally controlled release can be accomplished if drug delivery vehicles, such as liposomes or polyelectrolyte multilayer capsules, incorporate nanoparticle (NP) actuators. More specifically, controlled drug delivery systems (DDS) have several advantages compared to the traditional forms of drugs. A drug is transported to the site of action, hence, its influence on vital tissues and undesirable side effects can be minimized. Accumulation of therapeutic compounds in the target site increases and, consequently, the required doses of drugs are lower. This form of therapy is especially important when there is a discrepancy between the dose or the concentration of a drug and its therapeutic results or toxic effects. Cell-specific targeting can be accomplished by attaching drugs to specially designed carriers. Various nanostructures, including liposomes, polymers, dendrimers, silicon or carbon materials, and magnetic nanoparticles, have been tested as carriers in drug delivery systems. It should be therefore appreciated that the complexes or any compositions thereof may be formulated in any of the nano- or micro-particles disclosed herein.

Another embodiment relates to the method for modulating cytokine levels in a cell. More specifically, the disclosed method may comprise the step of contacting said cell with an effective amount of at least one complex of DFO with at least one metal or any derivatives thereof, compositions or any vehicle, matrix, nano- or micro-particle comprising the same. Thus, in some embodiments the metal-DFO complexes levels in a cell. As indicated herein after, modulating as used herein may be either increasing or decreasing the levels of cytokines in a cell or in a subject as described herein after.

Still further, in some embodiments, for modulating the cytokine levels in a cell, the complexes described herein may be contacted with the cell. The term "contacting" means, to bring, put, incubate or mix together. As such, a first item is contacted with a second item when the two items are brought or put together, e.g., by touching them to each other or combining them. The term "contacting" includes all measures or steps, which allow interaction between the disclosed complexes and the cells or subjects to be modulated, as specified herein after.

In some embodiments the metal of the complexes used by the methods described herein may be selected from the group consisting of lanthanides, actinides, post-transition metals, and/or transition metals. In another embodiment, the metal of the

complexes used may be selected from the group consisting of zinc, gallium, silver, gold, molybdenum, vanadium or any ionic forms thereof. In further embodiments, the metal ion of the complexes used by the methods described herein may be selected from the group consisting of Zn^{2+} , Ga^{3+} , Ag^{1+} , Au^{3+} , vanadium, and molybdenum. In yet some particular
5 embodiments the metal ion of the complexes used by the described methods may be Zn^{2+} . In some specific embodiments the disclosed methods may use at least one complex of DFO with Zn^{2+} . In alternative particular embodiments, the metal ion of the complexes used by the described methods may be Ga^{3+} . In some further embodiments, the methods may use at least one complex of DFO with Ga^{3+} .

10 As indicated above, the disclosed method may modulate cytokine levels in a cell. The term modulation as used herein refers to reduction or alternatively, to elevation of cytokine levels in said cell. In yet more specific embodiments, the metal-DFO complexes may lead to decrease, reduction, elimination, attenuation or inhibition of the cytokine levels of at least about 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%,
15 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%,
20 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or about 100% in a cell contacted with, or in a subject administered with the described complexes as compared with a cell or a subject not treated with the disclosed complexes. Alternatively, in some embodiments, modulation may relate to increase, elevation, enhancement or augmentation of the cytokine levels of at least about 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%,
25 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, 20%, 21%, 22%, 23%, 24%, 25%, 26%, 27%, 28%, 29%, 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40%, 41%, 42%, 43%, 44%, 45%, 46%, 47%, 48%, 49%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, 76%, 77%, 78%, 79%, 80%, 81%, 82%, 83%,
30 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 100%, 200%, 300%, 400%, 500%, 600%, 700%, 800%, 900% or about 1000%, in a cell or in a subject contacted or administered with the disclosed complex as compared with a cell or a subject not treated with the complexes.

Specifically, the method of modulation of cytokines described herein relates to a modulation of at least one pro-inflammatory cytokine and at least one anti-inflammatory cytokine. "*Cytokines*" are a category of small proteins (about 5 to 20 kDa), released by cells and have a specific effect on the interactions between cells, on communications
5 between cells or on the behavior of cells. Cytokines can also be involved in autocrine signaling. Cytokines include chemokines, interferons, interleukins, lymphokines, tumor necrosis factor but generally not hormones or growth factors (despite some terminologic overlap). Cytokines are produced by a broad range of cells, including immune cells like macrophages, B lymphocytes, T lymphocytes and mast cells, as well as endothelial cells,
10 fibroblasts, and various stromal cells; a given cytokine may be produced by more than one type of cell. It should be noted that in some embodiments, the described methods may be applicable in modulating the levels of any cytokines as described above.

Still further, in some other embodiments, the described methods may be used for modulating the levels of pro-inflammatory cytokines in a cell. "*Pro-inflammatory*
15 *cytokines*" are cytokines which promote systemic inflammation. Due to their pro-inflammatory action, they initiate the pathologic process or aggravate it by producing fever, edema, inflammation, tissue destruction, and in some cases, even shock and death. Non-limiting examples for pro-inflammatory cytokines include but are not limited to IL1- α , IL1- β , IL-6, and TNF- α , members of the IL-20 family, IL-33 LIF, IFN- γ , OSM,
20 CNTF, TGF- β , GM-CSF, IL-11, IL-12, IL-17, IL-18, IL-8 and a variety of other chemokines that chemo-attract inflammatory cells.

In several embodiments, the modulation of pro-inflammatory cytokines as used herein refers to the following cytokines: IL-1 α , TNF- α , IL-6 and IL-17. In more specific
25 embodiments, the methods described herein may lead to reduction in the levels of pro-inflammatory cytokines, specifically, to reduction in the levels of at least one of IL-1 α , TNF- α , IL-6 and IL-17.

In yet some further embodiments, the methods described herein may be used for modulating the levels of anti-inflammatory cytokines in a cell. The anti-inflammatory cytokines are a series of immuno-regulatory molecules that control the pro-inflammatory
30 cytokines response and act in concert with specific cytokine inhibitors and soluble cytokine receptors to down-regulate the inflammatory immune response. Major anti-inflammatory cytokines include but are not limited to interleukin IL-1 receptor antagonist, IL-4, IL-10, IL-11, and IL-13. Leukemia inhibitory factor, interferon-alpha and transforming

growth factor TGF- β are categorized as either anti-inflammatory or pro-inflammatory cytokines, under various circumstances. Specific cytokine receptors for IL-1, TNF- α , and IL-18 also function as inhibitors for pro-inflammatory cytokines. In some specific embodiments, the methods described herein may lead to modulation of the levels of at least one of IL-13, IL-10 and IL-4. In yet some other embodiments, the methods described herein may lead to elevation of the levels of at least one anti-inflammatory cytokine in a cell and more specifically, the levels of at least one of IL-13, IL-4 and IL-10.

By further embodiments the described methods for modulating cytokine levels in a subject. More specifically, in some embodiments, the method disclosed herein may comprise the step of administering to said subject an effective amount of at least one complex of DFO with at least one metal thereof and any compositions or any vehicle, matrix, nano- or micro-particle comprising the same. It should be appreciated that in certain embodiments, this method may use any complex described herein, any combinations thereof with other metal-DFO complexes or any compositions comprising the same.

Thus, in yet some specific embodiments, the described methods may modulate one or more pro-inflammatory cytokines levels in a subject. In further specific embodiments, the methods may reduce the level of at least one pro-inflammatory cytokine in a subject. In more specific embodiments, such pro-inflammatory cytokines may be at least one of IL-1 α , IL-6, TNF- α and IL-17.

Still further, in some specific embodiments, the described methods may modulate one or more anti-inflammatory cytokines levels in a subject. In more specific embodiments, the methods may elevate the level of at least one anti-inflammatory cytokine in a subject. In more specific embodiments, such anti-inflammatory cytokines may be at least one of IL-13, IL-4 and IL-10.

Reducing the biological activities of pro-inflammatory cytokines, or alternatively or additionally, elevating the levels or activities of anti-inflammatory cytokines, can reduce the severity of attack of diseases mediated by pro-inflammatory cytokines. Thus, reducing the biological activities of IL-1 α and TNF- α may be accomplished by several different, but highly specific, strategies, which involve neutralizing antibodies, soluble receptors, receptor antagonist, and inhibitors of proteases that convert inactive precursors to active, mature molecules. Blocking IL-1 α or TNF- α has been highly

successful in patients with psoriasis, rheumatoid arthritis, inflammatory bowel disease, or graft-versus-host disease.

Thus, in certain embodiments, the methods described herein may be particularly applicable for subjects suffering from a disorder associated with at least one of elevated
5 levels of pro-inflammatory cytokines and reduced levels of anti-inflammatory cytokines or from any other immune-mediated or related disorder.

More specifically, the metal-DFO complexes may be appropriate for a subject suffering from a disorder such as inflammatory, infectious, proliferative, neuro-degenerative, ischemic, metabolic, spinal cord injury, trauma, autoimmune disorders and
10 acute or chronic wound or injury. It should be noted that in some embodiments, the common denominator of these groups of disorders may be their relationship to pro-inflammatory cytokines, namely, IL-1 α , IL-6, TNF- α and IL-17 that are elevated and/or anti-inflammatory cytokines, specifically, any one of IL-13, IL-10 or IL-4, that are reduced while a disorder is active, and they return to base line level following a specific treatment.

15 The terms "decrease", "attenuation" and "elimination" as used herein relate to the act of becoming progressively smaller in size, amount, number, or intensity. Particularly, a decrease of 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 100% of the expression as compared to a suitable control. It should be further noted that decrease or reduction may be also a reduction of about 2
20 to 100 folds. Still further, it should be appreciated that the decrease in the levels or expression of said pro-inflammatory cytokines may be either in the transcription, translation or the stability of said cytokine. With regards to the above, it is to be understood that, where provided, percentage values such as, for example, 10%, 50%, 120%, 500%, etc., are interchangeable with "fold change" values, i.e., 0.1, 0.5, 1.2, 5, etc., respectively.

25 In some embodiments, *Interleukin-1 alpha* (IL-1 α) as used herein, also known as hematopoietin-1 is a protein of the interleukin 1 family that in humans is encoded by the *IL1A* gene. In general, Interleukin 1 is responsible for the production of inflammation, as well as the promotion of fever and sepsis. IL-1 α inhibitors are being developed to interrupt those processes and treat diseases.

30 IL-1 α is produced mainly by activated macrophages, as well as neutrophils, epithelial cells, and endothelial cells. A wide variety of other cells upon stimulation can produce the precursor form of IL-1 α . Among them are fibroblasts, macrophages, granulocytes, eosinophils, mast cells and basophils, endothelial cells, platelets,

monocytes and myeloid cell lines, blood T-lymphocytes and B-lymphocytes, astrocytes, kidney mesangial cells, Langerhans cells, dermal dendritic cells, natural killer cells, large granular lymphocytes, microglia, neutrophils, lymph node cells, maternal placental cells and several other cell types. IL-1 α possesses metabolic, physiological, hematopoietic activities, and plays one of the central roles in the regulation of the immune responses. It binds to the interleukin-1 receptor and, thereby, initiates the pathway that activates tumor necrosis factor- α .

Still further, *Interleukin-6* (IL-6), as used herein is an interleukin, acting as a classic pro-inflammatory cytokine. It is an important mediator of the acute phase response. It can be secreted by macrophages, neutrophils, adipocytes and muscle cells in response to a number of stress mediators, thus, stimulating further production of neutrophils and initiating several cellular stress-induced mechanisms. IL-6 stimulates inflammatory and auto-immune processes in numerous diseases, such as psoriasis, diabetes of both types, rheumatoid arthritis, atopic dermatitis, irritant contact dermatitis and sepsis.

Tumor necrosis factor- α (TNF- α), also known as cachexin, or cachectin is a cytokine involved in systemic inflammation. TNF- α is a member of a group of cytokines that stimulate the acute phase reaction. It is predominantly produced by activated macrophages, but can be secreted also by neutrophils, mast cells, eosinophils, myocytes, endothelial cells, fibroblasts, and natural killer cells. The main function, but not the only one, of this cytokine is to regulate the immune cells. Following activation by a different stress-related stimuli, it can induce fever, inflammation, and apoptotic cell death, using several different mechanisms in numerous types of cells. An increase in TNF- α concentration has been implicated in a huge variety of inflammatory diseases. It was demonstrated that a local increase in concentration of TNF- α will induce the typical signs of inflammation: heat, swelling, redness, pain and loss of function. There are multiple reports about a cross-talk and mutual activation of cytokines such as IL-1 super family, IL-6 and TNF- α .

Interleukin 17A (IL-17 or IL-17A) as used herein, originally identified as a transcript from a rodent T-cell hybridoma, is the founding member of a group of cytokines called the IL-17 family. Known as CTLA8 in rodents, IL-17 shows high homology to viral IL-17 encoded by an open reading frame of the T-lymphotropic rhadinovirus *Herpesvirus saimiri*. Interleukin 17 is a cytokine that acts as a potent mediator in delayed-type reactions by increasing chemokine production in various tissues to recruit monocytes and

neutrophils to the site of inflammation, similar to Interferon gamma. IL-17 is produced by T-helper cells and is induced by IL-23, which results in destructive tissue damage in delayed-type reactions. Interleukin 17 functions as a pro-inflammatory cytokine that responds to the invasion of the immune system by extracellular pathogens and induces
5 destruction of the pathogen's cellular matrix. Interleukin 17 acts synergistically with tumor necrosis factor and interleukin-1. To elicit its functions, IL-17 binds to a type I cell surface receptor called IL-17R of which there are at least three variants IL17RA, IL17RB, and IL17RC.

Numerous immune regulatory functions have been reported for the IL-17 family of
10 cytokines, presumably due to their induction of many immune signaling molecules. The most notable role of IL-17 is its involvement in inducing and mediating pro-inflammatory responses. IL-17 is commonly associated with allergic responses. IL-17 induces the production of many other cytokines (such as IL-6, G-CSF, GM-CSF, IL-1 β , TGF- β , TNF- α), chemokines (including IL-8, GRO- α , and MCP-1), and prostaglandins (e.g., PGE₂)
15 from many cell types (fibroblasts, endothelial cells, epithelial cells, keratinocytes, and macrophages). The release of cytokines causes many functions, such as airway remodeling, a characteristic of IL-17 responses. The increased expression of chemokines attracts other cells including neutrophils but not eosinophils. IL-17 function is also essential to a subset of CD4+ T-Cells called T helper 17 (T_H17) cells. As a result
20 of these roles, the IL-17 family has been linked to many immune/autoimmune related diseases including rheumatoid arthritis, asthma, lupus, allograft rejection, anti-tumor immunity and recently psoriasis and multiple sclerosis. Notably, among this family, IL-17F has been well characterized both *in vitro* and *in vivo* and has been shown to have a pro-inflammatory role in asthma and its expression level is correlated with disease
25 severity. Hence, IL-17F may have a crucial role in allergic airway inflammation, and have important therapeutic implications in asthma. Because of its involvement in immune regulatory functions, IL-17 inhibitors are being investigated as possible treatments for autoimmune diseases such as rheumatoid arthritis, psoriasis and inflammatory bowel disease.

30 Recently, new treatments for inflammatory disorders have been developed where at least one of the rationales was to reduce the levels of pro-inflammatory cytokines. For example, as TNF- α is known to promote inflammatory response, monoclonal antibodies have been developed to inhibit this cytokine in order to treat diseases associated with inflammation, such as psoriasis, rheumatoid arthritis, ulcerative colitis, Crohn's disease,

and ankylosing spondylitis. Another TNF- α inhibitor, the circulating receptor fusion protein has been in use for treatment of psoriasis, rheumatoid arthritis and ankylosing spondylitis.

Reducing the biological activities of IL-1 and TNF is accomplished by several
5 different, but highly specific, strategies, which involve neutralizing antibodies, soluble receptors, receptor antagonist, and inhibitors of proteases that convert inactive precursors to active, mature molecules. Blocking IL-1 or TNF has proven a highly successful treatment of patients with rheumatoid arthritis, inflammatory bowel disease, or graft-versus-host disease. Likewise, using an inhibitor of IL-17 has also been a
10 strategy for treatment of other disorders associated with inflammation. Based on emerging evidence from animal models, IL-17 has been suggested as a target for anti-inflammatory therapies to improve recovery post-stroke and to reduce the formation of skin cancer. IL-17 has also been implicated in multiple sclerosis. IL-17A, IL-17F and IL-17A/F-receptor inhibitors: brodalumab, ixekizumab and secukinumab received recently
15 an approval for the treatment of psoriasis. Thus, the disclosed metal-DFO E complexes, compositions, kits and methods provide novel tools for treating and preventing any disorder associated with elevated levels of the pro-inflammatory cytokines, specifically, the disorders mentioned herein above.

Still further, the methods described herein may lead to an increase in the levels of
20 anti-inflammatory cytokines, specifically of at least one of IL-13 IL-10 and IL-4. According to some embodiments, wherein indicate "increasing" or "enhancing" the expression of the levels of an anti-inflammatory cytokine, for example, any one of IL-13, IL-10 and IL-4, specifically of IL-13, it is meant that such increase or enhancement may be an increase or elevation of between about 10% to 100% of the expression of such cytokines. The
25 terms "increase", "augmentation" and "enhancement" as used herein relate to the act of becoming progressively greater in size, amount, number, or intensity. Particularly, an increase of 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95% or 100% of the expression as compared to a suitable control. It should be further noted that increase or elevation may be also an increase of about 2
30 to 100 folds. Still further, it should be appreciated that the increase of the levels or expression of said IL-13 cytokine may be either in the transcription, translation or the stability of said cytokine. With regards to the above, it is to be understood that, where provided, percentage values such as, for example, 10%, 50%, 120%, 500%, etc., are interchangeable with "fold change" values, i.e., 0.1, 0.5, 1.2, 5, etc., respectively.

Interleukin-13 (IL-13), as used herein is an example for anti-inflammatory cytokine. IL-13 is secreted by many cell types, but especially by the T-helper Type 2 (Th2) cells. Several publications describe it as a mediator of allergic "*inflammation*" and disease, while on the other hand it has also been described as a mediator playing a potent anti-inflammatory role. Additionally, IL-13 was shown to induce several changes in the gut that create an environment hostile to parasites (helminthes), that ultimately lead to detachment of the parasitic organisms from the gut wall and their removal.

Interleukin-10 (IL-10) is a major anti-inflammatory cytokine found within the human immune response. It is a potent inhibitor of Th1 cytokines, including both IL-2 and IFN- γ . This activity accounts for its initial designation as cytokine synthesis inhibition factor. In addition to its activity as a Th2 lymphocyte cytokine, IL-10 is also a potent deactivator of monocyte/macrophage pro-inflammatory cytokine synthesis. After engaging its high-affinity 110-kd cellular receptor, IL-10 inhibits monocyte/macrophage-derived TNF- α , IL-1, IL-6, IL-8, IL-12, granulocyte colony-stimulating factor, MIP-1a, and MIP-2a.

The pharmaceutical composition described herein may be specifically suitable for treating disorders associated with inflammation. Based on the insufficient availability of specific anti-inflammatory treatments and the awareness of the roles of pro-inflammatory cytokines in the pathogenesis of several groups of disorders, the development of new anti-inflammatory treatments is anticipated. Thus, there is a current need for the employment of the metal-DFO complexes described herein in therapy.

Thus, the disclosed metal-DFO complex may be useful for methods of treating, preventing, inhibiting, reducing, eliminating, protecting or delaying the onset of a pathological condition or a disorder in a subject in need thereof. In some specific embodiments, the method comprises the step of administering to the treated subject a therapeutically effective amount of at least one complex of DFO with at least one metal or any combinations thereof with other metal-DFO complexes, or any pharmaceutical compositions, carriers, matrix or vehicles comprising the same. In some specific embodiments, these disorders and/or diseases may be characterized by having a clinical beneficial effect when the labile iron or copper are chelated, and more specifically, when pro-inflammatory cytokines associated with these disorders are reduced (down regulated) and/or when anti-inflammatory cytokines associated with these disorders are elevated (up regulated). In more specific embodiments, the disclosed metal-DFO

complex provides a method for treating, preventing, reducing, attenuating, inhibiting and eliminating a disorder associated with elevated pro-inflammatory cytokines by administering to said a subject in need thereof a therapeutically effective amount of at least one complex of DFO with at least one metal, carriers, matrix or vehicles comprising
5 the same.

In some embodiments the metal of the complexes used by the described methods may be post-transition metals and/or transition metals.

In another embodiment the metal of the complexes used by the methods described herein may be selected from the group consisting of zinc, gallium, silver, gold,
10 molybdenum, vanadium, or any ionic forms thereof. In further embodiments the metal ion of the complexes used by the methods may be selected from the group consisting of Zn^{2+} , Ga^{3+} , Ag^{1+} , and Au^{3+} , vanadium, and molybdenum. In yet a particular embodiment the metal ion of the complexes used by the disclosed methods may be Zn^{2+} . In some
15 embodiments the methods may use at least one complex of DFO with Zn^{2+} as described herein before. In alternative particular embodiments, the metal ion of the complexes used by the methods may be Ga^{3+} . In some further embodiments, the methods may use at least one complex of DFO with Ga^{3+} .

As disclosed earlier herein, according to specific embodiments, the disclosed method may be useful for treating, preventing, inhibiting, reducing, eliminating,
20 protecting, or delaying the onset of a disease or a pathological condition or a disorder, wherein said disorder is associated with at least one of elevated levels of pro-inflammatory cytokine/s and reduced levels of anti-inflammatory cytokines. Specifically, the pro-inflammatory cytokines may be at least one of $\text{IL-1}\alpha$, $\text{TNF-}\alpha$, IL-6 and IL-17 . In some further embodiments, the anti-inflammatory cytokines may be at least one of IL-13 ,
25 IL-10 , and IL-4 .

As noted above, some embodiments provide a method of treating, preventing, inhibiting, reducing, eliminating, protecting or delaying the onset of a disease or a disorder, which is associated with at least one of elevated levels of pro-inflammatory cytokines and reduced levels of anti-inflammatory cytokines. In more specific
30 embodiments, the disorder may be at least one of inflammatory, infectious, proliferative, neuro-degenerative, ischemic, metabolic, spinal cord injury, trauma, autoimmune disorders and acute or chronic wound or injury.

In specific embodiments, are provided methods for treating inflammatory disorders in a subject in need thereof, comprising the step of administering to said subject a therapeutically effective amount of at least one complex of DFO with at least one metal, carriers, matrix or vehicles comprising the same, wherein inflammatory disorder relates to any disorder/disease, condition selected from Type 2 diabetes, metabolic syndrome and any other diabetes-related conditions and complications, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), Wilson's disease; Type 1 diabetes and its complications; neoplastic diseases with inflammatory component in pathophysiology; diseases of the blood and blood-forming organs, involving the immune mechanism; metabolic disorders involving the inflammatory component; neurodegenerative and demyelinating disorders, such as multiple sclerosis, amyotrophic lateral sclerosis, age-related macular degeneration, Parkinson's disease, Alzheimer disease; inflammatory diseases of the central nervous system; immune-related disorders of circulatory and cardiovascular system; inflammatory diseases of respiratory system, especially asthma, cystic fibrosis, allergic rhinitis, nasal polyposis and COPD; skin inflammatory disorders, especially, psoriasis, rheumatic arthritis, psoriatic arthritis, wound healing, injury due to exposure to chemical agents, heat or cold; ischemia and reperfusion injury; stroke; immune-related diseases of digestive system, especially inflammatory bowel disease; thalassemia; hemochromatosis; autoimmune disorders; inflammatory diseases of oral cavity and salivary glands; and infectious diseases caused by *Escherichia coli*, *Staphylococcus aureus*, *Alcaligenes faecalis*, *Neisseria meningitidis*, *Prevotella intermedia*, *Porphyromonas gingivalis*, and species of *Salmonella*, *Shigella*, *Proteus*, *Providencia*, *Enterobacter*, *Morganella* and *Pseudomonas*.

The general term "*inflammatory disorder*" relates to disorders where inflammation is a main response to harmful stimuli, such as pathogens, damaged cells, or irritants. Inflammation is a protective response that involves immune cells, blood vessels, and molecular mediators, as well as the end result of long-term oxidative stress. "*Inflammatory disorders*" are a large group of disorders that underlie a vast variety of human diseases. Also, the immune system can be involved in inflammatory disorders, stemming from abnormal immune response of the organism against substances of its own, or initiation the inflammatory process for unknown reason, i.e. autoimmune and auto-inflammatory disorders, respectively. Non-immune diseases with etiological origins in inflammatory processes include cancer, atherosclerosis, and ischemic heart disease.

The purpose of inflammation is to eliminate the initial cause of cell injury, clear out necrotic cells and tissues and to initiate tissue repair. The classical physiological signs of acute inflammation are pain, heat, redness, swelling, and loss of function. A series of biochemical events propagates and matures the inflammatory response, involving the local vascular system, the immune system, and various cells within the injured tissue. Prolonged inflammation, known as "*chronic inflammation*", leads to a progressive shift in the type of cells present at the site of inflammation and is characterized by simultaneous destruction and healing of the tissue from the inflammatory process. Inflammation also induces high systemic levels of specific cytokines designated as pro-inflammatory cytokines which include IL-1 α , IL-6, IL-8, IFN- γ , TNF- α , IL-17 and IL-18. The inflammatory response must be actively terminated when no longer needed to prevent unnecessary "*bystander*" damage to tissues. Failure to do so results in chronic inflammation, and cellular destruction. Resolution of inflammation occurs by different mechanisms in different tissues. Acute inflammation normally resolves by mechanisms that have remained somewhat elusive. Emerging evidence now suggests that an active, coordinated program of resolution initiates in the first few hours after an inflammatory response begins. After entering tissues, granulocytes promote the switch of arachidonic acid-derived prostaglandins and leukotrienes to lipoxins, which initiate the termination sequence. Neutrophil recruitment thus ceases, and programmed death by apoptosis (programmed cell death) is engaged. These events coincide with the biosynthesis, from omega-3 polyunsaturated fatty acids, of resolvins and protectins, which critically shorten the period of neutrophil infiltration by initiating apoptosis. As a consequence, apoptotic neutrophils undergo phagocytosis by macrophages, leading to neutrophil clearance and release of anti-inflammatory and reparative cytokines such as transforming growth factor- β 1. The anti-inflammatory program ends with the departure of macrophages through the lymphatics.

The term "*pathological conditions associated with inflammation*" as used herein relates to at least one but not limited to the following: Type 2 diabetes, metabolic syndrome and any other diabetes-related conditions and complications, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), Wilson's disease; Type 1 diabetes and its complications; neoplastic diseases with inflammatory component in pathophysiology; diseases of the blood and blood-forming organs, involving the immune mechanism; metabolic disorders involving the inflammatory component; neurodegenerative and demyelinating disorders, such as multiple sclerosis, amyotrophic

lateral sclerosis, age-related macular degeneration, Parkinson's disease, Alzheimer disease; inflammatory diseases of the central nervous system; immune-related disorders of circulatory and cardiovascular system; inflammatory diseases of respiratory system, especially asthma, cystic fibrosis, allergic rhinitis, nasal polyposis and COPD; skin
5 inflammatory disorders, especially, psoriasis, rheumatic arthritis, psoriatic arthritis, wound healing, injury due to exposure to chemical agents, heat or cold; ischemia and reperfusion injury; stroke; immune-related diseases of digestive system, especially inflammatory bowel disease; thalassemia; hemochromatosis; autoimmune disorders; inflammatory diseases of oral cavity and salivary glands; and infectious diseases caused
10 by *Escherichia coli*, *Staphylococcus aureus*, *Alcaligenes faecalis*, *Neisseria meningitidis*, *Prevotella intermedia*, *Porphyromonas gingivalis*, and species of *Salmonella*, *Shigella*, *Proteus*, *Providencia*, *Enterobacter*, *Morganella* and *Pseudomonas*,

Chronic or acute inflammatory skin pathologic conditions include dermatitis, inflammatory skin disorders, inflammatory-related disturbances of skin pigmentation, for
15 example, vitiligo and eczemas. More specifically, certain embodiments relate to the use of the disclosed metal-DFO complex, as well as compositions, methods and kits thereof for treating dermatitis. The term "dermatitis" refers to inflammation of the skin, in general. The different kinds usually have in common an allergic reaction to specific allergens. The term may be used to refer to eczema, which is also known as dermatitis eczema or eczematous
20 dermatitis. A diagnosis of eczema often implies atopic dermatitis (childhood eczema), but without proper context, it means nothing more than a "rash", i.e. a transient skin inflammation. In some languages, "dermatitis" and eczema are synonyms, while in other languages "dermatitis" implies an acute condition and "eczema" a chronic one. The two conditions are often classified together. In some specific embodiments, the methods,
25 complexes and compositions described herein, may be applicable for any type of dermatitis, specifically, atopic dermatitis, contact dermatitis, seborrheic dermatitis or seborrheic dermatitis and xerotic eczema. More specifically, as used herein, atopic dermatitis is an allergic disease believed to have a hereditary component, and often runs in families whose members also have asthma. Itchy rash is particularly noticeable on head and
30 scalp, neck, inside of elbows, behind knees, and buttocks. It is very common, and rising, in developed countries. Irritant contact dermatitis is sometimes misdiagnosed as atopic dermatitis. Still further, contact dermatitis, as used herein is of two types: allergic (resulting from a delayed reaction to an allergen, such as poison ivy, nickel, or Balsam of Peru), and irritant (resulting from direct a reaction to a detergent, such as sodium lauryl

sulfate, for example). Xerotic eczema, as used herein (aka asteatotic e., e. craquele or craquelatum, winter itch, pruritus hiemalis) is dry skin that becomes so serious it turns into eczema. It worsens in dry winter weather, and limbs and trunk are most often affected. The itchy, tender skin resembles a dry, cracked, river bed. Finally, the methods
5 may be used for treating seborrheic dermatitis ("cradle cap" in infants), that as used herein, is a condition sometimes classified as a form of eczema that is closely related to dandruff. It causes dry or greasy peeling of the scalp, eyebrows, and face, and sometimes trunk. The condition is harmless except in severe cases of cradle cap. In newborns it causes a thick, yellow, crusty scalp rash called cradle cap, which seems
10 related to lack of biotin and is often curable. It should be appreciated that the methods described herein may be applicable for any form of dermatitis disclosed herein.

It should be appreciated that based on its anti-inflammatory qualities the complexes, and compositions described herein could be applicable for treatment of another inflammatory skin disorder, specifically, psoriasis.

15 Psoriasis is also an inflammatory disorder mediated by pro- and anti-inflammatory cytokines. Although the exact causes and pathogenesis of psoriasis are unknown, over-expression of pro-inflammatory, type 1 (Th1) cytokines has been demonstrated in psoriasis and is believed to be of pathophysiological importance. Importantly, a relative deficiency in cutaneous IL-10 mRNA expression compared with other inflammatory
20 dermatoses was demonstrated. Moreover, previous publications demonstrate that patients during established antipsoriatic therapy showed higher IL-10 mRNA expression of peripheral blood mononuclear cells than patients before therapy. This suggested that IL-10 may have antipsoriatic capacity. Indeed, subcutaneous administration of IL-10 produced immunosuppressive effects in patients (depressed monocytic HLA-DR
25 expression, TNF-alpha and IL-12 secretion capacity, IL-12 plasma levels, and responsiveness to recall antigens) as well as a shift toward a type 2 (Th2) cytokine pattern (increasing proportion of IL-4, IL-5, and IL-10 producing T cells, selective increase in IgE serum levels) were observed. More specifically, psoriasis is a common skin condition that features patchy, raised, red areas of skin inflammation with scaling. Psoriasis
30 often affects the tips of the elbows and knees, the scalp, the navel, and the area surrounding the genitals or anus. It occurs when the immune system sends out faulty signals that speed up the growth cycle of skin cells. The scaly patches commonly caused by psoriasis, called psoriatic plaques, are areas of inflammation and excessive skin production. Skin rapidly accumulates at these sites which gives it a silvery-white appearance. Plaques frequently

occur on the skin of the elbows and knees, but can affect any area including the scalp, palms of hands and soles of feet, and genitals. In contrast to eczema, psoriasis is more likely to be found on the outer side of the joint. The disorder is a chronic recurring condition that varies in severity from minor localized patches to complete body coverage. Fingernails and toenails
5 are frequently affected (psoriatic nail dystrophy) and can be seen as an isolated symptom. Psoriasis can also cause inflammation of the joints, which is known as psoriatic arthritis. Ten to fifteen percent of people with psoriasis develop psoriatic arthritis, which is of chronic recurrent nature. The symptoms of psoriasis can manifest in a variety of forms. Variants include plaque, pustular, guttate and flexural psoriasis. Psoriasis may be classified into
10 nonpustular and pustular types.

Nonpustular psoriasis includes Psoriasis vulgaris and Psoriatic erythroderma. Psoriasis vulgaris (also known as Chronic stationary psoriasis or Plaque-like psoriasis), is the most common form of psoriasis. It affects 80 to 90% of people with psoriasis. Plaque psoriasis typically appears as raised areas of inflamed skin covered with silvery white scaly
15 skin. These areas are called plaques.

Psoriatic erythroderma (Erythrodermic psoriasis) involves the widespread inflammation and exfoliation of the skin over most of the body surface. It may be accompanied by severe itching, swelling and pain. It is often the result of an exacerbation of unstable plaque psoriasis, particularly following the abrupt withdrawal of systemic treatment.
20 This form of psoriasis can be fatal, as the extreme inflammation and exfoliation disrupt the body's ability to regulate temperature and for the skin to perform barrier functions.

In yet another specific embodiment, the methods described herein may be used for treating Pustular psoriasis. Pustular psoriasis appears as raised bumps that are filled with non-infectious pus (pustules). The skin under and surrounding the pustules is red and tender.
25 Pustular psoriasis can be localized, commonly to the hands and feet (palmoplantar pustulosis), or generalized with widespread patches occurring randomly on any part of the body. Pustular psoriasis subtypes include Generalized pustular psoriasis (Pustular psoriasis of von Zumbusch), Pustulosis palmaris et plantaris (Persistent palmoplantar pustulosis, Pustular psoriasis of the Barber type, Pustular psoriasis of the extremities), Annular pustular
30 psoriasis, Acrodermatitis continua and Impetigo herpetiformis.

It should be appreciated that the methods described herein may be also applicable for treating any additional types of psoriasis, for example, drug-induced psoriasis, inverse psoriasis, or flexural psoriasis. The latter appears as smooth inflamed patches of skin in skin

folds, particularly around the genitals (between the thigh and groin), the armpits, under an overweight stomach (pannus), and under the breasts (inframammary fold). It is aggravated by friction and sweat and is vulnerable to fungal infections.

Still further, the methods reported herein may be used for treating guttate psoriasis.

- 5 This type of psoriasis is characterized by numerous small, scaly, red or pink, teardrop-shaped lesions. These numerous spots of psoriasis appear over large areas of the body, primarily the trunk, but also the limbs, and scalp. Guttate psoriasis is often preceded by a streptococcal infection, typically streptococcal pharyngitis.

- 10 Nail psoriasis that may be also treated by the disclosed methods to produce a variety of changes in the appearance of finger and toe nails. These changes include discoloring under the nail plate, pitting of the nails, lines going across the nails, thickening of the skin under the nail, and the loosening (onycholysis) and crumbling of the nail.

- In yet another embodiment, the metal-DFO complex may be used for treating psoriatic arthritis. Psoriatic arthritis involves joint and connective tissue inflammation.
- 15 Psoriatic arthritis can affect any joint but is most common in the joints of the fingers and toes. This can result in a sausage-shaped swelling of the fingers and toes known as dactylitis. Psoriatic arthritis can also affect the hips, knees and spine (spondylitis). About 10-15% of people who have psoriasis also have psoriatic arthritis.

- In some embodiments, treatment of a subject suffering from psoriasis may improve
- 20 the physiological state of the subject, for example, smoothing skin that was rough due to the disease. In preferred embodiments, such psychological improvement can be achieved by topical application of the metal-complexes described herein, which does not irritate the skin and does not promote inflammation.

- It should be appreciated that the complexes described herein, as well as
- 25 compositions, and methods thereof, may be applicable for treating psoriasis, as well as the extra-dermatological features of psoriasis including psoriatic arthritis.

- Acne is another non-limiting example for skin inflammatory disorders that may be treated by the disclosed method. Acne is a general term used for eruptive disease of the skin. It is sometimes used as a synonym for acne vulgaris. However, there are several
- 30 different types of acne. These include Acne vulgaris, acne conglobata, acne miliaris necrotica, tropical acne, infantile acne/neonatal acne, excoriated acne, acne fulminans, drug-induced acne/acne medicamentosa (steroid acne), halogen acne (iododerma, bromoderma, chloracne), oil acne, tar acne, acne cosmetica, occupational acne, acne

aestivalis, acne keloidalis nuchae, acne mechanica, acne with facial edema, pomade acne, acne necrotica, blackhead, and lupus miliaris disseminatus faciei.

Inflammation-related skin disorder that may be treated by the method described herein, and may include also insect bites and stings. During the sting insects inject formic acid and/or toxins. These can cause an immediate skin reaction, often resulting in redness and swelling, in the injured area. The sting from Hymenoptera order are usually painful, and may stimulate, in patients at risk, a life-threatening systemic allergic reaction, called anaphylaxis. Systemic allergic sting reactions often result in cutaneous, vascular or respiratory symptoms and signs, either alone or in any combination with possible involvement of other less common target tissues. Cardiac anaphylaxis can also cause bradycardia, arrhythmias, angina or myocardial infarction. Bites from mosquitoes, fleas, and mites are more likely to cause itching than pain. The skin reaction to insect bites and stings usually lasts for up to a few days. However, in some cases the local reaction can last for up to two years. The reaction to a sting is of three types. The normal reaction involves the area around the bite with redness, itchiness, and pain. A large local reaction occurs when the area of swelling is greater than five cm (in diameter). Systemic reactions are when symptoms occur in areas besides that of the bites.

In yet another embodiment, the method described herein may be applicable for treating vitiligo. Vitiligo as used herein is a chronic disorder that causes depigmentation of patches of skin. It occurs when melanocytes, die or are unable to function. The cause of vitiligo is unknown, but research suggests that it may arise from autoimmune, genetic, oxidative stress, neural, or viral causes. The incidence worldwide is less than 1%, with the most common form being non-segmental vitiligo. Symptoms usually begin between ages 10 years and age 30 years, including whitening or graying of hair, loss of skin color inside the mouth and loss of eye color. The most notable symptom of vitiligo is depigmentation of patches of skin that occurs on the extremities. In non-segmental vitiligo (NSV), there is usually some form of symmetry in the location of the patches of depigmentation. New patches also appear over time and can be generalized over large portions of the body or localized to a particular area. Vitiligo where little pigmented skin remains is referred to as vitiligo universalis. NSV can come about at any age, unlike segmental vitiligo which is far more prevalent in teenage years. Classes of non-segmental vitiligo include generalized vitiligo, universal vitiligo, focal vitiligo, acrofacial vitiligo and mucosal vitiligo. Segmental vitiligo (SV) differs in appearance, etiology, and prevalence from associated illnesses. Its treatment is different from that of NSV. It tends

to affect areas of skin that are associated with dorsal roots from the spine. It spreads much more rapidly than NSV and, without treatment, it is much more stable/static in course and is not associated with auto-immune diseases, being a treatable condition that responds to topical treatment.

5 It should be appreciated that the metal-DFO complexes described herein, compositions, complexes, kits and methods, may be applicable for any form of inflammatory skin disorder, specifically, any form of dermatitis or psoriasis disclosed herein.

 Still further, it should be appreciated that in certain embodiments, the methods described herein may be applicable for treating an acute or chronic wound. In yet some
10 further embodiments, the methods may be applicable for treating acute or chronic injury caused by a chemical or thermal burn, and by mechanical hit/blow. As such, the disclosed methods may be useful for wound healing.

 The term *wound* as used herein is a type of injury which happens relatively quickly in which a skin is torn, cut, or punctured (an *open* wound), or where blunt force trauma
15 causes a contusion (a *closed* wound). In pathology, it specifically refers to a sharp injury which damages the dermis of the skin. The wounds can be further classified as penetrating and non-penetrating. Penetrating wounds result from a trauma that breaks through the full thickness of the skin; reaching down to the underlying tissue and organs. Non-penetrating wounds are usually the result of blunt trauma or friction with other
20 surfaces and this kind of wound does not break through the skin. Miscellaneous wounds may include, but are not limited to: *Thermal wounds*: Extreme temperatures, either hot or cold, can result in thermal injuries (like burns, sunburns and frostbite). Thermal burn is a type of burn resulted from making contact with heated objects, such as boiling water, steam, hot cooking oil, fire, and hot objects. Scalds are the most common type of thermal
25 burn suffered by children, while for adults thermal burn is most commonly caused by fire. Burns are generally classified by severity from first degree up to fourth degree, but the American Burn Association (ABA) has categorized thermal burns as minor, moderate, and major, based almost solely on the depth and size of the burn. *Chemical wounds*: These result from contact with or inhalation of chemical materials that cause skin or lung
30 damage. A chemical burn occurs when a living tissue is exposed to a corrosive substance such as a strong acid or base. Chemical burns follow standard burn classification and may cause extensive tissue damage. The main types of irritant and/or corrosive products are: acids, bases, oxidizers/reducing agents, solvents, and alkylants. Additionally,

chemical burns can be caused by some types of chemical weapons, e.g., vesicants such as mustard gas and Lewisite, or urticants such as phosgene oxime. *Bites and Stings*: Bites can be from humans, dogs, bats, rodents, snakes, scorpions, spiders and ticks. *Electrical wounds*: These usually present with superficial burn-like or sting-like wounds
5 secondary to the passage of high-voltage electrical currents through the body, and may include more severe internal damage.

Depending on the healing time of a wound, it can be classified as acute or chronic. Those classified as acute wounds heal uneventfully (with no complications) in the predicted amount of time. Those classified as chronic wounds take a longer time to heal
10 and might have some complications. Factors that contribute to non-healing chronic wounds are diabetes, venous or arterial disease, infection, and metabolic deficiencies of old age.

Non-healing wounds of the diabetic foot are considered one of the most significant complications of diabetes, representing a major worldwide medical, social, and economic
15 burden that greatly affects patient quality of life. Associated with inadequate circulation, poorly functioning veins, and immobility, non-healing wounds occur most frequently in the elderly and in people with diabetes — populations that are sharply rising as the nation ages and chronic diseases increase.

Although diabetes can ravage the body in many ways, non-healing ulcers on the
20 feet and lower legs are common outward manifestations of the disease. Also, diabetics often suffer from nerve damage in their feet and legs, allowing small wounds or irritations to develop without awareness. Given the abnormalities of microvasculature and other side effects of diabetes, these wounds take a long time to heal and require a specialized treatment approach for proper healing.

25 *Pressure ulcers*, also known as *pressure sores*, *bedsores* and *decubitus ulcers*, are localized injuries to the skin and/or underlying tissue that usually occur over a bony prominence as a result of pressure, or pressure in combination with shear and/or friction. The most common sites are the skin overlying the sacrum, coccyx, heels or the hips, but other sites such as the elbows, knees, ankles or the back of the cranium can be affected.

30 Pressure ulcers occur due to pressure applied to soft tissue resulting in completely or partially obstructed blood flow to the soft tissue. Shear is also a cause, as it can pull on blood vessels that feed the skin. Pressure ulcers most commonly develop in individuals who are not moving about, such as those being bedridden or confined to a

wheelchair. It is widely believed that other factors can influence the tolerance of skin for pressure and shear, thereby increasing the risk of pressure ulcer development. These factors are protein-calorie malnutrition, microclimate (skin wetness caused by sweating or incontinence), diseases that reduce blood flow to the skin, such as arteriosclerosis, or
5 diseases that reduce the sensation in the skin, such as paralysis or neuropathy. The healing of pressure ulcers may be slowed by the age of the person, medical conditions (such as arteriosclerosis, diabetes or infection), smoking or medications such as anti-inflammatory drugs.

As indicated above, in some embodiments, the disclosed methods may be for
10 wound healing. *Wound healing* is an intricate process where the skin or other body tissue repairs itself or is being repaired after injury. In normal skin, the epidermis (surface layer) and dermis (deeper layer) form a protective barrier against the external environment. When the barrier is broken, an orchestrated cascade of biochemical events is quickly set
15 into motion to repair the damage. This process is divided into predictable phases: blood clotting (hemostasis), inflammation, the growth of new tissue (proliferation), and the remodeling of tissue (maturation).

It should not be overlooked that the composition described herein, particularly when used for treating inflammatory skin disorders, may be acceptable as topically applied composition. Specific embodiments contemplate skin inflammatory conditions,
20 specifically, psoriasis treatment by topical administration of the affected skin areas of an ointment, cream, suspensions, paste, lotions, powders, solutions, oils, encapsulated gel, liposomes containing the complexes, any nano-particles containing the complexes, or sprayable aerosol or vapors containing a combination of these complexes. Conventional pharmaceutical carriers, aqueous, powder or oily bases, thickeners and the like may be
25 necessary or desirable. The term "topically applied" or "topically administered" means that the ointment, cream, emollient, balm, lotion, solution, salve, unguent, or any other pharmaceutical form is applied to some or all of that portion of the skin of the patient skin that is, or has been, affected by, or shows, or has shown, one or more symptoms of psoriasis or other skin lesion.

30 By analogy, the metal-DFO complexes described herein or any pharmaceutical compositions thereof, as well as methods may be applicable for preventing, treating, ameliorating or inhibiting another inflammation/immune-mediated disorder, e.g. inflammatory bowel disease (IBD), specifically, ulcerative colitis and Crohn's disease.

Inflammatory bowel diseases (IBD) are common gastrointestinal disorders, that can be perceived as being the result of a dysbalance between Th1-pro-inflammatory and Th2-anti-inflammatory subtypes of immune responses. IBD is a group of inflammatory conditions of the colon and small intestine. The major types of IBD are Crohn's disease and ulcerative colitis (UC). Other forms of IBD account for far fewer cases. These are collagenous colitis, lymphocytic colitis, ischaemic colitis, diversion colitis, and indeterminate colitis, in cases where it is impossible to make a definitive diagnosis distinguishing Crohn's disease from ulcerative colitis.

The main difference between Crohn's disease and UC is the location and nature of the inflammatory changes. Crohn's disease can affect any part of the gastrointestinal tract, from mouth to anus (skip lesions), although a majority of the cases start in the terminal ileum. Ulcerative colitis, in contrast, is restricted to the colon and the rectum. Microscopically, ulcerative colitis is restricted to the mucosa (epithelial lining of the gut), while Crohn's disease affects the whole bowel wall. Finally, Crohn's disease and ulcerative colitis present with extra-intestinal manifestations (such as liver problems, arthritis, skin manifestations and eye problems) in different proportions. Crohn's disease and ulcerative colitis share the same symptoms such as diarrhea, vomiting, weight loss, fever, and abdominal pain.

Since an inflammatory process is a mainstay of immune-mediated disorders, the anti-inflammatory effect, of compositions described herein make them appropriate for the treatment of subjects suffering from an immune-mediated disorders, for example, various forms of arthritis. It should be appreciated that various forms of arthritis may be generally grouped into two main categories, inflammatory arthritis, and degenerative arthritis, each with different causes. Therefore, according to one specific embodiment, the metal-DFO complexes or any pharmaceutical compositions thereof may be specifically intended for the treatment and/or amelioration of an inflammatory disorder, for example, an inflammatory arthritis.

Inflammatory arthritis is characterized by synovitis, bone erosions, osteopenia, soft-tissue swelling, and uniform joint space narrowing. More specifically, the hallmarks of joint inflammation are synovitis and erosion of bone. The latter will initially appear as a focal discontinuity of the thin, white, subchondral bone plate. Normally, this subchondral bone plate can be seen even in cases of severe osteopenia, whereas its discontinuity indicates erosion. Although it is true that periarticular osteopenia and focal subchondral

osteopenia can appear prior to true bone erosion, it is the presence of bone erosion that indicates definite joint inflammation. As the bone erosion enlarges, osseous destruction extends into the trabeculae within the medullary space. One important feature of inflammatory arthritis relates to the concept of marginal bone erosion. This term is given to bone erosion that is located at the margins of an inflamed synovial joint. This specific location represents that portion of the joint that is intra-articular but not covered by hyaline cartilage. Therefore, early joint inflammation will produce marginal erosions prior to erosions of the subchondral bone plate beneath the articular surface. When looking for bone erosions, multiple views of a joint are essential to profile the various bone surfaces.

A second important characteristic of an inflammatory joint process is uniform joint space narrowing. This occurs because destruction of the articular cartilage is uniform throughout the intra-articular space. A third finding of inflammatory joint disease is soft-tissue swelling.

It should be appreciated that inflammatory arthritis may be further divided into several subgroups, and therefore, the metal-DFO complexes, compositions, and the methods described herein, may be applicable for treating every inflammatory arthritis including an arthritis of the different subgroup. A systemic arthritis is characterized by involvement of multiple joints, and includes two main categories, rheumatoid arthritis and seronegative spondyloarthropathy.

According to one embodiment, the metal-DFO complexes, compositions as well as methods, described herein may be used for the treatment and/or amelioration of rheumatoid arthritis. Rheumatoid arthritis (RA) is a chronic, systemic autoimmune disorder that most commonly causes inflammation and tissue damage in joints (arthritis) and tendon sheaths, together with anemia. It can also produce diffuse inflammation in the lungs, pericardium, pleura, and the sclera of the eye, and also nodular lesions, most common in subcutaneous tissue. It can be a disabling and painful condition, which can lead to substantial loss of functioning and mobility. Serologic markers such as rheumatoid factor and antibodies to cyclic citrullinated peptide are important indicators of rheumatoid arthritis. The radiographic features of rheumatoid arthritis are those of joint inflammation and include particular osteopenia, uniform joint space loss, bone erosions, and soft-tissue swelling. Because of the chronic nature of the inflammation, additional findings such as joint subluxation and subchondral cysts may also be evident.

The seronegative spondyloarthropathy category includes psoriatic arthritis, reactive arthritis, and ankylosing spondylitis, and is characterized by signs of inflammation, multiple joint involvement, and distal involvement in the hands and feet with added features of bone proliferation. Thus, according to one embodiment, the disclosed
5 metal-DFO complexes, compositions and methods may be used for the treatment and/or amelioration of any condition of the seronegative spondyloarthropathy category.

More specifically, according to a non-limited embodiment, the metal-DFO complexes, compositions and methods described herein may be used for preventing, treating, ameliorating or inhibiting any type of arthritis, including psoriatic arthritis.
10 Psoriatic arthritis is a chronic disease characterized by inflammation of the skin (psoriasis) and joints (arthritis).

Males and females are equally likely to suffer from psoriasis. For psoriatic arthritis, males are more likely to have the spondylitic form (in which the spine is affected), and females are more likely to have the rheumatoid form (in which many joints may be
15 involved). Psoriatic arthritis usually develops in people aged 35-55 years. However, it can develop in people of almost any age. Psoriatic arthritis shares many features with several other arthritic conditions, such as ankylosing spondylitis, reactive arthritis, and arthritis associated with Crohn's disease and ulcerative colitis. All of these conditions can cause inflammation in the spine and joints, in the eyes, skin, mouth, and various organs.

20 In yet another embodiment, the metal-DFO complexes, compositions, as well as methods described herein, may be used for preventing, treating, ameliorating or inhibiting reactive arthritis (ReA). Reactive arthritis, another type of seronegative spondyloarthropathy, is an autoimmune condition that develops in response to an infection in another part of the body. Coming into contact with bacteria and developing
25 an infection can trigger reactive arthritis. It has symptoms similar to various other conditions collectively known as "arthritis," such as rheumatism. It is caused by another infection and is thus "reactive", i.e., dependent on the other condition. The "trigger" infection has often been cured or is in remission in chronic cases, thus making determination of the initial cause difficult.

30 The symptoms of reactive arthritis very often include a combination of three seemingly unlinked symptoms, an inflammatory arthritis of large joints, inflammation of the eyes (conjunctivitis and uveitis), and urethritis. It should be indicated that ReA is also

known as Reiter's syndrome, after the German physician Hans Reiter, it is also known as arthritis urethritica, venereal arthritis and polyarteritis enterica.

It should be appreciated that there are many other forms of inflammatory arthritis, including juvenile idiopathic arthritis, gout and pseudo gout, as well as arthritis associated with colitis or psoriasis. It should be therefore appreciated that the metal-DFO complexes, compositions, as well as methods are also applicable for these conditions.

Therefore, the metal-DFO complexes, compositions and methods described herein, may be used for preventing, treating, ameliorating or inhibiting juvenile idiopathic arthritis (JIA). JIA, is the most common form of persistent arthritis in children (juvenile in this context refers to an onset before age 16, idiopathic refers to a condition with no defined cause, and arthritis is the inflammation of the synovium of a joint). JIA is a subset of arthritis seen in childhood, which may be transient and self-limited or chronic. It differs significantly from arthritis commonly seen in adults (rheumatoid arthritis), and other types of arthritis that can present in childhood which are chronic conditions (e.g. psoriatic arthritis and ankylosing spondylitis).

Still further, in some specific embodiments for inflammatory disorders, any inflammatory-respiratory disease, such as asthma can benefit from the treatment with the metal-DFO complexes, composition described herein, where a therapeutically effective amount of the composition thereof is administered to a subject suffering from the disease. Thus, in specific embodiments, the method may be used for the prophylaxis, treatment and/or amelioration of respiratory disorders, specifically, asthma.

Asthma is a common chronic inflammatory disease of the airways characterized by variable and recurring symptoms, reversible airflow obstruction and bronchospasm. Common symptoms include wheezing, coughing, chest tightness, and shortness of breath. Asthma is thought to be caused by a combination of genetic and environmental factors. Its diagnosis is usually based on the pattern of symptoms, response to therapy over time and spirometry. It is clinically classified according to the frequency of symptoms, forced expiratory volume in one second (FEV1), and peak expiratory flow rate. Asthma may also be classified as atopic (extrinsic) or non-atopic (intrinsic) where atopy refers to a predisposition toward developing type 1 hypersensitivity reactions.

Treatment of acute symptoms of asthma is usually with an inhaled short-acting beta-2 agonists (such as salbutamol) and oral corticosteroids. In very severe cases, intravenous corticosteroids, magnesium sulfate, and hospitalization may be required.

Symptoms can be prevented by avoiding triggers, such as allergens and irritants, and by the use of inhaled corticosteroids. Long-acting beta agonists (LABA) or antileukotriene agents may be used in addition to inhaled corticosteroids if asthma symptoms remain uncontrolled.

5 Asthma is the result of chronic inflammation of the airways which subsequently results in increased contractability of the surrounding smooth muscles. This among other factors leads to bouts of narrowing of the airway and the classic symptoms of wheezing. The narrowing is typically reversible with or without treatment. Occasionally the airways themselves change. Typical changes in the airways include an increase in eosinophils
10 and thickening of the lamina reticularis. Chronically the airways' smooth muscle may increase in size along with an increase in the numbers of mucous glands. Other cell types involved include: T lymphocytes, macrophages, and neutrophils. There may also be involvement of other components of the immune system including: cytokines, chemokines, histamine, and leukotrienes.

15 While there is no cure for asthma, symptoms can typically be improved. A specific, customized plan for proactively monitoring and managing symptoms should be created. This plan should include the reduction of exposure to allergens, testing to assess the severity of symptoms, and the usage of medications. The treatment plan should be written down and advise adjustments to treatment according to changes in symptoms.

20 Importantly, the metal-siderophore, specifically, metal-DFO complexes disclosed herein provide an additional therapeutic dimension to the current available medications, as they do not only serve as preventive measures against the development of the described respiratory disorder pathologies, but also diminish the ensuing tissue damage.

It should be noted that medications for asthma and other respiratory-associated disorders
25 are typically provided as metered-dose inhalers (MDIs) in combination with an asthma spacer or as a dry powder inhaler. The spacer is a plastic cylinder that mixes the medication with air, making it easier to receive a full dose of the drug. A nebulizer may also be used. The metal-DFO B complexes described herein may be therefore administered using such MDIs, and may be also combined with any other asthma medications, specifically those
30 indicated above.

As indicated above, the present disclosure contemplates methods for the treatment of various immune-related respiratory diseases. In addition to asthma, such respiratory diseases may include any other acute allergy manifestations in airways, chronic

rhinosinusitis (CRS), allergic rhinitis, COPD, nasal polyposis (NP), vasomotor rhinitis, airways hyper-responsiveness, cystic fibrosis and lung fibrosis, or allergic sinusitis. The disclosure therefore provides methods, combined compositions and kits for preventing, treating, ameliorating or inhibiting any of the respiratory diseases described above.

5 Thus, in certain embodiments, the metal-DFO described herein may be used for treating sinusitis. Sinusitis is inflammation of the paranasal sinuses, which may be due to infection, allergy or autoimmune issues. Most cases are due to a viral infection and resolve over the course of 10 days. It is a common condition with more than 24 million cases occurring in the United States annually.

10 Chronic sinusitis, by definition, lasts longer than three months and can be caused by many different diseases that share chronic inflammation of the sinuses as a common symptom. Chronic sinusitis cases are subdivided into cases with polyps and cases without polyps. When polyps are present, the condition is called chronic hyperplastic sinusitis; however, the causes are poorly understood and may include allergy, environmental factors
15 such as dust or pollution, bacterial infection, or fungus (either allergic, infective, or reactive). Non-allergic factors, such as vasomotor rhinitis, can also cause chronic sinus problems.

 Allergic rhinitis, pollinosis or hay fever that may be treated by the method described herein, is an allergic inflammation of the nasal airways. It occurs when an allergen such as pollen or dust is inhaled by an individual with a sensitized immune system, and triggers
20 antibody production. These antibodies mostly bind to mast cells, which contain histamine. When the mast cells are stimulated by pollen and dust, histamine (and other chemicals) is released. This causes itching, swelling and mucus production. Symptoms vary in severity between individuals. Very sensitive individuals can experience hives or other rashes.

 Chronic obstructive pulmonary disease (COPD), also known as chronic obstructive
25 lung disease (COLD), chronic obstructive airway disease (COAD), chronic airflow limitation (CAL) and chronic obstructive respiratory disease (CORD), refers to chronic bronchitis and emphysema, a pair of commonly co-existing diseases of the lungs in which the airways become narrowed. This leads to a limitation of the flow of air to and from the lungs causing shortness of breath. In contrast to asthma, the limitation of airflow is poorly reversible and
30 usually gets progressively worse over time. COPD is caused by noxious particles or gas, most commonly from tobacco smoking, which triggers an abnormal inflammatory response in the lung. The inflammatory response in the larger airways is known as chronic bronchitis, which is diagnosed clinically when people regularly cough up sputum. In the alveoli, the

inflammatory response causes destruction of the tissues of the lung, a process known as emphysema. The natural course of COPD is characterized by occasional sudden worsening of symptoms called acute exacerbations, most of which are caused by infections or air pollution. The methods, combined compositions, and kits are applicable for treating COAD
5 and COPD.

Still further, the metal-DFO described herein may be used for treating nasal polyps. Nasal polyps are polypoidal masses arising mainly from the mucous membranes of the nose and paranasal sinuses. They are overgrowths of the mucosa that frequently accompany allergic rhinitis. They are freely moveable and non-tender. Nasal polyps are usually classified
10 into antrochoanal polyps and ethmoidal polyps. Antrochoanal polyps arise from the maxillary sinuses and are the much less common, ethmoidal polyps arise from the ethmoidal sinuses. Antrochoanal polyps are usually single and unilateral whereas ethmoidal polyps are multiple and bilateral.

Non-allergic rhinitis refers to runny nose that is not due to allergy. Non-allergic rhinitis
15 can be classified as either non-inflammatory or inflammatory rhinitis. One very common type of non-inflammatory, non-allergic rhinitis that is sometimes confused with allergy is called vasomotor rhinitis, in which certain non-allergic triggers such as smells, fumes, smoke, dusts, and temperature changes, cause rhinitis. It is thought that these non-allergic triggers cause dilation of the blood vessels in the lining of the nose, which results in swelling, and
20 drainage. Vasomotor rhinitis can coexist with allergic rhinitis, and this is called "mixed rhinitis." Vasomotor rhinitis appears to be significantly more common in women than men, leading some researchers to believe that hormones play a role. In general, age of onset occurs after 20 years of age, in contrast to allergic rhinitis which can be developed at any age. Individuals suffering from vasomotor rhinitis typically experience symptoms year-round,
25 though symptoms may exacerbate in the spring and autumn when rapid weather changes are more common. An estimated 17 million United States citizens have vasomotor rhinitis. The antihistamine azelastine has been shown to be effective for allergic, mixed and vasomotor rhinitis.

Airway hyperresponsiveness (or other combinations with bronchial or hyper-
30 reactivity) is a state characterized by easily triggered bronchospasm (contraction of the bronchioles or small airways). Airway hyperresponsiveness can be assessed with a bronchial challenge test. This most often uses products like metacholine or histamine. These chemicals trigger bronchospasm in normal individuals as well, but people with bronchial

hyperresponsiveness have a lower threshold. Bronchial hyperresponsiveness is a hallmark of asthma but also occurs frequently in people suffering from chronic obstructive pulmonary disease (COPD).

5 Cystic fibrosis (also known as CF) that is another example for conditions that may be treated by the disclosed metal-DFO is a common disease which affects the entire body, causing progressive disability and often early death. The name cystic fibrosis refers to the characteristic scarring (fibrosis) and cyst formation within the pancreas. Difficulty breathing is the most serious symptom and results from frequent lung infections that are treated, though not cured, by antibiotics and other medications. A multitude of other symptoms, including sinus infections, poor growth, diarrhea, and infertility result from the effects of CF on other parts of the body. CF is caused by a mutation in the gene for the protein cystic fibrosis transmembrane conductance regulator (CFTR), and is considered as an autosomal recessive disease.

15 Pulmonary fibrosis is the formation or development of excess fibrous connective tissue (fibrosis) in the lungs. It can be described as "scarring of the lung". Pulmonary fibrosis involves gradual replacement of normal lung parenchyma with fibrotic tissue. Thickening of scar tissue causes irreversible decrease in oxygen diffusion capacity. In addition, decreased compliance makes pulmonary fibrosis a restrictive lung disease. It is the main cause of restrictive lung disease that is intrinsic to the lung parenchyma.

20 Some embodiments relate to methods particularly for treating respiratory diseases with the disclosed metal-DFO. According to one embodiment, such compositions may be particularly adapted for pulmonary delivery by oral or nasal inhalation. More specifically, pulmonary delivery may require the use of liquid nebulizers, aerosol-based metered dose inhalers (MDI's), or dry powder dispersion devices.

25 In further embodiments, the metal-DFO provides a method of treating or preventing an infectious disease or condition in a mammalian subject caused by any pathogen, specifically, at least one of, bacterial pathogen, a viral pathogen and a parasite. More specifically, the method comprises the step of administering to a subject in need the effective amount of the metal-DFO complexes or any compositions thereof.

30 "*Infection*" as used herein, is the invasion of an organism's body tissues by disease-causing agents, their multiplication, and the reaction of host tissues to these organisms and the toxins they produce. Infectious disease, also known as transmissible disease or communicable disease, is illness resulting from an infection. It should be

appreciated that an infectious disease as used herein also encompasses any infectious disease caused by a pathogenic agent. Pathogenic agents include bacteria, viruses, prokaryotic microorganisms, lower eukaryotic microorganisms, complex eukaryotic organisms, prions, parasites, yeasts, nematodes such as parasitic roundworms and
5 pinworms, arthropods such as ticks, mites, fleas, and lice, fungi such as ringworm, and other macroparasites such as tapeworms and other helminths.

Prokaryotic microorganisms includes bacteria as detailed herein after, for example, Gram positive, Gram negative, Gram variable bacteria, acid fast organisms and intracellular bacteria. A lower eukaryotic organism includes a yeast or fungus such
10 as but not limited to *Pneumocystis carinii*, *Candida albicans*, *Aspergillus*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Cryptococcus neoformans*, *Trichophyton* and *Microsporum*.

A complex eukaryotic organism includes worms, insects, arachnids, nematodes, aemobe, *Entamoeba histolytica*, *Giardia lamblia*, *Trichomonas vaginalis*, *Trypanosoma*
15 *brucei gambiense*, *Trypanosoma cruzi*, *Balantidium coli*, *Toxoplasma gondii*, *Cryptosporidium* or *Leishmania*.

The term "viruses" is used in its broadest sense to include viruses of the families adenoviruses, papovaviruses, herpesviridae (simplex, varicella zoster, Epstein-Barr, CMV), hepatitis A, hepatitis B, hepatitis C, influenza viruses A and B, pox viruses:
20 smallpox, vaccinia, rhinoviruses, poliovirus, rubella virus, arboviruses, rabies virus, flaviviruses, measles virus, mumps virus, HIV, HTLV I and II.

The term "fungi" includes for example, fungi that cause diseases such as ringworm, histoplasmosis, blastomycosis, aspergillosis, cryptococcosis, sporotrichosis, coccidioidomycosis, paracoccidio-idoynycosis, and candidiasis.

25 The term "parasite" includes, but is not limited to, infections caused by somatic tapeworms, blood flukes, tissue roundworms, ameba, and Plasmodium, Trypanosoma, Leishmania, and Toxoplasma species.

It should be noted that the complex of DFO with at least one metal may chelate labile iron and/or copper, reducing the availability of labile iron for synthetic and
30 proliferative purposes of the microorganism, thereby inhibiting growth of pathogenic microorganisms, and diminishing the extent of infection/inflammation. Thus, in some embodiments, the metal DFO may be useful in methods for treating an infectious disease caused by a bacterial pathogen. In some specific embodiments, the bacterial pathogen

may be at least one of enteropathogenic *Escherichia coli* (EPEC), *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

Bacterial infection is an example of inflammation-related disorder. The metal-DFO described herein, including complexes or any combinations thereof, as well as
5 pharmaceutical compositions thereof, may be used for preventing, treating, ameliorating or inhibiting bacterial infections. More specifically, the term "*bacterial infections*" relates to infection caused by bacteria. The term "*bacteria*" (in singular a "bacterium") in this context refers to any type of a single celled microbe. This term encompasses herein
10 bacteria belonging to general classes according to their basic shapes, namely spherical (cocci), rod (bacilli), spiral (spirilla), comma (vibrios) or corkscrew (spirochaetes), as well as bacteria that exist as single cells, in pairs, chains or clusters.

In more specific embodiments, the term "*bacteria*" specifically refers to Gram positive, Gram negative or acid fast organisms. The Gram-positive bacteria can be recognized as retaining the crystal violet stain used in the Gram staining method of
15 bacterial differentiation, and therefore appear to be purple-colored under a microscope. The Gram-negative bacteria do not retain the crystal violet, making positive identification possible. In other words, the term 'bacteria' applies herein to bacteria with a thicker peptidoglycan layer in the cell wall outside the cell membrane (Gram-positive), and to bacteria with a thin peptidoglycan layer of their cell wall that is sandwiched between an
20 inner cytoplasmic cell membrane and a bacterial outer membrane (Gram-negative).

The disclosed metal-DFO may act as an anti-inflammatory agent, as a bacteriostatic and/or bacteriocidal agent, and as a strong chelator of labile and redox-active iron. In some embodiments, examples of bacteria contemplated herein include the species of the genera *Treponema* sp., *Borrelia* sp., *Neisseria* sp., *Legionella* sp.,
25 *Bordetella* sp., *Escherichia* sp., *Salmonella* sp., *Shigella* sp., *Klebsiella* sp., *Yersinia* sp., *Vibrio* sp., *Hemophilus* sp., *Rickettsia* sp., *Chlamydia* sp., *Mycoplasma* sp., *Staphylococcus* sp., *Streptococcus* sp., *Bacillus* sp., *Clostridium* sp., *Corynebacterium* sp., *Propionibacterium* sp., *Mycobacterium* sp., *Ureaplasma* sp. and *Listeria* sp. In yet some more specific embodiments, bacterial pathogens may include but are not limited to
30 enteropathogenic *Escherichia coli* (EPEC), *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Streptococcus pyogenes*, *Clostridium difficile*, *Enterococcus faecium*, *Klebsiella pneumoniae*, *Acinetobacter baumannii* and *Enterobacter* species, *Mycobacterium tuberculosis*, *Alcaligenes faecalis*, *Neisseria meningitis*, *Prevotella intermedia*,

Porphyromonas gingivalis, species of *Salmonella*, *Shigella*, *Proteus*, *Providencia*, *Enterobacter* and *Morganella*.

Thus, composition comprising the disclosed metal-DFO exhibits substantial antibacterial effect, which makes it applicable for the treatment of infection-mediated disorders. It should be also appreciated that the beneficial antibacterial effect of the metal-DFO complexes or any compositions thereof may be enhanced by combination thereof with other known anti-bacterial agents.

In yet some embodiments, the disclosed methods may be applicable for treating proliferative disorder in a subject in need thereof. In some specific embodiments, the method may comprise the step of administering to the subject a therapeutically effective amount of at least one complex of DFO with at least one metal, or any disclosed pharmaceutical compositions, carriers, matrix or vehicles comprising the same. It should be further appreciated that the method may be specifically relevant for proliferative disorders that are malignancies associated with at least one of elevated pro-inflammatory cytokines and reduced levels of anti-inflammatory cytokines.

The term "*proliferative disorder*" means cell division and growth that is not part of normal cellular turnover, metabolism, growth, or propagation of the whole organism. Unwanted proliferation of cells is seen in tumors and other pathological proliferation of cells, it does not serve normal function, and for the most part will continue unbridled at a growth rate exceeding that of cells of a normal tissue in the absence of outside intervention. A pathological state that ensues because of the unwanted proliferation of cells is referred herein as a "hyper proliferative disease" or "hyper proliferative disorder." It should be noted that the term "proliferative disorder", "cancer", "tumor" and "malignancy" all relate equivalently to a hyperplasia of a tissue or organ. In general, the compositions and methods described herein may be used in the treatment of non-solid and solid tumors.

Still further, malignancy, as contemplated herein may be any one of carcinomas, melanomas, lymphomas, leukemias, myeloma and sarcomas. Carcinoma as used herein refers to an invasive malignant tumor consisting of transformed epithelial cells. Alternatively, it refers to a malignant tumor composed of transformed cells of unknown histogenesis, but which possess specific molecular or histological characteristics that are associated with epithelial cells, such as the production of cytokeratins or intercellular bridges.

Melanoma as used herein is a malignant tumor of melanocytes. Melanocytes are cells that produce the dark pigment, melanin, which is responsible for the color of skin. They predominantly occur in skin, but are also found in other parts of the body, including the bowel and the eye. Melanoma can occur in any part of the body that contains melanocytes.

Leukemia refers to progressive, malignant diseases of the blood-forming organs and is generally characterized by a distorted proliferation and development of leukocytes and their precursors in the blood and bone marrow. Leukemia is generally clinically classified on the basis of (1) the duration and character of the disease-acute or chronic; (2) the type of cell involved; myeloid (myelogenous), lymphoid (lymphogenous), or monocytic; and (3) the increase or non-increase in the number of abnormal cells in the blood-leukemic or aleukemic (subleukemic).

Sarcoma is a cancer that arises from transformed connective tissue cells. These cells originate from embryonic mesoderm, or middle layer, which forms the bone, cartilage, and fat tissues. This is in contrast to carcinomas, which originate in the epithelium. The epithelium lines the surface of structures throughout the body, and is the origin of cancers in the breast, colon, and pancreas.

Myeloma as mentioned herein is a cancer of plasma cells, a type of white blood cell normally responsible for the production of antibodies. Collections of abnormal cells accumulate in bones, where they cause bone lesions, and in the bone marrow where they interfere with the production of normal blood cells. Most cases of myeloma also feature the production of a paraprotein, an abnormal antibody that can cause kidney problems and interferes with the production of normal antibodies leading to immunodeficiency. Hypercalcemia (high calcium levels) is often encountered.

Lymphoma is a cancer in the lymphatic cells of the immune system. Typically, lymphomas present as a solid tumor of lymphoid cells. These malignant cells often originate in lymph nodes, presenting as an enlargement of the node (a tumor). It can also affect other organs in which case it is referred to as extranodal lymphoma. Non-limiting examples for lymphoma include Hodgkin's disease, non-Hodgkin's lymphomas and Burkitt's lymphoma.

Further malignancies that may be treated and/or prevented by the metal-DFO complex described herein comprise but are not limited to hematological malignancies (including lymphoma, leukemia and myeloproliferative disorders, as described above),

hypoplastic and aplastic anemia (both virally induced and idiopathic), myelodysplastic syndromes, all types of paraneoplastic syndromes (both immune mediated and idiopathic) and solid tumors (including GI tract, colon, lung, liver, breast, prostate, pancreas and Kaposi's sarcoma. The metal-DFO complex may be applicable as well for the treatment or

5 inhibition of solid tumors such as tumors in lip and oral cavity, pharynx, larynx, paranasal sinuses, major salivary glands, thyroid gland, esophagus, stomach, small intestine, colon, colorectum, anal canal, liver, gallbladder, extrahepatic bile ducts, ampulla of Vater (hepatopancreatic duct), exocrine pancreas, lung, pleural mesothelioma, bone, soft tissue sarcoma, carcinoma and malignant melanoma of the skin, breast, vulva, vagina, cervix uteri,

10 corpus uteri, ovary, fallopian tube, gestational trophoblastic tumors, penis, prostate, testis, kidney, renal pelvis, ureter, urinary bladder, urethra, carcinoma of the eyelid, carcinoma of the conjunctiva, malignant melanoma of the conjunctiva, malignant melanoma of the uvea, retinoblastoma, carcinoma of the lacrimal gland, sarcoma of the orbit, brain, spinal cord, vascular system, hemangiosarcoma and Kaposi's sarcoma

15 In some further embodiments the disclosed metal-DFO may be useful for treatment of neurodegenerative disorder in a subject in need thereof, comprising the step of administering to said subject a therapeutically effective amount of at least one complex of DFO with at least one metal, or any combinations thereof or any pharmaceutical compositions, carriers, matrix or vehicles comprising the same. In some embodiments,

20 neurodegenerative disorder is at least one of a group of "neurodegenerative diseases" characterized by neurodegenerative processes, and include at least one of the following: amyotrophic lateral sclerosis, Parkinson's, Alzheimer's, and Huntington's. Such diseases are incurable, resulting in progressive degeneration and/or death of neuron cells.

The term "*Neurodegeneration*" is the general term for the progressive loss of

25 structure or function of neurons, leading to their death. The greatest risk factor for neurodegenerative diseases is aging. Mitochondrial DNA mutations as well as oxidative stress both contribute to aging. Many of these diseases are late-onset, meaning there is some factor that change as a person ages, for each disease. One constant factor is that in each disease, neurons gradually lose function as the disease progresses with age.

30 In yet some further embodiments, the metal DFO complex, and compositions thereof, may be applicable for treating spinal cord injury and trauma. Spinal cord injury (SCI) is the damage to the spinal cord that causes changes in its function. Injuries can occur at any level of the spinal cord and can be classified as *complete injury*, a total loss

of sensation and muscle function, or *incomplete*, meaning some nervous signals are able to travel past the injured area of the cord. Depending on the location and severity of damage along the spinal cord, the symptoms can vary widely, from mild such as pain or numbness to severe, such as paralysis and incontinence.

5 Spinal cord injury can be traumatic or non-traumatic, and can be classified into three types based on cause: mechanical forces, toxic, and ischemic (from insufficient blood supply). The damage can also be divided into primary and secondary injury: in primary injury, the cell death that occurs immediately at the original injury; in secondary injury, biochemical cascades that are initiated by the original insult can cause further
10 tissue damage including activation of the ischemic cascade, inflammation, swelling, cell suicide, and neurotransmitter imbalances. They can take place for minutes or weeks following the injury.

 Usually the damage results from physical trauma such as car accidents, gunshots, falls, or sports injuries, but it can also result from other causes such as infection,
15 insufficient blood flow, or pressure from a tumor. Non-physical-traumatic SCI ranges from 30 to 80% of all SCI. SCI may occur in infection, intervertebral disc disease, and spinal cord vascular disease. Spontaneous bleeding can occur within or outside of the protective membranes that line the cord, and intervertebral disks can herniate. Damage can result from dysfunction of the blood vessels, as in arteriovenous malformation, or
20 when a blood clot becomes lodged in a blood vessel and cuts off blood supply to the cord. When systemic blood pressure drops, blood flow to the spinal cord may be reduced, potentially causing a loss of sensation and voluntary movement in the areas supplied by the affected level of the spinal cord. Congenital conditions and tumors that compress the cord can also cause SCI, as can vertebral spondylosis and ischemia. Multiple sclerosis
25 is a disease that can damage the spinal cord, as can infectious or inflammatory conditions such as tuberculosis, herpes zoster or herpes simplex, meningitis, myelitis, and syphilis. In developed countries, the most common cause of non-traumatic SCI is degenerative diseases, followed by tumors; in many developing countries the leading cause is infection such as HIV and tuberculosis.

30 SCI is also classified by the degree of impairment. The *International Standards for Neurological Classification of Spinal Cord Injury* (ISNCSCI), published by the American Spinal Injury Association (ASIA), is widely used to document sensory and motor impairments following SCI. It is based on neurological responses, touch and pinprick

sensations tested in each dermatome, and strength of the muscles that control key motions on both sides of the body.

The prognosis ranges widely, from full recovery to permanent paralysis of the four limbs, called tetraplegia (also called quadriplegia) in injuries at the level of the neck, and paraplegia (paralysis of two limbs) in lower injuries. Complications that can occur in the short and long term after injury include muscle atrophy, pressure sores, infections, and respiratory problems. Swelling can cause further damage to the spinal cord by reducing the blood supply and causing ischemia, which can give rise to an ischemic cascade with a release of toxins that damage neurons.

It should be further appreciated that the disclosed metal-DFO complexes may be applicable for any of the spinal injuries described herein and for any related conditions or complications. In further embodiments the disclosed metal-DFO complexes may be useful for the treatment of ischemic disorders in a subject in need thereof, comprising the step of administering to said subject a therapeutically effective amount of at least one complex of DFO with at least one metal, any combinations thereof, or any pharmaceutical compositions, carriers, matrix or vehicles comprising the same, wherein ischemic disorder is at least one of: atherosclerosis of arteries in the heart, brain, arms, legs, pelvis, and kidneys.

The term "*ischemia*" means a "reduced blood supply". The term "*ischemic disorder*" as used herein refers to Ischemic Vascular Disease – a group of disorders characterized by a waxy substance called plaque that builds up inside blood vessels, and thereby restricts the normal flow of blood. When plaque builds up in the arteries, the condition is called "*atherosclerosis*". Atherosclerosis can affect any artery in the body, including arteries in the heart, brain, arms, legs, pelvis, and kidneys. As a result, different diseases may develop based on which arteries are affected.

"*Ischemic Vascular Disease*" (IVD) is a term that includes a group of diseases caused by the build-up of plaque. In some embodiments, the metal DFO complex described herein may be applicable for Coronary Heart Disease (CHD). Coronary heart disease is where atherosclerosis affects the coronary arteries in the heart. If the flow of oxygen-rich blood to the heart muscle is reduced or blocked, angina (pain) or a heart attack, respectively, may occur.

In some embodiments, the metal-DFO complex disclosed herein may be applicable for the treatment of heart attack. A heart attack occurs if the flow of oxygen-

rich blood to a section of heart muscle is blocked. If blood flow isn't restored quickly, the section of heart muscle begins to die. Without quick treatment, a heart attack can lead to serious problems and even death. Still further, in some embodiments, the methods may be applicable for Carotid Artery Disease (CAD). Carotid artery disease occurs if plaque
5 builds up in the arteries on any side of the carotid arteries. These arteries supply oxygen-rich blood to the brain. Thus, if blood flow to the brain is reduced or blocked, even for a few minutes, the lack of oxygen may cause damage, or death of brain cells, which is called stroke. If brain cells die or are damaged because of a stroke, symptoms occur in the parts of the body that these brain cells control. Examples of stroke symptoms include
10 sudden weakness; paralysis or numbness of the face, arms, or legs; trouble speaking or understanding speech; and trouble seeing.

In yet some further embodiments, the metal-DFO complex described herein may be applicable for treating Peripheral Arterial Disease (PAD). PAD is a disease in which plaque builds up in the arteries of the legs or arms. Blocked blood flow to the legs can
15 cause pain and numbness. It also can raise the risk of getting an infection in the affected limbs. If severe enough, blocked blood flow can cause gangrene (tissue death).

As mentioned above, all types of ischemic vascular disease are caused by atherosclerosis. Atherosclerosis may start when certain factors damage the inner layers of the arteries. These factors include: smoking, high amounts of certain fats and
20 cholesterol in the blood, high blood pressure and high amounts of sugar in the blood due to insulin resistance or diabetes.

In some further embodiments the metal-DFO complex described herein may be useful for treatment of metabolic disorders in a subject in need thereof, comprising the step of administering to said subject a therapeutically effective amount of at least one
25 complex of DFO with at least one metal, any combinations thereof, or any pharmaceutical compositions, carriers, matrix or vehicles comprising the same. In some embodiments, the methods may be specifically relevant for metabolic disorder, specifically, at least one of diabetes mellitus type I, diabetes mellitus type II and any diabetic related conditions.

Metabolism is the process by which the body uses food to get or make energy.
30 Food is made up of proteins, carbohydrates, and fats. Chemicals in the digestive system break the food parts down into sugars and acids, and the body can use these break down products right away, or it can store the energy in body tissues, such as liver, muscles, and body fat.

A "*metabolic disorder*" occurs when abnormal chemical reactions disrupt this process. An individual can develop a metabolic disorder when some organs, such as liver or pancreas, become diseased or do not function normally. Diabetes is a non-limited example of metabolic disorder. Diabetes mellitus (DM), commonly referred to as
5 diabetes, is a group of metabolic diseases in which there are high blood sugar levels over a prolonged period. If left untreated, diabetes can cause many complications. Acute complications include diabetic ketoacidosis and nonketotic hyperosmolar coma. Serious long-term complications include cardiovascular disease, stroke, chronic kidney failure, foot ulcers, and damage to the eyes. Diabetes is due to either not producing enough
10 insulin by the pancreas (diabetes mellitus type I), or the lack of proper response by the cells of the body to the insulin produced (diabetes mellitus type II).

There is growing evidence for a link between inflammation and the pathogenesis of Type 2 diabetes. This evolving concept, which suggests that insulin resistance and type 2 diabetes may have an immune component, provides a new avenue for anti-
15 inflammatory therapy for type 2 diabetes. Therefore, based on its anti-inflammatory effects, the composition, as well as methods described herein may be used for the treatment and/or amelioration of an autoimmune disorder, such as diabetes.

Diabetes mellitus, is a syndrome characterized by disordered metabolism and inappropriately high blood sugar (hyperglycemia) resulting from either low levels of the
20 hormone insulin or from abnormal resistance to insulin's effects coupled with inadequate levels of insulin secretion to compensate. The characteristic symptoms are excessive urine production (polyuria), excessive thirst and increased fluid intake (polydipsia), and blurred vision; these symptoms are likely absent if the blood sugar is only mildly elevated.

There are three main forms of diabetes: type 1, type 2 and gestational diabetes
25 (occurs during pregnancy). Type 1 diabetes mellitus is characterized by loss of the insulin-producing beta cells of the islets of Langerhans in the pancreas, leading to a deficiency of insulin. The main cause of this beta cell loss is a T-cell mediated autoimmune attack. There is no known preventative measure that can be taken against type 1 diabetes. Most affected people are otherwise healthy and of a healthy weight when
30 onset occurs. Sensitivity and responsiveness to insulin are usually normal, especially in the early stages. Type 1 diabetes can affect children or adults and was traditionally termed "juvenile diabetes" as it represents a majority of cases of diabetes affecting children.

In yet another specific embodiment, the metal-DFO compositions described herein may be used for preventing, treating, ameliorating or inhibiting diabetes type 2. Diabetes mellitus type 2, or non-insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes, is a metabolic disorder that is characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency. As the condition progresses, medications may be needed. Long-term complications from high blood sugar include an increased risk of heart attacks, strokes, amputation, and kidney failure. There are many factors which can potentially give rise to or exacerbate type 2 diabetes. These include obesity, hypertension, elevated cholesterol (combined hyperlipidemia), and with the condition often termed metabolic syndrome (it is also known as Syndrome X, Reavan's syndrome, or CHAOS). Other causes include acromegaly, Cushing's syndrome, thyrotoxicosis, pheochromocytoma, chronic pancreatitis, cancer and drugs. Additional factors found to increase the risk of type 2 diabetes include aging, high-fat diets and a less active lifestyle.

Insulin resistance means that body cells do not respond appropriately when insulin is present. Unlike type 1 diabetes mellitus, insulin resistance is generally "post-receptor", meaning it is a problem with the cells that respond to insulin rather than a problem with the production of insulin. Severe complications can result from improperly managed type 2 diabetes, including renal failure, erectile dysfunction, blindness, slow healing wounds (including surgical incisions), and arterial disease, including coronary artery disease. The onset of type 2 has been most common in middle age and later life, although it is being more frequently seen in adolescents and young adults due to an increase in child obesity and inactivity.

It should be further appreciated that the methods, kits and complexes of the metal-DFO complex described herein may be applicable for treating diabetes-related conditions. It is understood that the interchangeably used terms "associated" and "related", when referring to pathologies herein, mean diseases, disorders, conditions, or any pathologies which at least one of: share causalities, co-exist at a higher than coincidental frequency, or where at least one disease, disorder condition or pathology causes the second disease, disorder, condition or pathology. Such conditions may include for example, eye related complications (cataract, glaucoma, retinopathy), neuropathy, nephropathy, cardiomyopathy, stroke, hypertension, peripheral arterial disease and sores and any ulcers, chronic ulcers or any slow healing ulcers or skin or organ injuries associated with a diabetic condition. In

accordance with the current disclosure, the undesired side effect treated or prevented is preferably an undesired side effect related to the eye and/or vision such as cataract.

The methods of treatment and uses described herein may also be utilized for the benefit of subjects suffering from diabetes-related or associated diseases or disorders, comprising hyperinsulinemia, dyslipidemia, hypercholesterolemia, impaired glucose tolerance, hypertension, cardiovascular disease, diabetic cardiomyopathy, diabetic cardiac dysrhythmia, atherosclerosis, diabetic nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis, end stage renal disease, microalbuminuria and albuminuria.

Hyperinsulinemia is a condition in which there are excess levels of circulating insulin in the blood. Also known as pre-diabetes, insulin resistance, and syndrome X, it is commonly associated with PCOS (Polycystic Ovarian Syndrome) in females. Hyperinsulinemia is often mistaken for diabetes or hypoglycemia, both of which are separate conditions. Hyperinsulinemia can develop into diabetes if unmonitored and untreated, and may remain present when diabetes occurs. It is not caused by diabetes, as is commonly believed. Hyperinsulinemia may cause hypoglycemia in some patients.

Dyslipidemia as used herein is a disruption in the amount of lipids in the blood. In societies of developed countries, most dyslipidemias are hyperlipidemias; that is, an elevation of lipids in the blood, often due to diet and lifestyle. The prolonged elevation of insulin levels can lead to dyslipidemia. Increased levels of O-GlcNAc transferase (OGT) are known to cause dyslipidemia. Impaired glucose tolerance (IGT) is a pre-diabetic state of dysglycemia that is associated with insulin resistance and increased risk of cardiovascular pathology. IGT may precede type II diabetes mellitus by many years.

Hypertension (HTN) or high blood pressure as used herein is a chronic medical condition in which the blood pressure in the arteries is elevated. It is the opposite of hypotension. It is classified as either primary (essential) or secondary. About 90–95% of cases are termed "primary hypertension", which refers to high blood pressure for which no medical cause can be found. The remaining 5–10% of cases (Secondary hypertension) are caused by other conditions that affect the kidneys, arteries, heart, or endocrine system. Persistent hypertension is one of the risk factors for strokes, heart attacks, heart failure and arterial aneurysm, and is a leading cause of chronic kidney failure.

Cardiomyopathy, as used herein is deterioration of myocardium functioning e.g. a clinical or sub-clinical condition diagnosed when ventricular dysfunction develops in patients

with diabetes in the absence of coronary atherosclerosis and hypertension. It is characterized functionally by ventricular dilation, myocyte hypertrophy, interstitial fibrosis, and decreased or preserved systolic function in the presence of a diastolic dysfunction.

Atherosclerosis (also known as arteriosclerotic vascular disease or ASVD) is a condition in which an artery wall thickens as the result of a build-up of fatty materials such as cholesterol. It is a syndrome affecting arterial blood vessels, a chronic inflammatory response in the walls of arteries, in large part due to the accumulation of macrophage white blood cells and promoted by low-density lipoproteins (plasma proteins that carry cholesterol and triglycerides) without adequate removal of fats and cholesterol from the macrophages by functional high density lipoproteins (HDL). It is commonly referred to as a hardening or furring of the arteries. It is caused by the formation of multiple plaques within the arteries.

Diabetic nephropathy (nephropatia diabetica), also known as Kimmelstiel-Wilson syndrome, or nodular diabetic glomerulosclerosis and intercapillary glomerulonephritis, is a progressive kidney disease caused by angiopathy of capillaries in the kidney glomeruli. It is characterized by nephrotic syndrome and diffuse glomerulosclerosis. It is due to longstanding diabetes mellitus, and is a prime indication for dialysis in many Western countries.

Glomerulonephritis, also known as glomerular nephritis (GN), is a renal disease characterized by inflammation of the glomeruli, or small blood vessels in the kidneys. It may present with isolated hematuria and/or proteinuria (blood and/or protein presence in the urine); or as a nephrotic syndrome, a nephritic syndrome, acute renal failure, or chronic renal failure. They are categorized into several different pathological patterns, which are broadly grouped into non-proliferative or proliferative types. Primary causes are ones which are intrinsic to the kidney, whilst secondary causes are associated with certain infections (bacterial, viral or parasitic pathogens), drugs, systemic disorders (SLE, vasculitis) or diabetes.

Glomerular sclerosis refers to a hardening of the glomerulus in the kidney. It is a general term to describe scarring of the kidney glomeruli. Proteinuria (large amounts of protein in urine) is one of the signs of glomerulosclerosis. Diabetes is a frequent cause of glomerular sclerosis.

Nephrotic syndrome is a nonspecific disorder in which the kidneys are damaged, causing them to leak large amounts of protein (proteinuria at least 3.5 grams per day per 1.73m² body surface area) from the blood into the urine.

Kidneys affected by nephrotic syndrome have small pores in the podocytes, large enough to permit proteinuria (and subsequently hypoalbuminemia, because some of the protein albumin has gone from the blood to the urine) but not large enough to allow cells through (hence no hematuria). By contrast, in nephritic syndrome, RBCs pass through the pores, causing hematuria. Diabetes is often an underlying cause of nephrotic syndrome.

Hypertensive nephropathy, or hypertensive nephrosclerosis, or hypertensive renal disease, is a medical condition referring to damage to the kidney due to chronic high blood pressure. In the kidneys, as a result of benign arterial hypertension, hyaline (pink, amorphous, homogeneous material) accumulates in the wall of small arteries and arterioles, producing the thickening of their walls and the narrowing of the lumina - hyaline arteriolosclerosis. Consequent ischemia will produce tubular atrophy, interstitial fibrosis, glomerular alterations (smaller glomeruli with different degrees of hyalinization - from mild to sclerosis of glomeruli) and periglomerular fibrosis. In advanced stages, renal failure will occur. Functional nephrons have dilated tubules, often with hyaline casts in the lumens. Additional complications often associated with hypertensive nephropathy include glomerular damage resulting in proteinuria and hematuria.

End-stage renal disease is an advanced stage of chronic kidney disease (CKD), also known as chronic renal disease. CKD manifests as a progressive loss in renal function over a period of months or years. The symptoms of worsening kidney function are unspecific, and might include feeling generally unwell and experiencing a reduced appetite. Recent professional guidelines classify the severity of chronic kidney disease in five stages, with stage 1 being the mildest and usually causing few symptoms and stage 5 being a severe illness with poor life expectancy if untreated. Stage 5 CKD is also called established chronic kidney disease and is synonymous with the now outdated terms end-stage renal disease (ESRD), chronic kidney failure (CKF) or chronic renal failure (CRF).

As indicated above, the metal-DFO disclosed herein may be used for treating any immune-related disorder. It should be noted that an "Immune-related disorder" is a condition that is associated with the immune system of a subject, either through activation or suppression of the immune system, or that can be treated, prevented or diagnosed by targeting a certain component of the immune response in a subject, such as the adaptive or innate immune response. Such disorder may be any one of an inflammatory disease or an autoimmune disease.

According to one specific embodiment, the metal-DFO disclosed herein may be specifically suitable for treating an inflammatory disease or an inflammatory-associated condition. The terms "inflammatory disease" or "inflammatory-associated condition" refers to any disease or pathologically condition which can benefit from the reduction of
5 at least one inflammatory parameter, for example, induction of an inflammatory cytokine such as IFN-gamma and IL-2. The condition may be caused (primarily) from inflammation, or inflammation may be one of the manifestations of the diseases caused by another physiological cause.

Examples of other immune-related disorders that may be treated by the methods,
10 and kits described herein include, but are not limited to, ulcerative colitis, Crohn's disease, irritable bowel disease (IBD), alopecia areata, lupus, ankylosing spondylitis, Meniere's disease, antiphospholipid syndrome, mixed connective tissue disease, autoimmune Addison's disease, multiple sclerosis, autoimmune hemolytic anemia, myasthenia gravis, autoimmune hepatitis, pemphigus vulgaris, Behcet's disease,
15 pernicious anemia, bullous pemphigoid, polyarthritis nodosa, cardiomyopathy, polychondritis, dermatitis herpetiformis, polyglandular syndromes, chronic fatigue syndrome (CFIDS), polymyalgia rheumatica, chronic inflammatory demyelinating, polymyositis and dermatomyositis, chronic inflammatory polyneuropathy, primary agammaglobulinemia, Churg-Strauss syndrome, primary biliary cirrhosis, cicatricial
20 pemphigoid, psoriasis, CREST Syndrome, Raynaud's phenomenon, cold agglutinin disease, Reiter's syndrome, rheumatic fever, discoid lupus, rheumatoid arthritis, essential mixed cryoglobulinemia, sarcoidosis, fibromyalgia, scleroderma, Grave's disease, Sjogren's syndrome, Guillain Barre disease, Stiff person syndrome, Hashimoto's thyroiditis, Takayasu arteritis, idiopathic pulmonary fibrosis, temporal arteritis/giant cell
25 arteritis, idiopathic thrombocytopenia purpura (ITP), IgA nephropathy, uveitis, vasculitis, lichen planus, and vitiligo. The metal-DFO complexes described herein can be administered to a subject to treat or prevent disorders associated with an abnormal or unwanted immune response associated the above diseases.

The compositions comprising the disclosed metal-DFO may be useful for treating any
30 condition related to the disorders described above. It is understood that the interchangeably used terms "associated" and "related", when referring to pathologies herein, mean diseases, disorders, conditions, or any pathologies which at least one of: share causalities, co-exist at a higher than coincidental frequency, or where at least one disease, disorder, condition or pathology causes a second disease, disorder, condition or pathology.

Still further, it should be appreciated that there are numerous potential clinical applications for these complexes, including, but not limited to, the treatment of amyotrophic lateral sclerosis, age-related macular degeneration, cataract, sepsis, wound healing, injury due to exposure to chemical agents, heat or cold, ischemia and
5 reperfusion injury, stroke, ionizing irradiation damage, injury associated with thalassemia, and hemochromatosis and Wilson disease.

Still further, it should be noted that in certain embodiments, the metal-DFO complex disclosed herein may be applicable for treating any disorder associated with elevated levels of IL-1 α . Examples for such disorders include, but are not limited to any
10 one of sepsis, rheumatoid arthritis, Crohn's disease, inflammatory bowel disease, myocardial infarction, coronary artery disease, atherosclerosis, inflammatory cardiomyopathy, cardiac hypertrophy, osteoarthritis, CAPS, Schnitzler syndrome, ankylosing spondylitis, systemic lupus erythematosus, familial mediterranean fever, systemic-onset juvenile idiopathic arthritis, Muckle-Wells syndrome, gout, pseudogout,
15 type 2 diabetes, psoriatic arthritis, psoriasis, antisynthetase syndrome, anterior cruciate knee ligament tear, relapsing polychondritis, hemochromatosis-related arthritis of the hands, chronic recurrent multifocal osteomyelitis, erosive osteoarthritis of the hand, heart failure, diabetes-induced cardiomyopathy, smoldering myeloma, giant cells arteritis, dry eye disease, metabolic syndrome, hidradenitis suppurativa, acne, Behcet's disease,
20 Blau syndrome/granulomatous arthritis, mevalonate kinase deficiency, Majeed syndrome, Henoch-Schonlein purpura, idiopathic recurrent pericarditis, macrophage activation syndrome, Sweet's syndrome/neutrophilic dermatoses, neutrophilic panniculitis, Erdheim-Chester/histiocytoses, multicentric Castleman disease, Jessner-Kanof disease, Kawasaki disease, colitis in chronic granulomatous disease, PAPA
25 syndrome, SAPHO syndrome, hepatocellular carcinoma, pancreatic ductal adenocarcinoma, fibrosarcoma, type 1 diabetes, stroke, acute brain injury, Alzheimer's disease, colorectal cancer, breast cancer, melanoma, glioma, prostate, cervix, lung, and bladder cancer, Paget's disease, tumor necrosis factor-associated periodic syndrome.

In other embodiments, the metal-DFO disclosed herein may be applicable for treating
30 any disorder associated with elevated levels of TNF- α . Non-limiting examples include septic shock, inflammatory bowel disease, ulcerative colitis, juvenile idiopathic arthritis, Takayasu arteritis, pathological corneal hemangiogenesis and lymphangiogenesis, sarcoidosis, amyloidosis, post-operative cognitive dysfunction, ovarian cancer, stroke, rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, inflammatory bowel

disease, psoriasis, psoriatic arthritis, pediatric Crohn's disease, pediatric ulcerative colitis, colorectal cancer, idiopathic pulmonary fibrosis, cystic fibrosis, retinitis pigmentosa, pancreatic cancer, Paget's disease, tumor necrosis factor-associated periodic syndrome.

5 Still further, it should be noted that in certain embodiments, the metal-DFO complexes disclosed herein may be applicable for treating any disorder associated with elevated levels of IL-6. Such disorders include rheumatoid arthritis, Crohn's disease, inflammatory bowel disease, ulcerative colitis, periodontitis, pneumonitis, idiopathic pulmonary fibrosis, depression, colorectal cancer, uveitis, Castleman's disease, systemic
10 juvenile idiopathic arthritis, systemic lupus, systemic sclerosis, polymyositis, vasculitis syndrome, spondyloarthritis, relapsing polychondritis, acquired haemophilia A, autoimmune haemolytic anaemia, adult-onset Still's disease, amyloid A amyloidosis, polymyalgia rheumatica, remitting seronegative symmetrical synovitis with pitting oedema, Behçet's disease, graft-versus-host disease, tumour necrosis factor-
15 associated periodic syndrome, pulmonary arterial hypertension, atopic dermatitis, sciatica, relapsing polychondritis, type 2 diabetes, obesity, Grave's ophthalmopathy, cardiovascular disease in rheumatic arthritis, giant cells arteritis, non-ST elevated myocardial infarction, schizophrenia, ovarian cancer, fibrous dysplasia of bone, primary Sjögren's syndrome, ankylosing spondylitis, Erdheim Chester disease, ANCA-associated
20 vasculitis, neuromyelitis optica, chronic glomerulonephritis, Takayasu arteritis, prostate cancer, renal cell carcinoma, multiple myeloma, lymphoma, cytokines release syndrome, listeriosis, asthma, COPD, psoriasis, multiple sclerosis, osteoarthritis, sepsis, interstitial lung disease, intraocular inflammation, endometriosis, Alzheimer's disease, cerebral trauma, breast cancer, pancreatic cancer, AIDS-related pathologies, cutaneous and
25 systemic plasmacytosis, gastric cancer, cervical cancer, melanoma, hepatocellular carcinoma, leukemia, glioblastoma, uterine carcinoma, cystic fibrosis, oral cancer, Paget's disease.

In certain embodiments, the metal-DFO complexes disclosed herein may be applicable for treating any disorder associated with elevated levels of IL-17. Examples
30 for such disorders may include inflammatory bowel disease, Crohn's disease, ulcerative colitis, psoriasis, rheumatoid arthritis, psoriatic arthritis, ankylosing spondyloarthritis, multiple sclerosis, asthma, colorectal cancer, lung cancer, hepatocellular carcinoma, liver fibrosis, esophageal squamous cell carcinoma, glioblastoma, ovarian cancer, breast cancer, melanoma, gastric cancer, head and neck cancers, nasopharyngeal cancer,

COPD, SAPHO syndrom, lung fibrosis, cardiac fibrosis, renal fibrosis, Paget's disease, osteosarcoma, gastric ulcer, bladder cancer, systemic juvenile idiopathic arthritis, systemic lupus erythematosus, airway neutrophilia, cystic fibrosis, allergic rhinitis, alopecia areata, atopic dermatitis, cutaneous T-cell lymphomas, mastocytosis.

5 As used herein the term "*method*" refers to manners, means, techniques and procedures for accomplishing a given task including, but not limited to, those manners, means, techniques and procedures either known to, or readily developed from known manners, means, techniques and procedures by practitioners of the chemical, pharmacological, biological, biochemical and medical arts.

10 As used herein, "*disease*", "*disorder*", "*condition*" and the like, as they relate to a subject's health, are used interchangeably and have meanings ascribed to each and all of such terms.

 The term "*treatment*" as used herein refers to the administering of a therapeutic amount of the metal-DFO complex described herein which is effective to ameliorate
15 undesired symptoms associated with a disease, to prevent 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 the irreversible damage caused in the progressive chronic stage of the disease, to delay the onset of said progressive stage, to lessen the severity or cure the disease, to improve
20 survival rate or more rapid recovery, or to prevent the disease from occurring or a combination of two or more of the above.

 The "*effective amount*" for purposes disclosed herein is determined by such considerations as may be known in the art. The amount must be effective to achieve the desired therapeutic effect as described above, depending, *inter alia*, on the type and
25 severity of the disease to be treated and the treatment regime. The effective amount is typically determined in appropriately designed clinical trials (dose range studies) and the person versed in the art will know how to properly conduct such trials in order to determine the effective amount. As generally known, an effective amount depends on a variety of factors including the distribution profile within the body, a variety of
30 pharmacological parameters such as half life in the body, on undesired side effects, if any, on factors such as age and gender, etc.

 More specifically, the compositions containing the disclosed metal-DFO complexes, or any combination, mixture or cocktail thereof can be administered for prophylactic and/or

therapeutic treatments. In therapeutic application, compositions are administered to a patient already affected by an inflammation or immune-related disorder or specifically, a disorder associated with at least one of elevated levels of pro-inflammatory cytokines and reduced levels of anti-inflammatory cytokines, in an amount sufficient to cure or at least partially arrest the condition and its complications. An amount adequate to accomplish this is defined as a "therapeutically effective dose." Amounts effective for this use will depend upon the severity of the condition and the general state of the patient's own immune system, but generally range from about 0.01 to about 10,000 mg/kg, specifically, about 0.01 to about 1000, 500, 250, 100, 90, 80, 70, 60, 50, 40, 30, 20, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1, 0.1 mg/kg. It should be noted that in certain embodiments, the effective amount may be about 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 9.5, 10 mg/kg or more. In yet some further embodiments, the effective amount may be 2.5 mg/kg of the metal-DFO complexes or of any combinations thereof. Single or multiple administrations on a daily, weekly or monthly schedule can be carried out with dose levels and pattern being selected by the treating physician. More specific embodiments relate to the use of typically 2-3 doses per week.

The term "*prophylaxis*" refers to prevention or reduction the risk of occurrence of the biological or medical event, specifically, the occurrence or reoccurrence of disorders associated with at least one of elevated levels of pro-inflammatory cytokines and reduced levels of anti-inflammatory cytokines, that is sought to be prevented in a tissue, a system, an animal or a human being, by a researcher, veterinarian, medical doctor or other clinician, and the term "prophylactically effective amount" is intended to mean that amount of a pharmaceutical composition that will achieve this goal. Thus, in particular embodiments, the disclosed methods are particularly effective in the prophylaxis, i.e., prevention of conditions associated with infectious disease. Thus, subjects administered with said compositions are less likely to experience symptoms associated with said infectious condition that are also less likely to reoccur in a subject who has already experienced them in the past.

The term "*amelioration*" as referred to herein, relates to a decrease in the symptoms, and improvement in a subject's condition brought about by the compositions and methods, wherein said improvement may be manifested in the forms of inhibition of pathologic processes associated with the immune-related disorders described herein, a significant reduction in their magnitude, or an improvement in a diseased subject physiological state.

The term "*inhibit*" and all variations of this term is intended to encompass the restriction or prohibition of the progress and exacerbation of pathologic symptoms or a pathologic process progress, said pathologic process symptoms or process are associated with.

5 The term "*eliminate*" relates to the substantial eradication or removal of the pathologic symptoms and possibly pathologic etiology, optionally, according to the methods as below.

10 The terms "*delay*", "*delaying the onset*", "*retard*" and all variations thereof are intended to encompass the slowing of the progress and/or exacerbation of a pathologic disorder or an infectious disease and their symptoms slowing their progress, further exacerbation or development, so as to appear later than in the absence of the treatment.

15 More specifically, treatment or prevention include the prevention or postponement of development of the disease, prevention or postponement of development of symptoms and/or a reduction in the severity of such symptoms that will or are expected to develop. These further include ameliorating existing symptoms, preventing- additional symptoms and ameliorating or preventing the underlying metabolic causes of symptoms. It should be appreciated that the terms "*inhibition*", "*moderation*", "*reduction*" or "*attenuation*" as referred to herein, relate to the retardation, restraining or reduction of a process by any one of about 1% to 99.9%, specifically, about 1% to about 5%, about 5% to 10%, about 10% to 15%, about 15% to 20%, about 20% to 25%, about 25% to 30%, about 30% to 35%, about 35% to 40%, about 40% to 45%, about 45% to 50%, about 50% to 55%, about 55% to 60%, about 60% to 65%, about 65% to 70%, about 75% to 80%, about 80% to 85% about 85% to 90%, about 90% to 95%, about 95% to 99%, or about 99% to 99.9%.

25 The disclosed methods relate to the treatment of subjects, or patients, in need thereof. By "*patient*" or "*subject in need*" it is meant any organism who may be infected by the above-mentioned pathogens, and to whom the preventive and prophylactic kit/s, system/s and methods herein described is desired, including humans, domestic and non-domestic mammals such as canine and feline subjects, bovine, simian, equine and murine subjects, rodents, domestic birds, aquaculture, fish and exotic aquarium fish. It should be appreciated that the treated subject may be also any reptile or zoo animal. More specifically, the disclosed kits and methods are intended for preventing pathologic condition in mammals. By "*mammalian subject*" is meant any mammal for which the proposed therapy is desired, including human, equine, canine, and feline subjects, most

specifically humans. It should be noted that specifically in cases of non-human subjects, the method may be performed using administration via injection, drinking water, feed, spraying, oral lavage and directly into the digestive tract of subjects in need thereof.

Another aspect concerns a complex of DFO with at least one metal. In some
5 embodiments the complex of DFO with at least one metal wherein at least one metal may
be post-transition metals or transition metals. In another embodiment the complex of DFO
with at least one metal, wherein the metal is selected from the group consisting of zinc,
gallium, silver, gold, molybdenum, and vanadium. In further embodiment the complex is
of DFO with at least one metal, wherein the metal is selected from the group consisting
10 of Zn^{2+} , Ga^{3+} , Ag^{1+} and Au^{3+} . In a specific embodiment the complex is of DFO with Zn^{2+} .
In yet some other embodiments, the complex may be DFO with Ga^{3+} .

In some specific embodiments, the DFO described herein relates to a composition
of DFO with at least one metal, for use in a method of treating, preventing, inhibiting,
reducing, eliminating, protecting or delaying the onset of a pathological condition or a
15 disorder in a subject in need thereof.

Also describe are a combination combining separate pharmaceutical
compositions in a kit form. The kit includes at least two separate pharmaceutical
compositions: (i) at least one of lanthanides, actinides, post-transition metals or transition
metals, or any combinations thereof, in any form of salts, esters and amides thereof, and
20 a pharmaceutically acceptable carrier or diluent, and (ii) DFO, or a pharmaceutically
acceptable derivative thereof, and further combined with hydrophilic, non-ionic surfactant
comprising polyethylene glycol (PEG) and a non-ionic triblock copolymer, and optionally
further including wherein the nonionic triblock copolymers are composed of a central
hydrophobic chain of polyoxypropylene (poly(propylene oxide)) flanked by two
25 hydrophilic chains of polyoxyethylene (poly(ethylene oxide)). In some embodiments, the
hydrophilic nonionic surfactant is a poloxamer. In particular, the hydrophilic nonionic
surfactant may be poloxamer 407.

In yet some specific embodiments, the metal contained in the kit may be at least
one of zinc, gallium, silver, gold, molybdenum and vanadium. In some specific
30 embodiments, the kit may comprise zinc. In yet some further embodiments, the kits may
comprise gallium. Still further, in some embodiments, the kits may comprise zinc and
gallium.

More specifically, the kit includes container means for containing both separate compositions, such as a divided bottle or a divided foil packet. However, the separate compositions may also be contained within a single, undivided container. Typically the kit includes directions for the administration of the separate components. The kit form is particularly advantageous when the separate components are preferably administered in different dosage forms (e.g., parenteral vs. topical), are administered at different dosage intervals, or when titration of the individual components of the combination is desired by the prescribing physician.

The kit may further comprise an acid in a separated container. In some embodiments, the acid is selected from the list consisting of: 1-hydroxy-2-naphthoic acid, 2,2-dichloroacetic acid, 2-oxoglutaric acid, 4-acetamidobenzoic acid, 4-aminosalicylic acid, acetic acid, alkanesulphonic acid, alkenesulphonic acid, alkynesulphonic acid with any substitutions, adipic acid, ascorbic acid, aspartic acid, benzoic acid, camphoric acid, camphor-10-sulfonic acid, decanoic acid, hexanoic acid, octanoic acid, carbonic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, gluconic acid, glucuronic acid, glutamic acid, glutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, hydrobromic acid, hydrochloric acid, isobutyric acid, lactic acid, lactobionic acid, lauric acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid or its derivatives, or a substituted hydrocarbyl sulphonic acid, for example a hydroxy-, alkoxy-, acyloxy-, alkoxycarbonyl-, halogen-, aromatic- or amino- substituted alkylsulphonic acid, nicotinic acid, nitric acid, oleic acid, oxalic acid, palmitic acid, pamoic acid, phosphoric acid, propionic acid, pyroglutamic acid, salicylic acid, sebacic acid, seleninic acid, selenonic acid, or any seleninic or selenonic analogue of the previously mentioned sulfonic compounds, stearic acid, succinic acid, sulfuric acid, tartaric acid, thiocyanic acid, undecylenic acid.

In some embodiments the kit will enable the use of the active ingredients in a method of treating, preventing, inhibiting, reducing, eliminating, protecting or delaying the onset of a pathological condition or a disorder in a subject in need thereof.

In yet some other particular and non-limiting embodiments, the metal-DFO may be administered for reducing the levels of IL-1 α , TNF- α , IL-6 and IL-17 in a subject suffering from a disorder accompanied by elevated IL-1 α , TNF- α , IL-6 and IL-17, thereof comprising of the step of administering a therapeutically effective amount of the kit,

optionally in combination with at least one additional therapeutic compound, to a subject suffering from a pathological disorder or disease as outlined above. It should be further noted that the application of the kit or any component thereof, may form a complementary treatment regimen for subjects suffering from a pathological disorder or disease as
5 outlined above.

Still further, the kits and the complexes discussed herein and any components thereof may be applied as a single daily dose or multiple daily doses, preferably, every 1 to 7 days. It is specifically contemplated that such application may be carried out once, twice, thrice, four times, five times or six times daily, or may be performed once daily,
10 once every 2 days, once every 3 days, once every 4 days, once every 5 days, once every 6 days, once every week, two weeks, three weeks, four weeks or even a month. The application of the kits or of any component thereof may last up to a day, two days, three days, four days, five days, six days, a week, two weeks, three weeks, four weeks, a month, two months three months or even more. Specifically, application may last from
15 one day to one month. Most specifically, application may last from one day to 7 days.

The metal-DFO complex may include either zinc or gallium. The method comprising: mixing DFO (e.g., Deferoxamine B) with zinc or gallium when contained at a molar ratio of metal to DFO between 1:0.01 to 1:100, typically, 1:1, under the conditions, described below.

20 By one option the mixing is in the presence of an acid, for example from the following list consisting of non limiting examples of 1-hydroxy-2-naphthoic acid, 2,2-dichloroacetic acid, 2-oxoglutaric acid, 4-acetamidobenzoic acid, 4-aminosalicylic acid, acetic acid, alkanesulphonic acid, alkenesulphonic acid, alkynesulphonic acid with any substitutions, adipic acid, ascorbic acid, aspartic acid, benzoic acid, camphoric acid,
25 camphor-10-sulfonic acid, decanoic acid, hexanoic acid, octanoic acid, carbonic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, gluconic acid, glucuronic acid, glutamic acid, glutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, hydrobromic acid, hydrochloric acid, isobutyric acid, lactic acid, lactobionic acid, lauric acid, maleic acid,
30 malic acid, malonic acid, mandelic acid, methanesulfonic acid or its derivatives, or a substituted hydrocarbonyl sulphonic acid, for example a hydroxy-, alkoxy-, acyloxy-, alkoxy carbonyl-, halogen-, aromatic- or amino- substituted alkylsulphonic acid, nicotinic acid, nitric acid, oleic acid, oxalic acid, palmitic acid, pantoic acid, phosphoric acid,

propionic acid, pyroglutamic acid, salicylic acid, sebacic acid, seleninic acid, selenonic acid, or any seleninic or selenonic analogue of the previously mentioned sulfonic compounds, stearic acid, succinic acid, sulfuric acid, tartaric acid, thiocyanic acid, undecylenic acid, at a molar ratio of acid to DFO between 1:0.01 to 1:100, typically 1:1.

5 Another embodiment encompasses a process of preparation of the complex of DFO with a metal ion, the process comprising: contacting DFO with a metal ion, such as zinc or gallium contained at a molar ratio of metal to DFO, between 1:0.01 to 1:100. In some selective embodiments, the stoichiometric ratio of metal to DFO is 1:1.

10 In some embodiments the process for the production of complexes of DFO with a metal ion comprises the following steps: contacting DFO (e.g., Deferoxamine B) with a metal ion, such as zinc or gallium, wherein either DFO and/or the metal ion is in the form of a salt, when contained at a molar ratio of metal to DFO, between 1:0.01 to 1:100 in the presence of an acid, wherein the acid is selected from the group consisting of : 1-hydroxy-2-naphthoic acid, 2,2-dichloroacetic acid, 2-oxoglutaric acid, 4-
 15 acetamidobenzoic acid, 4-aminosalicylic acid, acetic acid, alkanesulphonic acid, alkenesulphonic acid, alkynesulphonic acid with any substitutions, adipic acid, ascorbic acid, aspartic acid, benzoic acid, camphoric acid, camphor-10-sulfonic acid, decanoic acid, hexanoic acid, octanoic acid, carbonic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, formic acid, fumaric acid, galactaric acid, gentisic acid,
 20 glucoheptonic acid, gluconic acid, glucuronic acid, glutamic acid, glutaric acid, glycerophosphoric acid, glycolic acid, hippuric acid, hydrobromic acid, hydrochloric acid, isobutyric acid, lactic acid, lactobionic acid, lauric acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid or its derivatives, or a substituted hydrocarbyl sulphonic acid, for example a hydroxy-, alkoxy-, acyloxy-, alkoxycarbonyl-, halogen-,
 25 aromatic- or amino- substituted alkylsulphonic acid, nicotinic acid, nitric acid, oleic acid, oxalic acid, palmitic acid, pantoic acid, phosphoric acid, propionic acid, pyroglutamic acid, salicylic acid, sebacic acid, seleninic acid, selenonic acid, or any seleninic or selenonic analogue of the previously mentioned sulfonic compounds, stearic acid, succinic acid, sulfuric acid, tartaric acid, thiocyanic acid, undecylenic acid, at a molar ratio of acid to
 30 DFO between 1:0.01 to 1:100.

EXAMPLES

Simulated Gastric Fluid

At the first step of the study, the stability of Zn-DFO complex in simulated gastric fluid was tested. It is important to note – the stability of metal-ligand complexes is known to be pH-dependent. According to previous studies, zinc-deferoxamine complex can exist as an integral entity within the range of pH 3-9, dissociating into two separate entities, i.e., zinc and deferoxamine, beyond these conditions. Out of these entities, only

deferoxamine can be affected by the harsh conditions of the stomach fluid.

For this end, immediate release gelatin capsules containing Zn-DFO complex, were placed into the dissolution chamber, simulating stirring stomach media at 37°C (USP-NF General Chapter Monograph <711>), with (medium II) and without pepsin (medium I).

The release and the stability of deferoxamine were monitored. The dissolved and released Zn-DFO content was monitored, being determined by HPLC. The results are shown in Figure 1.

More than 90% of Zn-DFO complex was released from the capsule within 30 min in media II (with pepsin) and within 60 min in media I (without). These results can be explained by the ability of pepsin to cleave the cross-linked gelatin and therefore speed the dissolution. Yet, the results for media II meet the acceptance criteria for immediate release oral capsules. The reduction of Zn-DFO content within both media after more than 1 hour in simulated gastric conditions was less than 4%. Therefore, Zn-DFO can be considered stable in the harsh gastric conditions of pH 1.2 and pepsin.

First Pass Metabolism

At the next step the effect of first pass metabolism (hepatic passage) on Zn-DFO was investigated. Liver microsomes stability assay was conducted, using the hepatic vesicles obtained from 6 species, i.e., mini-pig, male SD rat, human, male Beagle dog, male Cynomolgus monkey and male CD-1 mouse. The drug was incubated for 1 hour, samples were taken for analysis at 6 time points (0, 5, 15, 30, 45, 60 min). Assay of exposure of Zn-DFO for 1 h to human liver microsomes resulted in 78.2% degradation. The obtained T_{1/2} value was 22.4 min. Similar results were obtained on microsomes from rat, dog, mouse and monkey. Yet, the degradation by porcine microsomes was less than 25%. These values were taken into consideration when developing the regimen of treatment and the formulation. A conclusion about the need to protect the complex against the effects of first pass metabolism was drawn.

Formulation Development

Further, the pharmacokinetics of Zn-DFO was evaluated in rats using intravenous, intraperitoneal and oral administrations. For this matter, a LC-MS/MS method was developed. Due to the technical characteristics of the LC-MS/MS apparatus, causing the separation of zinc ion from Zn-DFO during the processing of the samples in the apparatus, it was impossible to measure Zn-DFO directly and the method was targeted at detecting the free ligand (DFO alone) or Fe-DFO in rat plasma.

In the first study, rats were administered 6 mg/kg using the IV, PO and IP routes. This dose was found to be too low to enable detection of any free DFO (except for a few points in the IV route). The levels of Fe-DFO were detected in both the PO and IV routes, but only sporadically in the IP route. Subsequently, another study was carried out, using 30 mg/kg. In this study the IV route and PO route were examined, with several formulations, based on different permeability enhancers for administration via the oral route.

Table 1 shows the tested formulations.

Table 1	Formulation Class	Formulation Tested
Formulation 1	Class III - high solubility, low permeability: exhibits permeability-limited absorption	20% Labrafac™, 5% Poloxamer-407, 5% Labrasol®, 70% water
Formulation 2	Class IV: low solubility, low permeability: very poor oral bioavailability	20% PEG 1000, 10% Poloxamer-407, 70% water
Formulation 3	Class IV: low solubility, low permeability: very poor oral bioavailability	5% PEG 1000, 10% Gelucire® 48/14, 85% water

In this study, higher levels of free DFO were detected in the serum of the rats that received the drug intravenously, however, not in all the experimental time points. Minimal or no significant levels of free DFO above the LOQ were seen in all other groups. High and significant levels, however, were seen in all groups where the Fe-DFO was evaluated. The results are summarized in Table 2.

Table 2. Comparative PK of Zn-DFO after oral administration in different formulations

Group	AUC* DFO	AUC** Fe-DFO	Fe-DFO Bioavailability (%)
IV, 3 mg/ml diluted in water	17.58	2.18	12.41

PO, 3 mg/ml diluted in water	N/A	1.51	69.36
PO, 3 mg/ml in Formulation 1: 20% Labrafac™, 5% Poloxamer-407, 5% Labrasol®, 70% water - emulsion		1.13	51.99
PO, 3 mg/ml in Formulation 2: 20% PEG 1000, 10% Poloxamer-407, 70% water – homogenous hazy suspension		2.22	101.70
PO, 3 mg/ml in Formulation 3: 5% PEG 1000, 10% Gelucire® 48/14, 85% water – homogenous hazy suspension		0.86	39.42

* - AUC – Area under the curve; ** - calculated relatively to DFO

These results of comparison of levels of free DFO and Fe-DFO complexes in rat blood after single oral administration indicate that Zn-DFO is rapidly absorbed and rapidly metabolized (eventually through cellular exchange between Zn and Fe) into Fe-DFO. Compared with the values obtained after intravenous administration, that is defined as 100%, the AUC of Fe-DFO formed using the PO route was ~50%. Interesting data were obtained while investigating the dynamics of DFO and Fe-DFO in rat blood using various routes of administration. While the concentration of DFO using IV injection started to diminish immediately after its first detection (Figure 2A), in the case of Fe-DFO the second peak was observed (Figure 2B).

This finding can hint to temporary compartmentalization of Fe-DFO, presumably, in the liver. Further, it can be seen that Fe-DFO represents only a small fraction of the free DFO, with a relative AUC of 12.41%. On the other hand, using oral administration (diluted in water), no free DFO was detected. Yet, the levels of Fe-DFO were significant and gave the following figure (Figure 3).

Evaluating various oral formulations, the best outcomes, in terms of bioavailability, on one hand, and washout within the reasonable time on the other hand, were

demonstrated by formulation #2, based on Poloxamer 407: 30% PEG, 10% Poloxamer 407 and 70% water (Figure 4A). Applying this formulation, an extended half-life of the Fe-DFO, in comparison to all other formulations, was observed, represents relative bioavailability of 100%. Therefore, this formulation will be used in future studies. The dynamics of Fe-DFO in rat blood when administering Zn-DFO using this formulation are shown in Figure 4A and can be compared to two other formulations (Figures 4B – based on Gelucire®, and 4C – based on Labrasol®/Labrafac™).

Efficacy assessment on Zebrafish (Danio rerio) model of diet-induced Type 2 Diabetes

In this study, test compound Zygosid-50 was dosed at two routes of administration (orally and as an aqueous solution via intraperitoneal injection) and orally as a formulation with permeability enhancer to understand the activity of Zygosid-50 across the treatment groups. Zygosid-50 was administered thrice a week. Blood samples were taken for measuring of fasting blood glucose, oral glucose tolerance, fasting insulin and HOMA-IR (homeostatic model assessment of insulin resistance).

The strains of Zebrafish (*Danio rerio*) used were wild type animals adapted. All the fish were acclimated to constant laboratory conditions (14-h light:10-h dark photoperiod, diet, water, 28°C) for at least one week in stock aquaria before the experiment. The fish were fed with high calorie flakes feed for a period of 6 weeks, until the beginning of the experiment. Through purposive sampling, adult fish with no signs of infection, body weight $0.8 \text{ g} \pm 0.2$, and age 1.5 years were scrutinized and were used for the experiment analysis.

A light-dark cycle of 14/10hr with a water temperature of 27 ± 1 °C and pH between 7.2 ± 0.4 were adhered throughout the study. Good Animal Practice as per the Institutional Animal Ethics Committee (IAEC) in accordance with the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), India, was followed in adherence to established protocols. The washout process was carried out once in every 48 hrs to keep the fish in a clean environment and to eliminate the risk of infection.

Diet-induced Obesity and Type II diabetes in zebrafish follows similar metabolic pathways as in mammals. Hence a diet induced obesity model was adopted increase the body weight of the fish. The study fish were fed with calorie dense high fat diet (15mg dry weight/day/fish) for 6 weeks to develop adipose tissue deposits around the abdominal region. The zebrafish study groups were classified to vehicle, Diabetic model, Zygosid-50 I.P, Zygosid-50 Oral, Zygosid-50 with permeability enhancers, herein referred also as P.E (20% PEG, 10% Poloxamer-407, 70% water). The treated groups were administered

with known dilutions of the test compounds up to 11 doses. The study groups were screened for fasting glucose post 7 doses and 4 more doses were extended before major drug screening. Study fish were monitored twice per day for phenotype changes in terms of motility, visible clinical signs of redness (an indicative of inflammation) near extremities such as pelvic, pectoral, and caudal region. Post 11 dose, screening was carried out for all the study groups to evaluate the therapeutic efficacy of Zygosisid-50.

Fasting blood glucose

Fasting blood glucose level of the treated fish was evaluated using glucometer. The fish were sedated in 14-16°C ice cold water for 30 secs and the fish were placed laterally on a dissection tray with minimum water. Approximately 5 ul of blood sample was collected along the body axis and posterior to the anus in the region of the dorsal aorta. The blood was loaded to the glucometer strip and the readings were recorded.

Fasting serum insulin assay

Fasting serum insulin concentrations were measured with an ELISA kit (Invitrogen; Cat#KAQ1251) according to the manufacturer's instructions. The sandwich ELISA (enzyme-linked immunosorbent assay) is designed to measure the amount of the target bound between a matched antibody pair. A target-specific antibody has been pre-coated in the wells of the supplied microplate. Samples, standards, or controls are then added into these wells and bind to the immobilized (capture) antibody. The sandwich is formed by the addition of the second (detector) antibody, a substrate solution is added that reacts with the enzyme-antibody-target complex to produce measurable signal. The intensity of this signal is directly proportional to the concentration of target present in the original specimen.

A standard curve was fitted before sample investigation. The optical density (OD) readouts are measured spectrophotometrically at a wavelength of 450 nm $\pm$ 2 nm. The OD values provide a direct correlation with the serum insulin concentration and the values were computed by comparing the OD value of sample to the standard curve.

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HOMA-IR

Homeostasis model assessment of insulin resistance (HOMA-IR) which has previously been validated was used to measure insulin resistance in fasting state. The

results IR were significantly calculated in the fasting insulin (IF) and fasting glucose (GF) (reference) according to the following formula:

$$\text{HOMA-IR} = (\text{Fasting Serum Insulin} \times \text{Fasting blood glucose}) / 12.36$$

The denominator of 12.36 is a normalizing factor, i.e., the product of normal fasting plasma insulin of 3 μ I.U/mL and normal fasting plasma glucose of 4.12 mmol/L, obtained from Vehicle. HOMA-IR range of 2.22 to 3.16 are considered as normal.

Glucose Homeostasis by Oral Glucose Tolerance Test

The blood glucose homeostasis was evaluated with Oral glucose tolerance test. The time taken by the fish to return to the normal blood glucose range determines the blood glucose homeostasis. Glucose-D was dissolved in water and was given by oral gavage. The fish was fed with 1.25 mg/g body weight. Blood glucose was measured using glucometer at 0.5 hrs, 1 hr, 1.5 hr, 2 hr, 2.5 hrs post glucose administration.

Table 3: Fasting Blood Glucose post 7 doses

Study Groups	Fasting Blood Glucose levels mg/dl
Vehicle	78 $\pm$ 5.73
Diabetic Fish Model	142 $\pm$ 7.31
Diabetic fish treated with Zygosid-50 at 30 ng (10X); I.P administration	105 $\pm$ 5.44
Diabetic fish treated with Zygosid-50 at 30 ng (10X); Oral administration	127 $\pm$ 5.71
Diabetic fish treated with Zygosid-50 + Permeability enhancers at 30 ng (10X); Oral administration	114 $\pm$ 8.10

Both the intraperitoneal dose administration group and the oral Zygosid-50 (30 ng) with permeability enhancers treated group resulted in a significant reduction of fasting blood glucose levels, although the least significant ($p \leq 0.05$) reduction was observed in the oral Zygosid-50 (30 ng) treated group. Upon comparing the results with the route of dose administration, a significant difference was observed among the intraperitoneal (I.P.) and oral administration of Zygosid-50 (30 ng). However, no significance was observed between I.P. and oral dose administration with permeability enhancers.

Table 4: Fasting Blood Glucose post 11 doses

Study Groups	Fasting Blood Glucose levels mg/dl
Vehicle	75 $\pm$ 4.5

Diabetic Fish Model	150 ± 12.5
Diabetic fish treated with Zygosid-50 at 30 ng (10X); I.P administration	69 ± 6.4
Diabetic fish treated with Zygosid-50 at 30 ng (10X); Oral administration	48 ± 8.1
Diabetic fish treated with Zygosid-50 + Permeability enhancers at 30 ng (10X); Oral administration	55 ± 4.0

Upon comparing the results with the route of dose administration, a significant difference ($\leq p 0.01$) was observed among the intraperitoneal (I.P.) and oral administration of Zygosid-50 (30 ng). However, no significance was observed between I.P. and oral dose administration with permeability enhancers.

5 Table 5: Fasting Serum Insulin

Study Groups	Fasting Serum Insulin Conc. $\mu\text{IU/ml}$	Fold change
Vehicle	3	0
Diabetic Fish Model	21	7
Diabetic fish treated with Zygosid-50 at 30 ng (10X); I.P administration	7	2.3
Diabetic fish treated with Zygosid-50 at 30 ng (10X); Oral administration	10	3.3
Diabetic fish treated with Zygosid-50 + Permeability enhancers at 30 ng (10X); Oral administration	6	2

The serum insulin levels of the study groups were examined using ELISA assay and the data is represented as mean and standard deviation. A 7-fold elevation of serum insulin levels were observed among the diabetic fish, upon treatment with Zygosid-50, there was a relative reduction of elevated insulin levels among the Zygosid-50 I.P dosed and Zygosid-50 oral dosed with permeability enhancers to 2.3 and 2-fold respectively. Although the oral dose of Zygosid-50 also reduced insulin levels, the permeability enhancers were more effective than the oral dose alone.

15 Table 6: HOMA-IR

Study Groups	HOMA-IR
Vehicle	1.03 ± 0.11
Diabetic Fish Model	12 ± 0.70
Diabetic fish treated with Zygosid-50 at 30 ng (10X); I.P administration	3 ± 0.20
Diabetic fish treated with Zygosid-50 at 30 ng (10X); Oral administration	3 ± 0.27

Diabetic fish treated with Zygosid-50 + Permeability enhancers at 30 ng (10X); Oral administration	2 ± 0.23
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The treatment with Zygosid-50 significantly restored insulin homeostasis in the study groups, although variation was observed depending on the mode of dose administration. When comparing oral Zygosid-50 with Zygosid-50+ Permeability enhancers, the group treated with Zygosid-50+ Permeability enhancers showed a significant reduction in insulin resistance compared to the group that received only oral Zygosid-50.

Table 7: Blood glucose homeostasis by Oral Glucose Tolerance test

Study Group	Blood Glucose Post oral glucose administration mg/dl				
	0.5 hr	1 hr	1.5 hr	2 hr	2.5 hr
Vehicle	92 ± 10.3	113 ± 7.6	118 ± 14.8	109 ± 11.8	95 ± 9.5
Diabetic Fish Model	147 ± 11.6	157 ± 12.6	168 ± 9.7	180 ± 9.1	137 ± 6.0
Diabetic fish treated with Zygosid-50 at 30 ng (10X); I.P administration	76 ± 14.3	125 ± 9.3	131 ± 8.4	122 ± 7.7	92 ± 8.9
Diabetic fish treated with Zygosid-50 at 30 ng (10X); Oral administration	68 ± 11.5	120 ± 7.9	134 ± 17.2	105 ± 17.2	69 ± 13.1
Diabetic fish treated with Zygosid-50 + Permeability enhancers at 30 ng (10X); Oral administration	59 ± 15.7	138 ± 7.3	155 ± 7.8	99 ± 6.8	65 ± 7.9

A significant difference was observed among the diabetic fish group with elevated blood glucose until 2 hrs of glucose administration and did not return to normal range until 2.5 hrs. Among the Zygosid-50 treated groups, the blood glucose was observed to return to normal range from 1.5 hrs of glucose administration. Zygosid-50 was observed to restore glucose homeostasis across I.P and oral route of administration. However, blood glucose of oral Zygosid-50 and oral Zygosid-50 + Permeability enhancers returned to normal blood glucose range earlier than I.P dosed group with oral Zygosid-50 + Permeability enhancers slightly better efficacy.

This study evaluated the efficacy of the test compound Zygosid-50 in a zebrafish model of type 2 diabetes using various routes of dose administration. The screening

parameters included fasting blood glucose levels, fasting serum insulin levels, blood glucose homeostasis assessed by oral glucose tolerance test, and HOMA-IR.

The results showed that Zygosid-50 was effective in reducing elevated fasting glucose, elevated fasting insulin, and restoring blood glucose homeostasis regardless of the route of administration. However, statistical analysis was performed to determine the precise efficacy of Zygosid-50 with different routes of administration. The results showed that oral administration of Zygosid-50 with permeability enhancers significantly reduced serum insulin levels, improved blood glucose homeostasis, and reduced HOMA-IR.

CLAIMS:

1. A composition comprising:
a therapeutically effective amount of a complex comprising deferoxamine (DFO-
5 B), or a pharmaceutically acceptable salt thereof, and a metal; and
a hydrophilic, non-ionic surfactant comprising polyethylene glycol (PEG) and a
non-ionic triblock copolymer,
wherein the metal is selected from the group consisting of Zn, Ga, Ag, Au, V,
and Mo.
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2. The composition according to claim 1, wherein the metal is Zn^{2+} or Ga^{3+} .
3. The composition according to claim 1, wherein the pharmaceutically acceptable
salt is an acid addition salt.
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4. The composition according to claim 3, wherein the acid is selected from the group
consisting of 1-hydroxy-2-naphthoic acid, 2,2-dichloroacetic acid, 2-oxoglutaric acid, 4-
acetamidobenzoic acid, 4-aminosalicylic acid, acetic acid, alkanesulphonic acid,
alkenesulphonic acid, alkynesulphonic acid with any substitutions, adipic acid, ascorbic
20 acid, aspartic acid, benzoic acid, camphoric acid, camphor-10-sulfonic acid, decanoic
acid, hexanoic acid, octanoic acid, carbonic acid, cinnamic acid, citric acid, cyclamic acid,
dodecylsulfuric acid, formic acid, fumaric acid, galactaric acid, gentisic acid,
glucoheptonic acid, gluconic acid, glucuronic acid, glutamic acid, glutaric acid,
glycerophosphoric acid, glycolic acid, hippuric acid, hydrobromic acid, hydrochloric acid,
25 isobutyric acid, lactic acid, lactobionic acid, lauric acid, maleic acid, malic acid, malonic
acid, mandelic acid, methanesulfonic acid or its derivatives, a substituted hydrocarbyl
sulphonic acid, nicotinic acid, nitric acid, oleic acid, oxalic acid, palmitic acid, pamoic acid,
phosphoric acid, propionic acid, pyroglutamic acid, salicylic acid, sebacic acid, seleninic
acid, selenonic acid, stearic acid, succinic acid, sulfuric acid, tartaric acid, thiocyanic acid,
30 and undecylenic acid.
5. The composition according to claim 2, wherein the nonionic triblock copolymers
are composed of a central hydrophobic chain of polyoxypropylene (poly(propylene
oxide)) flanked by two hydrophilic chains of polyoxyethylene (poly(ethylene oxide)).

6. The composition according to claim 5, wherein the hydrophilic nonionic surfactant is a poloxamer.

5 7. The composition according to claim 5 wherein the concentration of the polyethylene glycol is in a range of 17-23%, and a concentration of the nonionic triblock copolymers composed of a central hydrophobic chain of polyoxypropylene (poly(propylene oxide)) flanked by two hydrophilic chains of polyoxyethylene (poly(ethylene oxide)) is in a range of 8-12%.

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8. The composition according to claim 1, wherein the metal is Zn^{2+} and the hydrophilic, non-ionic surfactant is poloxamer.

9. The composition according to claim 1, wherein the metal is Ga^{3+} and the
15 hydrophilic, non-ionic surfactant is poloxamer.

10. The composition according to claim 1, further comprising one or more pharmaceutically acceptable excipients selected from the group consisting of diluents, carriers, excipients.

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11. The composition according to claim 1, wherein the composition is formulated for oral, gavage, topical, ocular, nasal, administration to the ear, administration by inhalation, by eye drops, systemic administration including parenteral, by injection, by suppositories, by patches, or by any other clinically accepted method and means.

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12. The composition according to claim 1, wherein the composition is selected from the group consisting of a tablet, mini-tablet, pill, lozenge, pastille, capsule, drinkable preparation, oral suspension, soluble film, powder, ointment, cream, paste, encapsulated gel, patches, liposome, sprayable aerosol, and vapors.

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13. A method for modulating the level of a cytokine in a subject comprising administration of the composition claim 1.

14. The method according to claim 13, wherein a level of at least one pro-inflammatory cytokine is reduced.
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15. The method according to claim 14, wherein the pro-inflammatory cytokine is selected from the group consisting of IL-1 α , IL-6, TNF- α , IL-17, and combinations thereof.

5 16. The method according to claim 13, wherein a level of at least one anti-inflammatory cytokine is elevated.

17. The method according to claim 16, wherein the anti-inflammatory cytokine is selected from the group consisting of IL-13, IL-4, IL-10, and combinations thereof.

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18. A method for treating a disease, disorder, or condition in a subject in need thereof, comprising administration of the composition claim 1

wherein the disease, disorder, or condition is selected from the group consisting of Type 2 diabetes, metabolic syndrome and any other diabetes-related conditions and complications, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatohepatitis (NASH), Wilson's disease; Type 1 diabetes and its complications; neoplastic diseases with inflammatory component in pathophysiology; diseases of the blood and blood-forming organs, involving the immune mechanism; metabolic disorders involving the inflammatory component; neurodegenerative and demyelinating disorders, such as multiple sclerosis, amyotrophic lateral sclerosis, age-related macular degeneration, Parkinson's disease, Alzheimer disease; inflammatory diseases of the central nervous system; immune-related disorders of circulatory and cardiovascular system; inflammatory diseases of respiratory system, especially asthma, cystic fibrosis, allergic rhinitis, nasal polyposis and COPD; skin inflammatory disorders, especially, psoriasis, rheumatic arthritis, psoriatic arthritis, wound healing, injury due to exposure to chemical agents, heat or cold; ischemia and reperfusion injury; stroke; immune-related diseases of digestive system, especially inflammatory bowel disease; thalassemia; hemochromatosis; autoimmune disorders; inflammatory diseases of oral cavity and salivary glands; and infectious diseases caused by *Escherichia coli*, *Staphylococcus aureus*, *Alcaligenes faecalis*, *Neisseria meningitidis*, *Prevotella intermedia*, *Porphyromonas gingivalis*, and species of *Salmonella*, *Shigella*, *Proteus*, *Providencia*, *Enterobacter*, *Morganella* and *Pseudomonas*.

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19. The method according to claim 18, wherein the composition is administered at a dose within a range of 0.1 mg/kg to 10.0 mg/kg.