[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 associated with traumatic brain injury, wherein said medicament is to be administered to a patient suffering from traumatic brain injury.

[0005b] In 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 associated with traumatic brain injury, wherein said medicament is to be administered to a patient suffering from traumatic brain injury, 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

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

thereby reducing or inhibiting the inflammatory response associated with traumatic brain injury in said patient.

[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.

What is claimed is:

1. Use of PRG4 in the manufacture of a medicament for reducing or inhibiting an inflammatory response associated with traumatic brain injury, wherein said medicament is to be administered to a patient suffering from traumatic brain injury.

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 the patient's brain.

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 site that is non-cartilaginous, non-ostial, non-osseous, and non-articular, and is not the corner, urinary bladder, or tissue of the oral cavity.

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

11. 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.

12. 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.

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

14. Use of PRG4 in the manufacture of a medicament for reducing or inhibiting an inflammatory response associated with traumatic brain injury , wherein said medicament is to be administered to a patient suffering from traumatic brain injury, 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

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

thereby reducing or inhibiting the inflammatory response associated with traumatic brain injury in said patient.

15. The use of claim 14, wherein the patient is a human.

16. The use of claim 14, wherein said medicament is recombinant human lubricin.

17. The use of claim 14, wherein said recombinant human lubricin has the sequence of SEQ ID NO:1 less the signal sequence.

18. The use of claim 14, wherein said medicament is exogenous human lubricin.

19. The use of any one of claims 14-18 wherein said medicament is to be administered systemically to said patient.

20. The use of claim 19, wherein said systemic administration is intramuscular, intravenous, intraperitoneal, oral, rectal, sublingual, buccal, sublabial, nasal, or inhalational.

21. The use of any one of claims 14-16, wherein said medicament is to be administered locally to said patient’s brain.

22. The use of claim 14, wherein the cell is a brain cell.

23. The use of any of claims 14-22, wherein the PRG4 is to be administered in amount ranging from 0.1 μg/kg – 4000 μg/kg.

24. The use of any of claims 14-23, wherein the PRG4 is to be administered in an amount insufficient to provide boundary lubrication.

25. The use of claim 14, 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.