[0004] Prior to Applicants' inventions, PRG4 had been appreciated as a protein with only mechanical properties, providing mechanical functionalities such as lubricating joints, tendons, cartilage, and acting as a mechanical barrier to inhibit intercellular interactions. However, as shown herein, Applicants have discovered that lubricin has properties that extend beyond its ability to provide boundary lubrication and anti-adhesion. In particular, Applicants have determined that PRG4 has anti-inflammatory properties due to its ability to act as a ligand or signaling molecule, participating in ligand receptor interactions to modulate, for example, CD44 activation, NF-κB translocation, and cytokine-mediated inflammation.

SUMMARY

[0005] The present disclosure exploits the heretofore unknown anti-inflammatory properties of PRG4, also known as lubricin. Accordingly, the present disclosure provides, for example, methods of inhibiting or reducing inflammatory responses and methods for treating inflammatory conditions. Underlying the discovery of PRG4's anti-inflammatory properties is the understanding of various putative mechanisms by which PRG4 achieves its anti-inflammatory effect. These mechanisms were discovered by Applicants who have determined that PRG4 binds CD44 receptors, enabling it to act as a CD44 receptor antagonist. As a result, PRG4 is able to down-regulate pro-inflammatory responses mediated by CD44 receptor signaling. The ability of PRG4 to affect CD44 signaling also has the effect of down-regulating translocation of NF-κB. Further, administration of PRG4 has been shown to inhibit production of a number of pro-inflammatory cytokines, as well as to modulate cellular responses and proliferation due to pro-inflammatory cytokine induction (e.g., TNF-a); a feature unique to PRG4 and not to other lubricants such as high molecular weight hyaluronic acid. PRG4 can therefore be used in a number of novel ways in therapeutic and prophylactic contexts to effect anti-inflammatory action via its effect on signaling pathways involved in producing an inflammatory response.

[0005a] In one aspect of the present disclosure, there is provided a use of PRG4 in the manufacture of a medicament for reducing or inhibiting an inflammatory response in a patient, wherein said medicament is to be administered at a site that is non-cartilaginous, non-osteal, non-osseous, and non-articular, and is not the cornea, urinary bladder, or tissue of the oral cavity.

[0005b] In another aspect of the present disclosure, there is provided a use of PRG4 in the manufacture of a medicament for reducing or inhibiting an inflammatory response in a patient having an inflammatory condition, wherein the inflammatory condition is selected from the group consisting of acne; acute organ failure; acute respiratory distress syndrome (ARDS); Addison's disease; allergic rhinitis; allograft rejection; alopecia greata; Alzheimer's disease; anaphylaxis; Appendicitis; asthma; atherosclerosis; atopic dermatitis; autoimmune alopecia; autoimmune disease; autoimmune hyperthyroidism; autoimmune hypopituatarism; autoimmune polyglandular disease; Behcet's disease; brain injury; bronchitis; cancer; cardiopulmonary bypass syndrome; cardiorenal syndrome; Celiac disease; chronic actinic dermatitis; chronic obstructive pulmonary disease (COPD); chronic renal failure; colitis, contact dermatitis; Crohn's disease; dermatomyositis; diabetes; eczema; emphysema; foreign body rejection; glaucoma; glomerulonephritis; gout; graft vs. host disease; Graves' Disease; Guillain-Barre syndrome; Hashimoto's thyroiditis; hay fever; hepatorenal syndrome; hypersensitivity or allergy; inclusion body myositis; infection due to viral, fungal, parasitic or microbial infiltration; inflammatory bowel disease; inflammatory kidney disease; injury due to thermal or chemical exposure or irradiation; irritable bowel syndrome; ischemia; lung inflammation; morphea; multiple sclerosis; mycosis fungoides; myocardial infarction; necrosis; non-infectious lung injury; pancreatitis; pernicious anemia; pneumonia; polymyositis; prostatitis; pseudogout; psoriasis; Pustulosis palmoplanteris; Pyoderma gangrenum; respiratory allergy; scleroderma; sepsis; serum sickness; Sezary's syndrome; skin allergy; stroke; systemic inflammatory response syndrome (SIRS); systemic lupus erythematosus; systemic sclerosis; T-cell mediated hypersensitivity diseases; transplant rejection; trauma including from a gun wound, knife wound, automobile accident, fall, or combat; tuberculosis; ulcerative colitis; uticaria; pericarditis; and vitiligo.

[0005c] In yet another aspect of the present disclosure, there is provided use of PRG4 in the manufacture of a medicament for reducing or inhibiting an inflammatory response in a patient at a site that is non-cartilaginous, non-osteal, non-osseous, and non-articular, and is not the cornea, urinary bladder, or oral cavity, wherein said PRG4

a) binds a CD44 receptor on a cell in said patient;

b) reduces or inhibits the production of a pro-inflammatory cytokine in said patient; and/or

d) reduces or inhibits the translocation of NF-κB in a cell in said patient,

thereby reducing or inhibiting the inflammatory response in said patient.

[0005d] In a further aspect of the present disclosure, there is provided a use of PRG4 in the manufacture of a medicament for inhibiting binding of a ligand to CD44 present on a surface at a site that is non-cartilaginous, non-osteal, non-osseous, and non-articular, and is not the cornea, urinary bladder, or oral cavity, wherein the surface is exposed to PRG4, wherein PRG4 binds to CD44 and inhibits binding of the ligand.

[0005e] In another aspect of the present disclosure, there is provided a use of PRG4 in the manufacture of a medicament for reducing or inhibiting pro-inflammatory cytokine levels in blood, wherein the PGR4 is to be systemically administered in an amount sufficient to reduce or inhibit pro-inflammatory cytokine levels.

[0005f] In yet another aspect of the present disclosure, there is provided a use of PRG4 in the manufacture of a medicament for inhibiting NF-κB translocation in a cell at a site that is non-cartilaginous, non-osteal, non-osseous, and non-articular, and is not the cornea, urinary bladder, or oral cavity, wherein a cell containing NF-κB is to be contacted with PRG4, wherein PRG4 inhibits activation of the NF-κB signaling pathway.

[0005g] In a further aspect of the present disclosure, there is provided a use of PRG4 in the manufacture of a medicament for treating an inflammatory condition.

[0005h] In another aspect of the present disclosure, there is provided a use of PRG4 in the manufacture of a medicament for reducing or inhibiting inflammation or treating an inflammatory condition.

[0006] Accordingly, the present disclosure provides a method of reducing or inhibiting an inflammatory response in a patient comprising administering PRG4 to the patient systemically or locally at a site that is non-cartilaginous, non-osseous, non-osteal, and non-articular, and is not the urinary bladder, cornea, or surface tissue of the oral cavity.

[0007] In one embodiment, the PRG4 is administered systemically to the patient, for example, by intravenous, intramuscular, subcutaneous, intraperitoneal, oral, rectal, buccal, or sublingual administration, or by inhalation.

[0008] In another embodiment of the present disclosure, PRG4-containing compositions can be conveniently administered to patients by formulating PRG4 into a matrix/scaffold dosage form for injection/or placement within a location in a patient. Such a PRG4-containing composition may be in the form of a controlled release formulation that is capable of slowly releasing PRG4 at a location in the patient. Suitable matrix/scaffold dosage forms include, but are not limited to, biocompatible polymers, polymeric matrices, capsules, microcapsules, microparticles, diffusion devices and liposomes. Other such formulations of the present disclosure include liquids that, upon association with the matrix or upon administration to the patient, form a solid or a gel. In addition to such compositions being formulated to contain PRG4, such compositions may also be formulated to contain recombinantly engineered cells designed to express PRG4. The PRG4-containing compositions may be administered in any manner suitable to direct PRG4 to the location within a patient, including by direct injection or placement of a pre-formed PRG4 composition during an open surgery or during a laparoscopic or arthroscopic procedure.

[0009] In another embodiment, the PRG4 is administered locally to the patient, for example, topically or by injection. In some embodiments, the PRG4 is administered locally at a site selected from skin, kidney, lungs, liver, a wound such as a skin burn or surgical incision, thyroid, pancreas, spleen, thymus, ovary, testicle, uterus, adrenal gland, pituitary gland, hypothalamus, urethra, prostate, heart, artery or vessel, pericardial fluid, brain, stomach. Administration is also conducted in orifices including the rectum, nose, ear, pharynx, larynx, trachea. Other areas for administration include the tongue, posterior eye, or the site of a tumor. Administration is also performed in visci including the small intestine, large intestine, colon or esophagus. , pharynx, larynx, trachea, tongue, posterior eye, or the site of a tumor. In some embodiments, the site of local administration is a site of inflammation or of an inflammatory response in the patient.

[0010] In another embodiment, PRG4 is administered systemically to a patient who suffers from an inflammatory condition selected from arthritis, osteoarthritis, psoriatic arthritis,

boundary lubrication in the patient. In another embodiment, PRG4 is administered in an amount ranging from 0.1 μg/kg – 4,000 μg/kg or as a coating on a tissue surface applied from a PRG4 solution comprising, for example, a concentration of PRG4 between 10 μg/mL to about 2 mg/mL.

[0014] In one embodiment, the reduction or inhibition of the inflammatory response may be measured by the level of production of a pro-inflammatory cytokine in the patient. For example, in one embodiment, the pro-inflammatory cytokine is selected from the group consisting of IL-1α, IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-12p70, IL-13, IL-14, IL-15, IL-16, IL-17, IL-17α, IL-18, IL-19, IL-20, IL-21, IL-22, IL-23, IL-24, IL-25, IL-26, IL-27, IL-28, IL-29, IL-30, IL-31, IL-32, IL-33, IL-34, IL-35, IL-36, TNF-α, TNF-β (lymphotoxin-α), lymphotoxin-β, CXC31L (Fractalkine), CXCL-8, CCL2, CCL3, CCL4, CCL5, CCL11, CXCL10, IFN-α, IFN-β, IFN-ε, IFN-κ, IFN-ω, IFN-γ, VEGF, MCP-1, MCP-3, EGF, GMCSF, CD40L, CD27L, CD30L, FASL, 4-1BBL, OX40L, TRAIL, FGF-2, GRO, MDC, Rantes, G-CSF, M-CSF, FGF-2, EPO, MCSF, MIP3α, MG-CSF, and GCSF.

[0015] The present disclosure also provides a method of reducing or inhibiting an inflammatory response in a patient having an inflammatory condition, the method comprising administering PRG4 to the patient. The inflammatory condition may be any of the conditions mentioned herein.

[0016] The present disclosure also provides a method of reducing or inhibiting an inflammatory response in a patient by administering PRG4 to the patient. Administration of PRG4 binds a CD44 receptor on a cell in the patient, reduces or inhibits the production of a pro-inflammatory cytokine in the patient, and/or reduces or inhibits the translocation of NF-κB in a cell in the patient and thereby reduces or inhibits the inflammatory response in the patient.

[0017] In another embodiment, the PRG4 is administered locally to said patient to cells at or about a non-cartilaginous tissue, a non-osteal tissue, a non-osseous tissue, and is not corneal, urinary bladder or oral cavity tissue, which is a site of inflammation in the patient.

[0018] In a further embodiment, the cell is a mast cell, a spleen cell, a lung cell, a renal cell, a brain cell, a cardiac cell, a hepatic cell, a cancer cell, a skin cell, an epithelial cell, an endothelial cell, leukocyte, lymphocyte, neutrophil, eosinophil, basophil, monocyte,

macrophage, dendritic cell, fibroblast, muscle cell, urethral cell, vascular cell, nerve cell, pancreatic cell, gastric cell, intestinal cell, colon cell, rectal cell, gall bladder cell, stem cell, or thyroid cell.

[0019] In a further embodiment, PRG4 is administered to the patient systemically to contact a synoviocyte, a chondrocyte, an osteocyte, an osteoblast, an osteoclast, retinal cell, limbal cell, trabecular meshwork cell, corneal cell, conjunctival cell, an ocular cell, or an ophthalmic cell.

[0020] In yet another embodiment, whether PRG4 is administered locally or systemically, it is administered in an amount insufficient to provide boundary lubrication in the patient. For example, in one embodiment, the PRG4 is administered in amount ranging from 0.1 μg/kg – 4,000 μg/kg.

[0021] In a further embodiment, administration of PRG4 reduces or inhibits a pro-inflammatory cytokine selected from the group consisting of IL-2, IL-4, IL-6, IL-8, IL-10, VEGF, IFN-γ, TNF-α, IL-1α, IL-1β, MCP-1, EGF, FGF-2, Fractalkine, IFN-α2, GRO, MCP-3, MDC, EPO, IL-13, IL-18, MCSF, MIP-3α, MG-CSF, IL-7, IL-5, G-CSF, Rantes, IL-17α, or IL-12p70.

[0022] The present disclosure also provides a method of inhibiting binding of an activating ligand to CD44 present on a surface. The method comprises exposing the surface to PRG4 at a concentration sufficient to bind CD44 and to inhibit binding of the ligand. According to one embodiment, PRG4 is present at the surface in an amount sufficient to bind CD44 but insufficient to provide boundary lubrication. In another embodiment, the surface is a mammalian cell membrane while in another embodiment the surface is in a surface plasmon resonance detector. In yet another embodiment, the PRG4 is rhPRG4 (recombinant human PRG4) or nhPRG4 (native human PRG4).

[0023] In a further embodiment, the surface is in a human subject. In another embodiment, the PRG4 is administered systemically. In another embodiment, the PRG4 is administered topically to a patient. In yet another embodiment, the PRG4, for example rhPRG4, is administered to a human subject in amount ranging from 0.1 μg/kg – 4,000 μg/kg. In another embodiment, the PRG4, for example, rhPRG4, is administered in an amount of 0.1

μg/mL to 30 mg/mL in small volumes of 1-100 μL per dose. In another embodiment, the PRG4 is administered in an amount of 10 μg/mL to 4 mg/mL in volumes of 100 μL – 4 L per dose, for instance as an enema.

[0024] In one embodiment, when the surface is in a human subject, the human suffers from a bone metabolic disorder and exposing the receptor to PRG4 reduces or inhibits osteoclast differentiation. In a further embodiment, the human suffers from an inflammatory condition. Exemplary inflammatory conditions have been listed herein above. In one embodiment, exposing the receptor to PRG4, for example, rhPRG4 reduces inflammation or the level of a pro-inflammatory cytokine in the location of the inflammatory condition.

[0025] According to one embodiment, the cell is a synoviocyte, a mast cell, a spleen cell, a lung cell, a renal cell, a brain cell, a cardiac cell, an eye cell, a hepatic cell, a cancer cell, a skin cell, an epithelial cell, or an endothelial cell. In a further embodiment, the cell is a synoviocyte of a subject with rheumatoid arthritis, a pancreatic cell of a diabetic, a lung cell of an asthmatic, an ocular cell of a subject with an eye infection, burn or other irritation; a bronchiolar or alveolar epithelial cell of a subject with tuberculosis or another lung infection or injury or condition; a lung cell of a cystic fibrosis subject; a lower intestinal epithelial cell of a person with colitis or Crohn's disease; a skin cell of a subject with psoriasis, a skin cell of a subject with acne; a skin cell of a subject following treatment with laser ablation, or an endothelial cell of subject with sepsis. In yet another embodiment, the cell is a T-cell, while in a further embodiment, the cell is a lymphocyte, neutrophil, fibroblast, cancer cell, macrophage, dendritic cell, monocyte, eosinophil, or endothelial cell.

[0026] According to one embodiment, exposing a surface to PRG4, for example, rhPRG4, antagonizes a pro-inflammatory ligand of CD44. In one embodiment, the ligand is hyaluronan (HA), a hyaluronan serum-derived hyaluronan-associated protein complex (HA-SHAP), or a matrix metalloproteinase (e.g., MMP-9). In another embodiment, the ligand is hemopexin, EMMPRIN, somatomedin-B, osteopontin, OKT3, or a complement related protein such as C3a, CD3, CD46.

[0027] The present disclosure also provides a method of reducing or inhibiting pro-inflammatory cytokine levels in blood, for example, in a human subject. The method comprises the step of administering PRG4 systemically in an amount sufficient to reduce or

inhibit pro-inflammatory cytokine levels. Exemplary proinflammatory cytokines include IL-2, IL-4, IL-6, IL-8, IL-10, VEGF, IFN-γ, TNF-α, IL1-α, IL-1-β, MCP-1, EGF, FGF-2, fractalkine, IFN-α2, GRO, MCP-3, MDC, EPO, IL-13, IL-18, MCSF, MIP-3α, MG-CSF, IL-7, IL-5, G-CSF, Rantes, IL-17α, or IL-12p70.

[0028] The present disclosure also provides a method of inhibiting NF-κB translocation in a cell. The method comprises the step of contacting a cell containing NF-κB with PRG4, wherein PRG4 binds to a cell surface receptor to inhibit activation of the NF-κB signaling pathway. In a further embodiment, PRG4 inhibits a TNF-α receptor or an IL-1 receptor on the cell surface.

[0029] In yet another embodiment, the cell is in a human when contacted with PRG4. In a further embodiment, the cell is a synoviocyte, chondrocyte, or osteocyte, while in yet another embodiment, the cell is a spleen cell, a lung cell, a renal cell, a brain cell, a cardiac cell, a brain cell, a hepatic cell, an epithelial cell or an endothelial cell.

BRIEF DESCRIPTION OF THE DRAWINGS

[0030] **FIGS. 1A-C** are bar graphs presenting data demonstrating the binding of recombinant human proteoglycan 4 (rhPRG4), high-molecular weight hyaluronic acid (HMW HA), and medium molecular weight hyaluronic acid (MMW HA) to recombinant human CD44 receptor as detected by TMB-ELISA at 450 nm. Data represents the average of 4 independent experiments with triplicate wells per group. **FIG. 1A** depicts binding of rhPRG4, HMW HA, MMW HA and vitronectin to CD44-IgG1Fc and using IgG1 Fc. The star (*) indicates that the 450 nm absorbance in the CD44-IgG1 Fc wells were statistically significantly higher ($p<0.001$) than the IgG1 Fc wells for rhPRG4, HMW HA and MMW HA. **FIG. 1B** shows the concentration-dependent CD44 binding of rhPRG4, HMW HA and MMW HA. CD44 binding to rhPRG4 was significantly higher than to HMW HA or MMW HA ($p<0.001$). The double stars (**) indicate that CD44 binding to rhPRG4 was significantly higher than to MMW HA ($p<0.001$). **FIG. 1C** depicts the competition between rhPRG4 (5 μg/mL) and either HMW HA or MMW HA (0.01 μg/mL to 50 μg/mL) on binding to CD44 coated on 96-well ELISA plates. The star (*) indicates the percentage CD44 binding in HMW HA+rhPRG4 wells was significantly lower than rhPRG4 wells ($p<0.05$); (**) indicates the percentage CD44 binding in MMW HA+rhPRG4 wells was significantly lower than rhPRG4 wells ($p<0.05$).

What is claimed is:

1. Use of PRG4 in the manufacture of a medicament for reducing or inhibiting an inflammatory response in a patient, wherein said medicament is to be administered at a site that is non-cartilaginous, non-osteal, non-osseous, and non-articular, and is not the cornea, urinary bladder, or tissue of the oral cavity.

2. The use of claim 1, wherein the medicament is to be administered systemically to the patient.

3. The use of claim 2, wherein the medicament is to be administered intravenously, intraperitoneally, by inhalation, intramuscularly, subcutaneously, orally, rectally, buccally, or sublingually.

4. The use of claim 1, wherein the medicament is to be administered locally to said site.

5. The use of claim 4 wherein the medicament is to be administered topically or by injection or perfusion.

6. The use of any one of claims 1-5, wherein the PRG4 is recombinant exogenous human PRG4.

7. The use of any one of claims 1-6, wherein the PRG4 is effective to interfere with CD44 signaling.

8. The use of any one of claims 1-7, wherein the PRG4 has the sequence of SEQ ID NO:1 less the signal sequence.

9. The use of claim 1 wherein the medicament is to be administered locally to said patient at a location selected from skin, kidney, lungs, liver, a wound or surgical incision, thyroid, pancreas, spleen, thymus, ovary, testicle, ureter, uterus, adrenal gland, pituitary gland, hypothalamus, urethra, prostate, heart, artery or vessel, brain, stomach, small intestine, large intestine, colon, esophagus, pharynx, larynx, trachea, tongue, posterior eye, or tumor.

10. The use of claim 9 wherein the location is a site of inflammation in the patient.

11. The use of any preceding claim wherein the patient suffers from an inflammatory condition selected from the group consisting of acne; acute organ failure; acute respiratory distress syndrome (ARDS); Addison's disease; allergic rhinitis; allograft rejection; alopecia

areata; Alzheimer's disease; anaphylaxis; Appendicitis; asthma; atherosclerosis; atopic dermatitis; autoimmune alopecia; autoimmune disease; autoimmune hyperthyroidism; autoimmune hypopituatarism; autoimmune polyglandular disease; Behcet's disease; brain injury; bronchitis; cancer; cardiopulmonary bypass syndrome; cardiorenal syndrome; Celiac disease; chronic actinic dermatitis; chronic obstructive pulmonary disease (COPD); chronic renal failure; colitis, contact dermatitis; Crohn's disease; dermatomyositis; diabetes; eczema; emphysema; foreign body rejection; glaucoma; glomerulonephritis; gout; graft vs. host disease; Graves' Disease; Guillain-Barre syndrome; Hashimoto's thyroiditis; hay fever; hepatorenal syndrome; hypersensitivity or allergy; inclusion body myositis; infection due to viral, fungal, parasitic or microbial infiltration; inflammatory bowel disease; inflammatory kidney disease; injury due to thermal or chemical exposure or irradiation; irritable bowel syndrome; ischemia; lung inflammation; morphea; multiple sclerosis; mycosis fungoides; myocardial infarction; necrosis; non-infectious lung injury; pancreatitis; pernicious anemia; pneumonia; polymyositis; prostatitis; pseudogout; psoriasis; Pustulosis palmoplanteris; Pyoderma gangrenum; respiratory allergy; scleroderma; sepsis; serum sickness; Sezary's syndrome; skin allergy; stroke; systemic inflammatory response syndrome (SIRS); systemic lupus erythematosus; systemic sclerosis; T-cell mediated hypersensitivity diseases; transplant rejection; trauma including from a gun wound, knife wound, automobile accident, fall, or combat; tuberculosis; ulcerative colitis; uticaria; pericarditis, and vitiligo.

12. The use of claim 2, wherein the patient suffers from an inflammatory condition selected from the group consisting of arthritis, osteoarthritis, psoriatic arthritis, rheumatoid arthritis, diabetic retinopathy, retinal inflammation, retinitis, Sjogren's syndrome, macular degeneration, gout, pseudogout, pericarditis, and uveitis.

13. The use of claims 11 or 12, wherein the inflammatory response in the patient is associated with the inflammatory condition with which the patient suffers.

14. The use of any preceding claim wherein PRG4 is to be administered in an amount insufficient to provide boundary lubrication in the patient.

15. The use of any preceding claim wherein PRG4 is to be administered in an amount ranging from 0.1 μg/kg - 4000 μg/kg, or is to be administered locally to provide a coating of PRG4 from a PRG4 solution.

16. The use of any preceding claim, wherein the reduction or inhibition of the inflammatory response is measurable by level of production of a pro-inflammatory cytokine in the patient.

17. The use of claim 1 comprising treatment of inflammatory bowel disease wherein lubricin is to be administered to the bowel of a patient systemically, rectally, orally, or through a combination thereof.

18. The use of claim 1 comprising treatment of a brain injury wherein lubricin is to be administered to the brain of a patient systemically, topically during surgery, or through a combination thereof.

19. The use of claim 1 comprising treatment of an allergy symptom in a patient suffering from a symptom selected from the group consisting of congestion, post-nasal drip, coughing, wheezing, sneezing, runny nose, itchy throat, itchy skin, itchy eyes, and watery eyes, wherein the medicament is to be administered topically to a tissue surface exhibiting or at risk of developing the symptoms in an amount of a medicament comprising PRG4 sufficient to ameliorate the symptom.

20. The use of claim 19 wherein the medicament is to be administered intranasally, orally, or by inhalation.

21. Use of PRG4 in the manufacture of a medicament for reducing or inhibiting an inflammatory response in a patient having an inflammatory condition, wherein the inflammatory condition is selected from the group consisting of acne; acute organ failure; acute respiratory distress syndrome (ARDS); Addison's disease; allergic rhinitis; allograft rejection; alopecia greata; Alzheimer's disease; anaphylaxis; Appendicitis; asthma; atherosclerosis; atopic dermatitis; autoimmune alopecia; autoimmune disease; autoimmune hyperthyroidism; autoimmune hypopituatarism; autoimmune polyglandular disease; Behcet's disease; brain injury; bronchitis; cancer; cardiopulmonary bypass syndrome; cardiorenal syndrome; Celiac disease; chronic actinic dermatitis; chronic obstructive pulmonary disease (COPD); chronic renal failure; colitis, contact dermatitis; Crohn's disease; dermatomyositis; diabetes; eczema; emphysema; foreign body rejection; glaucoma; glomerulonephritis; gout; graft vs. host disease; Graves' Disease; Guillain-Barre syndrome; Hashimoto's thyroiditis; hay fever; hepatorenal

syndrome; hypersensitivity or allergy; inclusion body myositis; infection due to viral, fungal, parasitic or microbial infiltration; inflammatory bowel disease; inflammatory kidney disease; injury due to thermal or chemical exposure or irradiation; irritable bowel syndrome; ischemia; lung inflammation; morphea; multiple sclerosis; mycosis fungoides; myocardial infarction; necrosis; non-infectious lung injury; pancreatitis; pernicious anemia; pneumonia; polymyositis; prostatitis; pseudogout; psoriasis; Pustulosis palmoplanteris; Pyoderma gangrenum; respiratory allergy; scleroderma; sepsis; serum sickness; Sezary's syndrome; skin allergy; stroke; systemic inflammatory response syndrome (SIRS); systemic lupus erythematosus; systemic sclerosis; T-cell mediated hypersensitivity diseases; transplant rejection; trauma including from a gun wound, knife wound, automobile accident, fall, or combat; tuberculosis; ulcerative colitis; uticaria; pericarditis; and vitiligo.

22. The use of claim 21, wherein the medicament is to be administered systemically to the patient.

23. The use of claim 22, wherein the medicament is to be administered intravenously, by inhalation, intramuscularly, subcutaneously, orally, rectally, buccally, or sublingually.

24. The use of claim 21, wherein the medicament is to be administered locally to the patient.

25. The use of claim 24, wherein the medicament is to be administered topically or by injection.

26. The use of any one of claims 21-25, wherein the PRG4 is exogenous human PRG4.

27. The use of any one of claims 21-26, wherein the PRG4 is recombinant human PRG4.

28. The use of any one of claims 21-27, wherein the PRG4 has the sequence of SEQ ID NO:1 less the signal sequence.

29. The use of claim 24 or 25, wherein the medicament is to be administered to said patient at a location selected from skin, kidney, lungs, liver, a wound or surgical incision, thyroid, pancreas, spleen, thymus, ovary, testicle, uterus, adrenal gland, pituitary gland, hypothalamus, urethra, prostate, heart, artery or vessel, brain, stomach, small intestine, large intestine, colon, esophagus, pharynx, larynx, trachea, tongue, or tumor.

30. The use of any of claims 21-29 claim wherein the medicament is to be administered in an amount insufficient to provide boundary lubrication in the patient.

31. The use of any of claims 21-30 wherein the medicament is to be administered in an amount ranging from 0.1 μg/kg - 4000 μg/kg, or is to be administered locally to provide a coating of PRG4 from a PRG4 solution.

32. The use of any one of claims 21-31, wherein the reduction or inhibition of the inflammatory response is measurable by level of production of a pro-inflammatory cytokine in the patient.

33. Use of PRG4 in the manufacture of a medicament for reducing or inhibiting an inflammatory response in a patient at a site that is non-cartilaginous, non-osteal, non-osseous, and non-articular, and is not the cornea, urinary bladder, or oral cavity, wherein said PRG4

a) binds a CD44 receptor on a cell in said patient;

b) reduces or inhibits the production of a pro-inflammatory cytokine in said patient; and/or

d) reduces or inhibits the translocation of NF-κB in a cell in said patient,

thereby reducing or inhibiting the inflammatory response in said patient.

34. The use of claim 33, wherein the patient is a human.

35. The use of claim 33, wherein said medicament is recombinant human lubricin.

36. The use of claim 33, wherein said recombinant human lubricin has the sequence of SEQ ID NO:1 less the signal sequence.

37. The use of claim 33, wherein said medicament is exogenous human lubricin.

38. The use of any one of claims 33-37 wherein said medicament is to be administered systemically to said patient.

39. The use of claim 38, wherein said systemic administration is parenteral or enteral.

40. The use of claim 38, wherein said systemic administration is intramuscular, intravenously, intraperitoneal, oral, rectal, sublingual, buccal, sublabial, nasal, or inhalational.

41. The use of any one of claims 33-35, wherein said medicament is to be administered locally to said patient at a location that is a site of inflammation in said patient selected from skin, kidney, lungs, liver, a wound or surgical incision, thyroid, pancreas, spleen, thymus, ovary, testicle, uterus, adrenal gland, pituitary gland, hypothalamus, urethra, prostate, heart, pericardium, artery or vessel, brain, stomach, small intestine, large intestine, colon, esophagus, pharynx, larynx, trachea, tongue, or tumor .

42. The use of any one of the preceding claims wherein said patient suffers from an inflammatory condition and the inflammatory response is associated with said inflammatory condition.

43. The use of claim 33, wherein the inflammatory condition is selected from the group consisting of: acne; acute organ failure; acute respiratory distress syndrome (ARDS); Addison's disease; allergic rhinitis; allograft rejection; alopecia areata; Alzheimer's disease; anaphylaxis; Appendicitis; arthritis; asthma; atherosclerosis; atopic dermatitis; autoimmune alopecia; autoimmune disease; autoimmune hyperthyroidism; autoimmune hypopituatarism; autoimmune polyglandular disease; Behcet's disease; brain injury; bronchitis; cancer; cardiopulmonary bypass syndrome; cardiorenal syndrome; Celiac disease; chronic actinic dermatitis; chronic obstructive pulmonary disease (COPD); chronic renal failure; colitis, contact dermatitis; Crohn's disease; dermatomyositis; dermatomyositis; diabetes; diabetic retinopathy; eczema; emphysema; foreign body rejection; glaucoma; glomerulonephritis; gout; graft vs. host disease; Graves' Disease; Guillain-Barre syndrome; Hashimoto's thyroiditis; hay fever; hepatorenal syndrome; hypersensitivity or allergy; inclusion body myositis; infection due to viral, fungal, parasitic or microbial infiltration; inflammatory bowel disease; inflammatory kidney disease; injury due to thermal or chemical exposure or irradiation; irritable bowel syndrome; ischemia; lung inflammation; macular degeneration; morphea; multiple sclerosis; mycosis fungoides; myocardial infarction; necrosis; non-infectious lung injury; osteoarthritis; pancreatitis; pernicious anemia; pneumonia; polymyositis; prostatitis; pseudogout; psoriasis; psoriatic arthritis; Pustulosis palmoplanteris; Pyoderma gangrenum; respiratory allergy; retinal inflammation; retinitis; rheumatoid arthritis; scleroderma; sepsis; serum sickness; Sezary's

syndrome; Sjogren's syndrome; skin allergy; stroke; systemic inflammatory response syndrome (SIRS); systemic lupus erythematosus; systemic sclerosis; T-cell mediated hypersensitivity diseases; transplant rejection; trauma including from a gun wound, knife wound, automobile accident, fall, or combat; tuberculosis; ulcerative colitis; uticaria; uveitis; pericarditis, or vitiligo.

44. The use of claim 33, wherein the cell is a mast cell, a spleen cell, a lung cell, a renal cell, a brain cell, a cardiac cell, a hepatic cell, a cancer cell, a skin cell, an epithelial cell, an endothelial cell, leukocyte, lymphocyte, neutrophil, eosinophil, basophil, monocyte, macrophage, dendritic cell, fibroblast, muscle cell, urethral cell, vascular cell, nerve cell, pancreatic cell, gastric cell, intestinal cell, colon cell, rectal cell, gall bladder cell, stem cell, or thyroid cell.

45. The use of claim 33, wherein the cell is a synoviocyte, a chondrocyte, an osteocyte, an osteoblast, an osteoclast, retinal cell, limbal cell, trabecular meshwork cell, corneal cell, conjunctival cell, an ocular cell, or an ophthalmic cell and the medicament is to be administered to the patient systemically.

46. The use of any of claims 33-44 wherein the PRG4 is to be administered in amount ranging from 0.1 μg/kg – 4000 μg/kg.

47. The use of any of claims 33-45 wherein the PRG4 is to be administered in an amount insufficient to provide boundary lubrication.

48. The use of claim 33, wherein the pro-inflammatory cytokine is selected from the group consisting of IL-1α, IL-1β, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12, IL-12p70, IL-13, IL-14, IL-15, IL-16, IL-17, IL-17α, IL-18, IL-19, IL-20, IL-21, IL-22, IL-23, IL-24, IL-25, IL-26, IL-27, IL-28, IL-29, IL-30, IL-31, IL-32, IL-33, IL-34, IL-35, IL-36, TNF-α, TNF-β (lymphotoxin-α), lymphotoxin-β, CXC31L (Fractalkine), CXCL-8, CCL2, CCL3, CCL4, CCL5, CCL11, CXCL10, IFN-α, IFN-β, IFN-ε, IFN-κ, IFN-ω, IFN-γ, VEGF, MCP-1, MCP-3, EGF, GMCSF, CD40L, CD27L, CD30L, FASL, 4-1BBL, OX40L, TRAIL, FGF-2, GRO, MDC, Rantes, G-CSF, M-CSF, FGF-2, EPO, MCSF, MIP3α, MG-CSF, and GCSF.

49. Use of PRG4 in the manufacture of a medicament for inhibiting binding of a ligand to CD44 present on a surface at a site that is non-cartilaginous, non-osteal, non-osseous, and non-articular, and is not the cornea, urinary bladder, or oral cavity, wherein the surface is exposed to PRG4, wherein PRG4 binds to CD44 and inhibits binding of the ligand.

50. The use of claim 49, wherein the PRG4 is recombinant human PRG4.

51. The use of claim 49 or 50, wherein the PRG4 is not present at the surface in an amount sufficient to provide boundary lubrication.

52. The use of claim 49, wherein PRG4 is to be administered systemically to a human subject in amount ranging from 0.1 μg/kg – 4000 μg/kg.

53. The use of any one of claims 49-52, wherein the surface is a mammalian cell membrane.

54. The use of claim 53, wherein said medicament is to be administered systemically and the cell is a synoviocyte of a subject with rheumatoid arthritis, a mast cell of a subject with interstitial cystitis, a spleen cell of a diabetic, a lung cell of an asthmatic, a renal cell, a brain cell, a cardiac cell, a hepatic cell, a cancer cell, or an endothelial cell of subject with sepsis.

55. The use of claim 53, wherein the cell is a T cell.

56. The use of claim 53, wherein the cell is a lymphocyte, neutrophil, fibroblast, cancer cell, macrophage, dendritic cell, monocyte, eosinophil, or endothelial cell.

57. The use of any of claims 49-56 wherein the surface is in a human subject.

58. The use of claim 57, wherein the medicament is to be systemically administered to the human thereby exposing the surface to PRG4.

59. The use of claim 58, wherein the ligand is hyaluronan (HA), hyaluronan serum-derived hyaluronan-associated protein complex (HA-SHAP), or a matrix metalloproteinase-9.

60. Use of PRG4 in the manufacture of a medicament for reducing or inhibiting pro-inflammatory cytokine levels in blood, wherein the PGR4 is to be systemically administered in an amount sufficient to reduce or inhibit pro-inflammatory cytokine levels.

61. The use of claim 60, wherein the pro-inflammatory cytokine is selected from the group consisting of IL-2, IL-4, IL-6, IL-8, IL-10, VEGF, IFN-γ, TNF-α, IL-1α, IL-1β, MCP-1, EGF, FGF-2, Fractalkine, IFN-α2, GRO, MCP-3, MDC, EPO, IL-13, IL-18, MCSF, MIP-3α, MG-CSF, IL-7, IL-5, G-CSF, Rantes, IL-17α, or IL-12p70.

62. The use of claim 60 or 61, wherein the blood is of a subject with or at risk of sepsis.

63. The use of any one of claims 60-62, wherein said medicament is to be administered in amount of 0.1 μg/kg – 4000 μg/kg to a human patient.

64. Use of PRG4 in the manufacture of a medicament for inhibiting NF-κB translocation in a cell at a site that is non-cartilaginous, non-osteal, non-osseous, and non-articular, and is not the cornea, urinary bladder, or oral cavity, wherein a cell containing NF-κB is to be contacted with PRG4, wherein PRG4 inhibits activation of the NF-κB signaling pathway.

65. The use of claim 64, wherein PRG4 inhibits a TNF-α receptor or an IL-1 receptor on the cell surface.

66. The use of claim 64, wherein the cell is in a human when contacted with PRG4.

67. The use of any one of claims 64-66, wherein PRG4 is provided in an amount less than is required to provide boundary lubrication.

68. The use of claim 67, wherein PRG4 is to be administered in the amount of 0.1 μg/kg – 4000 μg/kg.

69. The use of any one of claims 64-68, wherein the medicament is to be administered to the human thereby contacting PRG4 with the cell.

70. Use of PRG4 in the manufacture of a medicament for treating an inflammatory condition.

71. Use of PRG4 in the manufacture of a medicament for reducing or inhibiting inflammation or treating an inflammatory condition.