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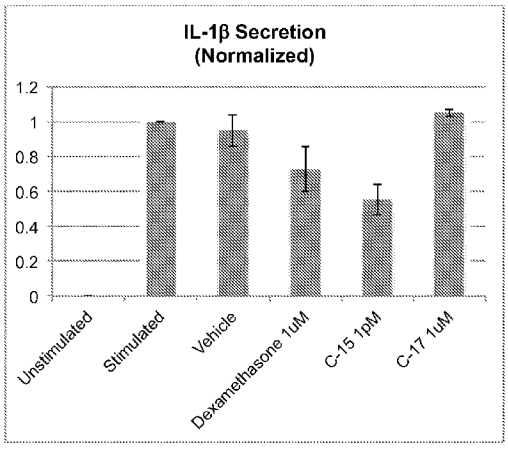
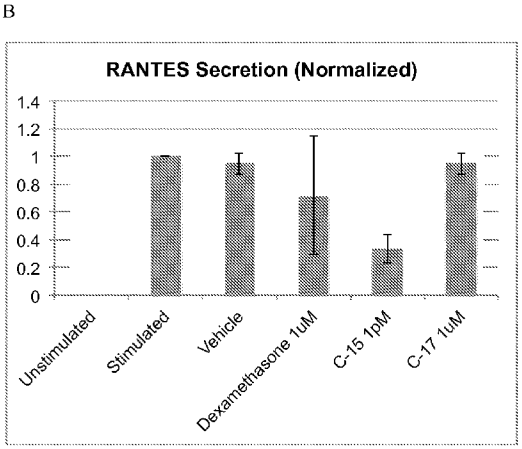
(54) Title: TOPICAL FORMULATIONS OF CHEMERIN C15 PEPTIDES FOR THE TREATMENT OF DERMATOLOGICAL CONDITIONS




(57) Abstract: Described herein, are topical formulations for treating a dermato logical disease, disorder, or condition. Topical formulation disclosed herein include a therapeutically-effective amount of a human chemerin C15 peptide formulated for dermal administration.

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# TOPICAL FORMULATIONS OF CHEMERIN C15 PEPTIDES FOR THE TREATMENT OF DERMATOLOGICAL CONDITIONS

## CROSS-REFERENCE

**[0001]** This application claims priority to U.S. Provisional Patent Application No. 61/546,833, titled "Highly potent antagonists of immune cells in the treatment of skin disorders" and filed 13 October 2011, which is incorporated herein by reference in its entirety.

## SUMMARY OF THE INVENTION

**[0002]** Disclosed herein, in certain embodiments, are chemerin C15 peptides. Further disclosed herein are topical formulations comprising a chemerin C15 peptide and optionally a pharmaceutically acceptable excipient. Additionally disclosed herein are methods of treating inflammatory dermatological disorders in an individual in need thereof comprising administering a chemerin C15 peptide disclosed herein or a topical formulation comprising a chemerin C15 peptide disclosed herein. Further disclosed herein are methods of inhibiting the activity of an inflammatory cytokine or chemokine in an individual in need thereof comprising administering a chemerin C15 peptide disclosed herein or a topical formulation comprising a chemerin C15 peptide disclosed herein. Also disclosed herein, in certain embodiments, are method of inhibiting inhibits nuclear translocation or NFκB-mediated gene transcription of an inflammatory cytokine in an individual in need thereof comprising administering a chemerin C15 peptide disclosed herein or a topical formulation comprising a chemerin C15 peptide disclosed herein. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is a salt of a chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is carboxylated. In some embodiments, the chemerin C15 peptide is amidated. In some embodiments, the chemerin C15 peptide is cyclic. In some embodiments, the chemerin C15 peptide is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9% homologous to a naturally occurring chemerin C15 peptide.

**[0003]** Described herein, in certain embodiments, are topical formulations for treating a dermatological disorder (i.e., an abnormal state of the epidermis, dermis, and/or subcutaneous tissues). Described herein, in certain embodiments, are topical formulations for treating an immune disorder (e.g. an autoimmune disorder (e.g., eczema, psoriasis)); a proliferative disorder (e.g., melanoma); contact with an allergen (e.g., uruishol), and/or an irritant (e.g., alcohol, xylene, turpentine, esters, acetone, ketones); an overproduction of sebum lipids (e.g., acne); a fibroblast disorder (e.g., scarring); or combinations thereof. Described herein, in certain embodiments, are topical formulations for treating psoriasis, atopic dermatitis, contact dermatitis, eczematous

dermatitis, alopecia areata, scleredoma, a bullous disorder, acne, urticaria, rosacea, scar formation, and/or melanoma. In some embodiments, a topical formulation disclosed herein comprises a therapeutically-effective amount of a chemerin C15 peptide. In some embodiments, a topical formulation disclosed herein is administered before or after contact with an allergen and/or irritant. In some embodiments, a topical formulation disclosed herein is administered before or after a physical trauma (e.g., surgery).

**[0004]** Described herein, in certain embodiments, is a topical formulation comprising: (a) a chemerin C15 peptide in an amount effective for the treatment of an inflammatory dermatological disorder; and (b) a pharmaceutically acceptable excipient for topical administration, wherein the formulation minimizes systemic exposure. In some embodiments of the topical formulations provided herein, the amount of chemerin C15 peptide is effective for inhibiting secretion of one or more inflammatory cytokines by an antigen presenting cell. In some embodiments of the topical formulations provided herein, the amount of chemerin C15 peptide is effective for inhibiting NFκB nuclear translocation or NFκB-mediated gene transcription of an inflammatory cytokine in an antigen presenting cell. In some embodiments of the topical formulations provided herein, the inflammatory cytokine is IL-23, TNFα, IL-1β, IL-6 or RANTES. In some embodiments of the topical formulations provided herein, the inflammatory cytokine is IL-23. In some embodiments of the topical formulations provided herein, the inflammatory cytokine is TNFα. In some embodiments of the topical formulations provided herein, the inflammatory cytokine is IL-1β. In some embodiments of the topical formulations provided herein, the inflammatory cytokine is RANTES. In some embodiments of the topical formulations provided herein, the antigen presenting cell is an activated macrophage cell, myeloid dendritic cell, or plasmacytoid dendritic cell. In some embodiments of the topical formulations provided herein, the dermatological disorder is an immune disorder, a proliferative disorder, contact with an allergen and/or an irritant, an overproduction of sebum lipids; a fibroblast disorder, or a combination thereof. In some embodiments of the topical formulations provided herein, the dermatological disorder is psoriasis, atopic dermatitis, contact dermatitis, eczematous dermatitis, alopecia areata, scleredoma, a bullous disorder, acne, urticaria, rosacea, scar formation, or melanoma. In some embodiments of the topical formulations provided herein, wherein the dermatological disorder is psoriasis. In some embodiments of the topical formulations provided herein, wherein the dermatological disorder is dermatitis. In some embodiments of the topical formulations provided herein, the dermatological disorder is atopic dermatitis. In some embodiments of the topical formulations provided herein, the dermatological disorder is contact dermatitis. In some embodiments of the topical formulations provided herein, the chemerin C15 peptide is a human chemerin C15 peptide. In some embodiments of the topical

formulations provided herein, human chemerin C15 peptide comprises the sequence of amino acids AGEDPHSFYFPGQFA. In some embodiments of the topical formulations provided herein, the human chemerin C15 peptide consists essentially of the sequence of amino acids AGEDPHSFYFPGQFA. In some embodiments of the topical formulations provided herein, the topical formulation is formulated as an ointment. In some embodiments of the topical formulations provided herein, the ointment comprises about 1-10 mg of the chemerin C15 peptide per gram of ointment. In some embodiments of the topical formulations provided herein, the ointment comprises petrolatum. In some embodiments of the topical formulations provided herein, the ointment comprises caprylic capric triglyceride. In some embodiments of the topical formulations provided herein, the ointment comprises beeswax. In some embodiments of the topical formulations provided herein, the ointment comprises petrolatum, caprylic triglyceride and beeswax. In some embodiments of the topical formulations provided herein, the ointment comprises about 50% petrolatum, about 45% caprylic triglyceride and about 5% beeswax. In some embodiments of the topical formulations provided herein, the ointment comprises butylated hydroxytoluene, PEG 400, Span 80, white wax, and white petrolatum. In some embodiments of the topical formulations provided herein, the ointment comprises about 0.02% w/w butylated hydroxytoluene, about 15% w/w PEG 400, about 2% w/w Span 80, about 10% w/w white wax, and about 71.98% w/w white petrolatum. In some embodiments of the topical formulations provided herein, the ointment comprises butylated dimethyl isosorbide, butylated hydroxytoluene , Span 80, white wax, and white petrolatum. In some embodiments of the topical formulations provided herein, the ointment comprises about 10% w/w dimethyl isosorbide, about 0.02% w/w butylated hydroxytoluene , about 2% w/w Span 80, about 10% w/w white wax, and about 76.98% w/w white petrolatum. In some embodiments of the topical formulations provided herein, the topical formulation is formulated as a solution. In some embodiments of the topical formulations provided herein, the topical formulation is formulated as a solution that is applied as a spray. In some embodiments of the topical formulations provided herein, the solution comprises about 1-10 mg of the chemerin C15 peptide per ml of solution. In some embodiments of the topical formulations provided herein, the solution comprises isopropyl myristate, alcohol, undecylenic acid and sodium lauryl sulfate. In some embodiments of the topical formulations provided herein, the solution comprises about 45% isopropyl myristate, about 45% alcohol, about 5% undecylenic acid and about 5% sodium lauryl sulfate. In some embodiments of the topical formulations provided herein, the solution comprises DMSO. In some embodiments of the topical formulations provided herein, the solution comprises about 50% DMSO, and about 50% water. In some embodiments of the topical formulations provided herein, the solution comprises dimethyl isosorbide, Transcutol,

hexylene glycol, and propylene glycol. In some embodiments of the topical formulations provided herein, the solution comprises about 15% w/w dimethyl isosorbide, about 25% w/w Transcutol, about 12% w/w hexylene glycol, and about 5% w/w propylene glycol. In some embodiments of the topical formulations provided herein, the topical formulation is formulated as a cream. In some embodiments of the topical formulations provided herein, the cream comprises about 1-10 mg of the chemerin C15 peptide per ml of cream. In some embodiments of the topical formulations provided herein, the topical formulation is formulatedas a lotion. In some embodiments of the topical formulations provided herein, the lotion comprises about 1-10 mg of the chemerin C15 peptide per ml of lotion. In some embodiments of the topical formulations provided herein, the lotion comprises Dimethyl isosorbide, Transcutol, Hexylene glycol, Propylene glycol, Methylparaben, Propylparaben, EDTA, Carbopol Ultrez 10, Penmulen TR-1, and Butylated hydroxytoluene. In some embodiments of the topical formulations provided herein, the lotion comprises Dimethyl isosorbide, Transcutol, Hexylene glycol, Propylene glycol, Methylparaben, Propylparaben, EDTA, Carbopol Ultrez 10, Penmulen TR-1, Isopropyl myristate, Oleyl alcohol, Butylated hydroxytoluene, and White petrolatum. In some embodiments of the topical formulations provided herein, the lotion comprises about 13% w/w Dimethyl isosorbide, about 20% w/w Transcutol, about 10% w/w Hexylene glycol, about 4% w/w Propylene glycol, about 0.015% w/w Methylparaben, about 0.05% w/w Propylparaben, about 0.01% w/w EDTA, about 0.5% w/w Carbopol Ultrez 10, about 0.2% w/w Penmulen TR-1, about 3% w/w Isopropyl myristate, about 5% w/w Oleyl alcohol, about 0.2% w/w Butylated hydroxytoluene, and about 5% w/w White petrolatum. In some embodiments of the topical formulations provided herein, the lotion comprises Dimethyl isosorbide, Transcutol, Hexylene glycol, Propylene glycol, Methylparaben, Propylparaben, EDTA, Carbopol Ultrez 10, Penmulen TR-1, Cetyl alcohol, Light mineral oil, Oleic acid, Butylated hydroxytoluene. In some embodiments of the topical formulations provided herein, the lotion comprises about 13% w/w Dimethyl isosorbide, about 20% w/w Transcutol, about 10% w/w Hexylene glycol, about 4% w/w Propylene glycol, about 0.015% w/w Methylparaben, about 0.05% w/w Propylparaben, about 0.01% w/w EDTA, about 0.3% w/w Carbopol Ultrez 10, about 0.2% w/w Penmulen TR-1, about 2% w/w Cetyl alcohol, about 5.5% w/w Light mineral oil, about 5% w/w Oleic acid, and about 0.2% w/w Butylated hydroxytoluene. In some embodiments of the topical formulations provided herein, the topical formulation comprises a skin penetration agent. In some embodiments of the topical formulations provided herein, the skin penetration agent is DMSO. In some embodiments of the topical formulations provided herein, the topical formulation comprises a gelling agent. In some embodiments of the topical formulations provided herein, the topical formulation comprises an emollient. In some embodiments of the topical formulations

provided herein, the topical formulation comprises an anti-oxidant. In some embodiments of the topical formulations provided herein, the topical formulation comprises a skin protecting agent. In some embodiments of the topical formulations provided herein, the topical formulation comprises an irritation-mitigating agent. In some embodiments of the topical formulations provided herein, the topical formulation comprises a dry-feel modifier. In some embodiments of the topical formulations provided herein, the topical formulation comprises a surfactant. In some embodiments of the topical formulations provided herein, the topical formulation comprises a preservative. In some embodiments of the topical formulations provided herein, the topical formulation comprises a chelating agent. In some embodiments of the topical formulations provided herein, wherein the topical formulation comprises a lubricant. In some embodiments of the topical formulations provided herein, the topical formulation comprises a thickening agent. In some embodiments of the topical formulations provided herein, the topical formulation comprises at least one additional therapeutic agent. In some embodiments of the topical formulations provided herein, the additional therapeutic agent is an antioxidant, anti-inflammatory agent, antiangiogenic agent, anti-apoptotic agent, vascular endothelial growth factor inhibitor, antimicrobial or antiviral agent. In some embodiments of the topical formulations provided herein, the additional therapeutic agent is a corticosteroid.

**[0005]** Described herein, in certain embodiments, is a topical formulation of a chemerin C15 peptide formulated as an aerosol, liquid, ointment, cream, lotion, solution, spray, suspension, emulsion, paste, gel, powder, salve, plaster, paint, foam, stick, slow release nanoparticle, slow release microparticle, bioadhesive, patch, bandage or wound dressing. In some embodiments of the topical formulations provided herein, the chemerin C15 peptide is a human chemerin C15 peptide. In some embodiments of the topical formulations provided herein, human chemerin C15 peptide comprises the sequence of amino acids AGEDPHSFYFPGQFA. In some embodiments of the topical formulations provided herein, the human chemerin C15 peptide consists essentially of the sequence of amino acids AGEDPHSFYFPGQFA. In some embodiments of the topical formulations provided herein, the topical formulation is formulated as an ointment. In some embodiments of the topical formulations provided herein, the ointment comprises about 1-10 mg of the chemerin C15 peptide per gram of ointment. In some embodiments of the topical formulations provided herein, the ointment comprises petrolatum. In some embodiments of the topical formulations provided herein, the ointment comprises caprylic capric triglyceride. In some embodiments of the topical formulations provided herein, the ointment comprises beeswax. In some embodiments of the topical formulations provided herein, the ointment comprises petrolatum, caprylic triglyceride and beeswax. In some embodiments of the topical formulations provided herein, the ointment

comprises about 50% petrolatum, about 45% caprylic triglyceride and about 5% beeswax. In some embodiments of the topical formulations provided herein, the ointment comprises butylated hydroxytoluene, PEG 400, Span 80, white wax, and white petrolatum. In some embodiments of the topical formulations provided herein, the ointment comprises about 0.02% w/w butylated hydroxytoluene, about 15% w/w PEG 400, about 2% w/w Span 80, about 10% w/w white wax, and about 71.98% w/w white petrolatum. In some embodiments of the topical formulations provided herein, the ointment comprises butylated dimethyl isosorbide, butylated hydroxytoluene , Span 80, white wax, and white petrolatum. In some embodiments of the topical formulations provided herein, the ointment comprises about 10% w/w dimethyl isosorbide, about 0.02% w/w butylated hydroxytoluene , about 2% w/w Span 80, about 10% w/w white wax, and about 76.98% w/w white petrolatum. In some embodiments of the topical formulations provided herein, the topical formulation is formulated as a solution. In some embodiments of the topical formulations provided herein, the topical formulation is formulated as a solution that is applied as a spray. In some embodiments of the topical formulations provided herein, the solution comprises about 1-10 mg of the chemerin C15 peptide per ml of solution. In some embodiments of the topical formulations provided herein, the solution comprises isopropyl myristate, alcohol, undecylenic acid and sodium lauryl sulfate. In some embodiments of the topical formulations provided herein, the solution comprises about 45% isopropyl myristate, about 45% alcohol, about 5% undecylenic acid and about 5% sodium lauryl sulfate. In some embodiments of the topical formulations provided herein, the solution comprises DMSO. In some embodiments of the topical formulations provided herein, the solution comprises about 50% DMSO, and about 50% water. In some embodiments of the topical formulations provided herein, the solution comprises dimethyl isosorbide, Transcutol, hexylene glycol, and propylene glycol. In some embodiments of the topical formulations provided herein, the solution comprises about 15% w/w dimethyl isosorbide, about 25% w/w Transcutol, about 12% w/w hexylene glycol, and about 5% w/w propylene glycol. In some embodiments of the topical formulations provided herein, the topical formulation is formulated as a cream. In some embodiments of the topical formulations provided herein, the cream comprises about 1-10 mg of the chemerin C15 peptide per ml of cream. In some embodiments of the topical formulations provided herein, the topical formulation is formulatedas a lotion. In some embodiments of the topical formulations provided herein, the lotion comprises about 1-10 mg of the chemerin C15 peptide per ml of lotion. In some embodiments of the topical formulations provided herein, the lotion comprises Dimethyl isosorbide, Transcutol, Hexylene glycol, Propylene glycol, Methylparaben, Propylparaben, EDTA, Carbopol Ultrez 10, Penmulen TR-1, and Butylated hydroxytoluene. In some embodiments of the topical formulations provided herein, the lotion

comprises Dimethyl isosorbide, Transcutol, Hexylene glycol, Propylene glycol, Methylparaben, Propylparaben, EDTA, Carbopol Ultrez 10, Penmulen TR-1, Isopropyl myristate, Oleyl alcohol, Butylated hydroxytoluene, and White petrolatum. In some embodiments of the topical formulations provided herein, the lotion comprises about 13% w/w Dimethyl isosorbide, about 20% w/w Transcutol, about 10% w/w Hexylene glycol, about 4% w/w Propylene glycol, about 0.015% w/w Methylparaben, about 0.05% w/w Propylparaben, about 0.01% w/w EDTA, about 0.5% w/w Carbopol Ultrez 10, about 0.2% w/w Penmulen TR-1, about 3% w/w Isopropyl myristate, about 5% w/w Oleyl alcohol, about 0.2% w/w Butylated hydroxytoluene, and about 5% w/w White petrolatum. In some embodiments of the topical formulations provided herein, the lotion comprises Dimethyl isosorbide, Transcutol, Hexylene glycol, Propylene glycol, Methylparaben, Propylparaben, EDTA, Carbopol Ultrez 10, Penmulen TR-1, Cetyl alcohol, Light mineral oil, Oleic acid, Butylated hydroxytoluene. In some embodiments of the topical formulations provided herein, the lotion comprises about 13% w/w Dimethyl isosorbide, about 20% w/w Transcutol, about 10% w/w Hexylene glycol, about 4% w/w Propylene glycol, about 0.015% w/w Methylparaben, about 0.05% w/w Propylparaben, about 0.01% w/w EDTA, about 0.3% w/w Carbopol Ultrez 10, about 0.2% w/w Penmulen TR-1, about 2% w/w Cetyl alcohol, about 5.5% w/w Light mineral oil, about 5% w/w Oleic acid, and about 0.2% w/w Butylated hydroxytoluene. In some embodiments of the topical formulations provided herein, the topical formulation comprises a skin penetration agent. In some embodiments of the topical formulations provided herein, the skin penetration agent is DMSO. In some embodiments of the topical formulations provided herein, the topical formulation comprises a gelling agent. In some embodiments of the topical formulations provided herein, the topical formulation comprises an emollient. In some embodiments of the topical formulations provided herein, the topical formulation comprises an anti-oxidant. In some embodiments of the topical formulations provided herein, the topical formulation comprises a skin protecting agent. In some embodiments of the topical formulations provided herein, the topical formulation comprises an irritation-mitigating agent. In some embodiments of the topical formulations provided herein, the topical formulation comprises a dry-feel modifier. In some embodiments of the topical formulations provided herein, the topical formulation comprises a surfactant. In some embodiments of the topical formulations provided herein, the topical formulation comprises a preservative. In some embodiments of the topical formulations provided herein, the topical formulation comprises a chelating agent. In some embodiments of the topical formulations provided herein, wherein the topical formulation comprises a lubricant. In some embodiments of the topical formulations provided herein, the topical formulation comprises a thickening agent. In some embodiments of the topical formulations provided herein, the topical formulation comprises at least one additional

therapeutic agent. In some embodiments of the topical formulations provided herein, the additional therapeutic agent is an antioxidant, anti-inflammatory agent, antiangiogenic agent, anti-apoptotic agent, vascular endothelial growth factor inhibitor, antimicrobial or antiviral agent. In some embodiments of the topical formulations provided herein, the additional therapeutic agent is a corticosteroid.

**[0006]** Described herein, in certain embodiments, is a method of treating of an inflammatory dermatological disorder in an individual in need thereof, comprising administering to the individual a therapeutically-effective amount of a topical formulation comprising a human chemerin C15 peptide, wherein the formulation is formulated to minimize systemic exposure to the individual. In some embodiments of the methods provided herein, administration inhibits the secretion one or more inflammatory cytokines by an antigen presenting cell. In some embodiments of the methods provided herein, administration inhibits NFκB nuclear translocation or NFκB-mediated gene transcription of an inflammatory cytokine in an antigen presenting cell. In some embodiments of the methods provided herein, the inflammatory cytokine is IL-23, TNFα, IL-1β, IL-6 or RANTES. In some embodiments of the methods provided herein, the inflammatory cytokine is IL-23. In some embodiments of the methods provided herein, the inflammatory cytokine is TNFα. In some embodiments of the methods provided herein, the inflammatory cytokine is IL-1β. In some embodiments of the methods provided herein, the inflammatory cytokine is RANTES. In some embodiments of the methods provided herein, the antigen presenting cell is an activated macrophage cell, myeloid dendritic cell, a plasmacytoid dendritic cell. In some embodiments of the methods provided herein, the chemerin C15 peptide comprises the sequence of amino acids AGEDPHSFYFPGQFA. In some embodiments of the methods provided herein, the chemerin C15 peptide consists essentially of the sequence of amino acids AGEDPHSFYFPGQFA. In some embodiments of the methods provided herein, the dermatological disorder is an immune disorder, a proliferative disorder, contact with an allergen and/or an irritant, an overproduction of sebum lipids; a fibroblast disorder, or a combination thereof. In some embodiments of the methods provided herein, the dermatological disorder is psoriasis, atopic dermatitis, contact dermatitis, eczematous dermatitis, alopecia areata, scleredoma, a bullous disorder, acne, urticaria, rosacea, scar formation, or melanoma. In some embodiments of the methods provided herein, the dermatological disorder is psoriasis. In some embodiments of the methods provided herein, the dermatological disorder is dermatitis. In some embodiments of the methods provided herein, the dermatological disorder is atopic dermatitis. In some embodiments of the methods provided herein, the dermatological disorder is contact dermatitis. In some embodiments of the methods provided herein, the topical formulation is in the form of an aerosol, liquid, ointment, cream, lotion, solution,

suspension, emulsion, paste, gel, powder, salve, plaster, paint, foam, stick, slow release nanoparticle, slow release microparticle, bioadhesive, patch, bandage or wound dressing. In some embodiments of the methods provided herein, the formulation is formulated as an ointment. In some embodiments of the methods provided herein, the ointment comprises about 1-10 mg of the chemerin C15 peptide per gram of ointment. In some embodiments of the methods provided herein, the ointment comprises petrolatum. n some embodiments of the methods provided herein, the ointment comprises caprylic capric triglyceride. In some embodiments of the methods provided herein, the ointment comprises beeswax. In some embodiments of the methods provided herein, the ointment comprises petrolatum, caprylic triglyceride and beeswax. In some embodiments of the methods provided herein, the ointment comprises about 50% petrolatum, about 45% caprylic triglyceride and about 5% beeswax. In some embodiments of the methods provided herein, the ointment comprises butylated hydroxytoluene, PEG 400, Span 80, white wax, and white petrolatum. In some embodiments of the methods provided herein, the ointment comprises about 0.02% w/w butylated hydroxytoluene, about 15% w/w PEG 400, about 2% w/w Span 80, about 10% w/w white wax, and about 71.98% w/w white petrolatum. In some embodiments of the methods provided herein, the ointment comprises butylated dimethyl isosorbide, butylated hydroxytoluene , Span 80, white wax, and white petrolatum. In some embodiments of the methods provided herein, the ointment comprises about 10% w/w dimethyl isosorbide, about 0.02% w/w butylated hydroxytoluene , about 2% w/w Span 80, about 10% w/w white wax, and about 76.98% w/w white petrolatum. In some embodiments of the methods provided herein, the formulation is formulated as a solution. In some embodiments of the methods provided herein, the formulation is formulated as a solution that is applied as a spray. In some embodiments of the methods provided herein, the solution comprises about 1-10 mg of the chemerin C15 peptide per ml of solution. In some embodiments of the methods provided herein, the solution comprises isopropyl myristate, alcohol, undecylenic acid and sodium lauryl sulfate. In some embodiments of the methods provided herein, the solution comprises about 45% isopropyl myristate, about 45% alcohol, about 5% undecylenic acid and about 5% sodium lauryl sulfate. In some embodiments of the methods provided herein, the solution comprises DMSO. In some embodiments of the methods provided herein, the solution comprises about 50% DMSO, and about 50% water. In some embodiments of the methods provided herein, the solution comprises dimethyl isosorbide, Transcutol, hexylene glycol, and propylene glycol. In some embodiments of the methods provided herein, solution comprises about 15% w/w dimethyl isosorbide, about 25% w/w Transcutol, about 12% w/w hexylene glycol, and about 5% w/w propylene glycol. In some embodiments of the methods provided herein, the formulation is formulated as a cream. In some embodiments of the methods

provided herein, the cream comprises about 1-10 mg of the chemerin C15 peptide per ml of cream. In some embodiments of the methods provided herein, the formulation is formulated as a lotion. In some embodiments of the methods provided herein, the lotion comprises about 1-10 mg of the chemerin C15 peptide per ml of lotion. In some embodiments of the methods provided herein, the lotion comprises Dimethyl isosorbide, Transcutol, Hexylene glycol, Propylene glycol, Methylparaben, Propylparaben, EDTA, Carbopol Ultrez 10, Penmulen TR-1, and Butylated hydroxytoluene. In some embodiments of the methods provided herein, the lotion comprises Dimethyl isosorbide, Transcutol, Hexylene glycol, Propylene glycol, Methylparaben, Propylparaben, EDTA, Carbopol Ultrez 10, Penmulen TR-1, Isopropyl myristate, Oleyl alcohol, Butylated hydroxytoluene, and White petrolatum. In some embodiments of the methods provided herein, the lotion comprises about 13% w/w Dimethyl isosorbide, about 20% w/w Transcutol, about 10% w/w Hexylene glycol, about 4% w/w Propylene glycol, about 0.015% w/w Methylparaben, about 0.05% w/w Propylparaben, about 0.01% w/w EDTA, about 0.5% w/w Carbopol Ultrez 10, about 0.2% w/w Penmulen TR-1, about 3% w/w Isopropyl myristate, about 5% w/w Oleyl alcohol, about 0.2% w/w Butylated hydroxytoluene, and about 5% w/w White petrolatum. In some embodiments of the methods provided herein, the lotion comprises Dimethyl isosorbide, Transcutol, Hexylene glycol, Propylene glycol, Methylparaben, Propylparaben, EDTA, Carbopol Ultrez 10, Penmulen TR-1, Cetyl alcohol, Light mineral oil, Oleic acid, Butylated hydroxytoluene. In some embodiments of the methods provided herein, the lotion comprises about 13% w/w Dimethyl isosorbide, about 20% w/w Transcutol, about 10% w/w Hexylene glycol, about 4% w/w Propylene glycol, about 0.015% w/w Methylparaben, about 0.05% w/w Propylparaben, about 0.01% w/w EDTA, about 0.3% w/w Carbopol Ultrez 10, about 0.2% w/w Penmulen TR-1, about 2% w/w Cetyl alcohol, about 5.5% w/w Light mineral oil, about 5% w/w Oleic acid, and about 0.2% w/w Butylated hydroxytoluene. In some embodiments of the methods provided herein, the topical formulation comprises a skin penetration agent. In some embodiments of the methods provided herein, the skin penetration agent is DMSO. In some embodiments of the methods provided herein, the topical formulation comprises a gelling agent. In some embodiments of the methods provided herein, the topical formulation comprises an emollient. In some embodiments of the methods provided herein, the topical formulation comprises an anti-oxidant. In some embodiments of the methods provided herein, the topical formulation comprises a skin protecting agent. In some embodiments of the methods provided herein, the topical formulation comprises an irritation-mitigating agent. In some embodiments of the methods provided herein, the topical formulation comprises a dry-feel modifier. In some embodiments of the methods provided herein, the topical formulation comprises a surfactant. In some embodiments of the methods provided

herein, the topical formulation comprises a preservative. In some embodiments of the methods provided herein, the topical formulation comprises a chelating agent. In some embodiments of the methods provided herein, the topical formulation comprises a lubricant. In some embodiments of the methods provided herein, the topical formulation comprises a thickening agent. In some embodiments of the methods provided herein, the topical formulation comprises at least one additional therapeutic agent. In some embodiments of the methods provided herein, the additional therapeutic agent is an antioxidant, anti-inflammatory agent, antiangiogenic agent, anti-apoptotic agent, vascular endothelial growth factor inhibitor, antimicrobial or antiviral agent. In some embodiments of the methods provided herein, the additional therapeutic agent is a corticosteroid. In some embodiments of the methods provided herein, the topical formulation is topically applied to the skin, eye, mouth, nose, vaginal mucosa or anal mucosa. In some embodiments of the methods provided herein, administration of the topical formulation results in a local tissue concentration of the chemerin C15 peptide of greater than about 0.1 pM-100 nM, greater than about 1 pM-10 nM, greater than about 1pM-1 nM, greater than about 1-100 pM, or greater than about 1-10 pM at about 1-12 hours following administration to the individual. In some embodiments of the methods provided herein, administration of the topical formulation results in a systemic concentration of the chemerin C15 peptide of less than about 100 pM, less than about 10 pM, less than about 1 pM, less than about 0.1 pM , or less than about 0.01 pM.

**[0007]** Described herein, in certain embodiments, is a use of a human chemerin C15 peptide for the manufacture of a topical formulation comprising a therapeutically-effective amount of the peptide for treating an inflammatory dermatological disorder, wherein the formulation is formulated to minimize systemic exposure. In some embodiments of the uses provided herein, the amount of the human chemerin C15 peptide is effective for inhibiting the secretion one or more inflammatory cytokines by an antigen presenting cell. In some embodiments of the uses provided herein, the amount of the human chemerin C15 peptide is effective for inhibiting the NFκB nuclear translocation or NFκB-mediated gene transcription of an inflammatory cytokine in an antigen presenting cell. In some embodiments of the uses provided herein, the inflammatory cytokine is IL-23, TNFα, IL-1β, IL-6 or RANTES. In some embodiments of the uses provided herein, the inflammatory cytokine is IL-23. In some embodiments of the uses provided herein, the inflammatory cytokine is TNFα. In some embodiments of the uses provided herein, the inflammatory cytokine is IL-1β. In some embodiments of the uses provided herein, the inflammatory cytokine is RANTES. In some embodiments of the uses provided herein, the antigen presenting cell is an activated macrophage cell, myeloid dendritic cell, a plasmacytoid dendritic cell. In some embodiments of the uses provided herein, the chemerin C15 peptide comprises the

sequence of amino acids AGEDPHSFYFPGQFA. In some embodiments of the uses provided herein, the wherein the chemerin C15 peptide consists essentially of the sequence of amino acids AGEDPHSFYFPGQFA. In some embodiments of the uses provided herein, the dermatological disorder is an immune disorder, a proliferative disorder, contact with an allergen and/or an irritant, an overproduction of sebum lipids; a fibroblast disorder, or a combination thereof. In some embodiments of the uses provided herein, the dermatological disorder is psoriasis, atopic dermatitis, contact dermatitis, eczematous dermatitis, alopecia areata, scleredoma, a bullous disorder, acne, urticaria, rosacea, scar formation, or melanoma. In some embodiments of the uses provided herein, the dermatological disorder is psoriasis. In some embodiments of the uses provided herein, the dermatological disorder is dermatitis. In some embodiments of the uses provided herein, the dermatological disorder is atopic dermatitis. In some embodiments of the uses provided herein, the dermatological disorder is contact dermatitis. In some embodiments of the uses provided herein, the topical formulation is in the form of an aerosol, liquid, ointment, cream, lotion, solution, suspension, emulsion, paste, gel, powder, salve, plaster, paint, foam, stick, slow release nanoparticle, slow release microparticle, bioadhesive, patch, bandage or wound dressing. In some embodiments of the uses provided herein, the topical formulation is formulated as an ointment. In some embodiments of the uses provided herein, the ointment comprises about 1-10 mg of the chemerin C15 peptide per gram of ointment. In some embodiments of the uses provided herein, the ointment comprises petrolatum. In some embodiments of the uses provided herein, the ointment comprises caprylic capric triglyceride. In some embodiments of the uses provided herein, the ointment comprises beeswax. In some embodiments of the uses provided herein, the ointment comprises petrolatum, caprylic triglyceride and beeswax. In some embodiments of the uses provided herein, the ointment comprises about 50% petrolatum, about 45% caprylic triglyceride and about 5% beeswax. In some embodiments of the uses provided herein, the ointment comprises butylated hydroxytoluene, PEG 400, Span 80, white wax, and white petrolatum. In some embodiments of the uses provided herein, the ointment comprises about 0.02% w/w butylated hydroxytoluene, about 15% w/w PEG 400, about 2% w/w Span 80, about 10% w/w white wax, and about 71.98% w/w white petrolatum. In some embodiments of the uses provided herein, the ointment comprises butylated dimethyl isosorbide, butylated hydroxytoluene , Span 80, white wax, and white petrolatum. In some embodiments of the uses provided herein, the ointment comprises about 10% w/w dimethyl isosorbide, about 0.02% w/w butylated hydroxytoluene , about 2% w/w Span 80, about 10% w/w white wax, and about 76.98% w/w white petrolatum. In some embodiments of the uses provided herein, the topical formulation is formulated as a solution. In some embodiments of the uses provided herein, the topical formulation is formulated as a solution

that is applied as a spray. In some embodiments of the uses provided herein, the solution comprises about 1-10 mg of the chemerin C15 peptide per ml of solution. In some embodiments of the uses provided herein, the solution comprises isopropyl myristate, alcohol, undecylenic acid and sodium lauryl sulfate. In some embodiments of the uses provided herein, the solution comprises about 45% isopropyl myristate, about 45% alcohol, about 5% undecylenic acid and about 5% sodium lauryl sulfate. In some embodiments of the uses provided herein, the solution comprises DMSO. In some embodiments of the uses provided herein, the solution comprises about 50% DMSO, and about 50% water. In some embodiments of the uses provided herein, the solution comprises dimethyl isosorbide, Transcutol, hexylene glycol, and propylene glycol. In some embodiments of the uses provided herein, the solution comprises about 15% w/w dimethyl isosorbide, about 25% w/w Transcutol, about 12% w/w hexylene glycol, and about 5% w/w propylene glycol. In some embodiments of the uses provided herein, the topical formulation is formulated as a cream. In some embodiments of the uses provided herein, the cream comprises about 1-10 mg of the chemerin C15 peptide per ml of cream. In some embodiments of the uses provided herein, the topical formulation is formulated as a lotion. In some embodiments of the uses provided herein, the lotion comprises about 1-10 mg of the chemerin C15 peptide per ml of lotion. In some embodiments of the uses provided herein, the lotion comprises Dimethyl isosorbide, Transcutol, Hexylene glycol, Propylene glycol, Methylparaben, Propylparaben, EDTA, Carbopol Ultrez 10, Penmulen TR-1, and Butylated hydroxytoluene. In some embodiments of the uses provided herein, the lotion comprises Dimethyl isosorbide, Transcutol, Hexylene glycol, Propylene glycol, Methylparaben, Propylparaben, EDTA, Carbopol Ultrez 10, Penmulen TR-1, Isopropyl myristate, Oleyl alcohol, Butylated hydroxytoluene, and White petrolatum. In some embodiments of the uses provided herein, the lotion comprises about 13% w/w Dimethyl isosorbide, about 20% w/w Transcutol, about 10% w/w Hexylene glycol, about 4% w/w Propylene glycol, about 0.015% w/w Methylparaben, about 0.05% w/w Propylparaben, about 0.01% w/w EDTA, about 0.5% w/w Carbopol Ultrez 10, about 0.2% w/w Penmulen TR-1, about 3% w/w Isopropyl myristate, about 5% w/w Oleyl alcohol, about 0.2% w/w Butylated hydroxytoluene, and about 5% w/w White petrolatum. In some embodiments of the uses provided herein, the lotion comprises Dimethyl isosorbide, Transcutol, Hexylene glycol, Propylene glycol, Methylparaben, Propylparaben, EDTA, Carbopol Ultrez 10, Penmulen TR-1, Cetyl alcohol, Light mineral oil, Oleic acid, Butylated hydroxytoluene. In some embodiments of the uses provided herein, the lotion comprises about 13% w/w Dimethyl isosorbide, about 20% w/w Transcutol, about 10% w/w Hexylene glycol, about 4% w/w Propylene glycol, about 0.015% w/w Methylparaben, about 0.05% w/w Propylparaben, about 0.01% w/w EDTA, about 0.3% w/w Carbopol Ultrez 10, about 0.2% w/w Penmulen TR-1, about 2% w/w Cetyl alcohol, about 5.5%

w/w Light mineral oil, about 5% w/w Oleic acid, and about 0.2% w/w Butylated hydroxytoluene. In some embodiments of the uses provided herein, the topical formulation comprises a skin penetration agent. In some embodiments of the uses provided herein, the skin penetration agent is DMSO. In some embodiments of the uses provided herein, the topical formulation comprises a gelling agent. In some embodiments of the uses provided herein, the topical formulation comprises an emollient. In some embodiments of the uses provided herein, the topical formulation comprises an anti-oxidant. In some embodiments of the uses provided herein, the topical formulation comprises a skin protecting agent. In some embodiments of the uses provided herein, the topical formulation comprises an irritation-mitigating agent. In some embodiments of the uses provided herein, the topical formulation comprises a dry-feel modifier. In some embodiments of the uses provided herein, the topical formulation comprises a surfactant. In some embodiments of the uses provided herein, the topical formulation comprises a preservative. In some embodiments of the uses provided herein, the topical formulation comprises a chelating agent. In some embodiments of the uses provided herein, the topical formulation comprises a lubricant. In some embodiments of the uses provided herein, the topical formulation comprises a thickening agent. In some embodiments of the uses provided herein, the topical formulation comprises at least one additional therapeutic agent. In some embodiments of the uses provided herein, the additional therapeutic agent is an antioxidant, anti-inflammatory agent, antiangiogenic agent, anti-apoptotic agent, vascular endothelial growth factor inhibitor, antimicrobial or antiviral agent. In some embodiments of the uses provided herein, the additional therapeutic agent is a corticosteroid. In some embodiments of the uses provided herein, the topical formulation is formulated for application to the skin, eye, mouth, nose, vaginal mucosa or anal mucosa.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0008]** The novel features of the invention are set forth with particularity in the appended claims. A better understanding of the features and advantages of the present invention will be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

**[0009]** FIGURE 1 exemplifies the effect of human chemerin C15 and C17 peptides on cytokine production in IFNγ/LPS stimulated human macrophages. A) IL-1β at 15 hours; B) RANTES at 15 hours; C) RANTES (Difference from 6 to 15 hours); D) IL-12p40 at 15 hours; and E) IL-10 at 15 hours.

**[0010]** FIGURE 2 exemplifies agonist and antagonist dose response curves for ChemR23 and GPR1 receptors in the presence of chemerin, human chemerin C15, 16, or C17 peptides, or mouse chemerin C15 peptide.

**[0011]** FIGURE 3 exemplifies loss of human chemerin C15 peptide anti-inflammatory activity by modification of the FYFP motif.

## DETAILED DESCRIPTION OF THE INVENTION

**[0012]** Disclosed herein, in certain embodiments, are chemerin C15 peptides. Further disclosed herein are topical formulations comprising a chemerin C15 peptide and optionally a pharmaceutically acceptable excipient. Additionally disclosed herein are methods of treating inflammatory dermatological disorders in an individual in need thereof comprising administering a chemerin C15 peptide disclosed herein or a topical formulation comprising a chemerin C15 peptide disclosed herein. Further disclosed herein are methods of inhibiting the activity of an inflammatory cytokine or chemokine in an individual in need thereof comprising administering a chemerin C15 peptide disclosed herein or a topical formulation comprising a chemerin C15 peptide disclosed herein. Also disclosed herein, in certain embodiments, are method of inhibiting inhibits nuclear translocation or NFκB-mediated gene transcription of an inflammatory cytokine in an individual in need thereof comprising administering a chemerin C15 peptide disclosed herein or a topical formulation comprising a chemerin C15 peptide disclosed herein. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is a salt of a chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is carboxylated. In some embodiments, the chemerin C15 peptide is amidated. In some embodiments, the chemerin C15 peptide is cyclic. In some embodiments, the chemerin C15 peptide is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9% homologous to a naturally occurring chemerin C15 peptide.

### Certain Terminology

**[0013]** As used herein, “chemerin C15 peptide” refers to a peptide that comprises the sequence of amino acids AGEDPHSFYFPGQFA of a human chemerin polypeptide, a species variant of the human chemerin C15 peptide, such as a mouse or rat chemerin C15 peptide, or other variants of the human chemerin C15 peptide as described herein.

**[0014]** As used herein, "peptide" is intended to have its art recognized meaning, i.e., two or more amino acids linked through amide bonds, for example, repeating units of formula --C(=O)CH(side chain)NH-- that, in the simplest form, terminate in either an amine or a carboxylic acid. As one of ordinary skill in the art will recognize, numerous modifications of the peptidic backbone are

possible without changing the overall nature of the molecule, including modification of the terminal groups such as those described herein.

**[0015]** As used herein, "amino acid" is intended to have its art-recognized meaning, i.e., a carboxylic acid of general formula HOC(=O)CH(side chain)($NH_2$). Side chains of amino acids are well known in the art and include naturally occurring and non-naturally occurring moieties. Non-naturally occurring (i.e., unnatural) amino acid side chains are moieties that are used in place of naturally occurring amino acid side chains in, for example, amino acid analogs.

**[0016]** The terms “individual,” “patient,” or “subject” are used interchangeably. As used herein, they mean any mammal. In one aspect, the mammal is a human. None of the terms require that the individual/patient/subject is under the care of a medical professional (e.g., a doctor, nurse, physician’s assistant, registered nurse, nurse practitioner, hospice worker, orderly, etc.).

**[0017]** The terms “treat,” “treating” or “treatment,” and other grammatical equivalents as used herein, include alleviating, abating, inhibiting, reducing, ameliorating, delaying the onset of, arresting the progression of, and/or inducing the regression of a disorder and/or the symptoms of a disorder. The terms also include prophylactic treatment of a disorder. The terms further include achieving any therapeutic benefit. Therapeutic benefit means the eradication or amelioration of the underlying disorder being treated, and/or the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed and/or perceived in the individual.

**[0018]** The terms “prevent,” “preventing” or “prevention,” and other grammatical equivalents as used herein include inhibiting (arresting or stopping) the development of a disorder, and/or inhibiting (arresting or stopping) the further progression of a disorder. These terms are intended to include prophylaxis. For prophylactic benefit, the compositions are administered to an individual at risk of developing a particular disorder, or to an individual reporting one or more of the physiological symptoms of a disease, or to an individual at risk of reoccurrence of the disease.

**[0019]** The terms “effective amount” or “therapeutically effective amount” as used herein, refer to an amount of an agent (e.g. a chemerin C15 peptide) being administered which achieves a desired result, e.g., to relieve to some extent one or more symptoms of a disease, disorder or condition being treated. In certain instances, the result is a reduction and/or alleviation of at least one sign, symptom, or cause of a disease, or any other desired alteration of a biological system. In certain instances, an “effective amount” for therapeutic uses is the amount of the composition comprising an agent as set forth herein required to provide a clinically significant decrease in at least one symptom of a disease, disorder or condition. An appropriate “effective” amount in any individual case is determined using any suitable technique, such as a dose escalation study. For

example, as used herein an appropriate effective amount of a topical agent (e.g. a chemerin C15 peptide) applied locally to a tissue is an amount sufficient to achieve a local therapeutic concentration which has been shown in vitro to inhibit a cellular process associated with inflammation, such as, for example, inhibition of NFκB and/or inhibition of the production and/or secretion of one or more inflammatory cytokines.

**[0020]** The terms "administer," "administering," "administration," and the like, as used herein, refer to the methods that are used to enable delivery of chemerin C15 peptides to the desired site of biological action (e.g., the site of a dermal disorder). These methods include any suitable method for dermatological (i.e., topical) administration.

**[0021]** As used herein, the terms "formulation" and "composition" are used interchangeably. They mean a product comprising a chemerin C15 peptide disclosed herein and a pharmaceutically-acceptable excipient.

**[0022]** As used herein, "topical" administration refers administration to the skin, eye or a mucosal surface, such as an oral, nasal, vaginal or anal surface, of the subject.

**[0023]** "Localized treatment" as used herein refers to treatment of an immune or inflammatory disorder wherein the drug is delivered locally and is not delivered via systemic delivery. In some embodiments, this includes many different local areas or a few different local areas within, for example, treatment of skin, wherein the drug is applied to many different locations or a few different locations on the skin, and wherein drug is delivered to tissues within and adjacent to the skin by absorption through the skin. In some embodiments, drug is delivered to a mucosal surface, such as the mouth, nose, anus or vagina, and absorbed through the epithelial surfaces of the tissue within and adjacent to the mucosa.

**[0024]** "Local tissue concentration" as used herein, refers to the concentration of the chemerin C15 peptide within the tissue area to which the chemerin C15 peptides has been delivered and absorbed.

**[0025]** The term "pharmaceutically acceptable" as used herein, refers to a material that does not abrogate the biological activity or properties of the agents described herein, and is relatively nontoxic (i.e., the toxicity of the material does not significantly outweigh the benefit of the material).

**Overview of Chemerin C-terminal Peptides and Inflammatory Skin Disorders**

**[0026]** Disclosed herein, in certain embodiments, are chemerin C15 peptides. Further disclosed herein are topical formulations comprising a chemerin C15 peptide and optionally a pharmaceutically acceptable excipient. Additionally disclosed herein are methods of treating inflammatory dermatological disorders in an individual in need thereof comprising administering a

chemerin C15 peptide disclosed herein or a topical formulation comprising a chemerin C15 peptide disclosed herein. Further disclosed herein are methods of inhibiting the activity of an inflammatory cytokine or chemokine in an individual in need thereof comprising administering a chemerin C15 peptide disclosed herein or a topical formulation comprising a chemerin C15 peptide disclosed herein. Also disclosed herein, in certain embodiments, are method of inhibiting inhibits nuclear translocation or NFκB-mediated gene transcription of an inflammatory cytokine in an individual in need thereof comprising administering a chemerin C15 peptide disclosed herein or a topical formulation comprising a chemerin C15 peptide disclosed herein. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is a salt of a chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is carboxylated. In some embodiments, the chemerin C15 peptide is amidated. In some embodiments, the chemerin C15 peptide is cyclic. In some embodiments, the chemerin C15 peptide is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9% homologous to a naturally occurring chemerin C15 peptide.

**[0027]** Skin disorders are, in certain instances, marked by increased inflammation in the skin. In certain instances, skin disorders result from the infiltration of inflammatory cells including macrophages, dendritic cells, monocytes, neutrophils and NK cells into skin tissue. Antigen presentation from these cells activate auto-reactive T-cells in skin diseases. Currently approved therapies for skin disorders include antibodies and biological agents targeting cytokines including, for example, TNFα, IL-12, IL-23, IL-1β and/or IL-6. Efficacy of these agents has been linked to a reduction in levels of TNFα, IL-12, IL-23, IL-1β and/or IL-6 in diseased skin tissue. Additional cytokines linked to inflammatory skin disorders and diseases include but are not limited to IL-1, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-11, IL-12, IL-13, IL-14, IL-15, IL-16, IL-17, 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, as well as TNF family members, IFN family members, RANTES, MCP-1, and MIP-1. These anti-cytokine antibodies and biological agents are typically administered systemically and as such lead to systemic immunosuppression which places the patient at increased risk for unintended side effects including increased infections and death. In one example, the monoclonal antibody, Raptiva, an approved psoriasis treatment, was removed from the market after several cases of PML and death were linked to its use.

**[0028]** Chemerin, also known as retinoic acid receptor responder protein 2 (RARRES2), tazarotene-induced gene 2 protein (TIG2), or RAR-responsive protein TIG2, is a 157 amino acid plasma protein derived from enzymatic cleavage of its 163 amino acid precursor, prochemerin.

**[0029]** Human prochemerin has the amino acid sequence:
MRRLLIPLALWLGAVGVGVAELTEAQRRGLQVALEEFHKHPPVQWAFQETSVESAVDTPF
PAGIFVRLEFKLQQTSCRKRDWKKPECKVRPNGRKRKCLACIKLGSEDKVLGRLVHCPIET
QVLREAEEHQETQCLRVQRAGEDPHSFYFPGQFAFSKALPRS.

**[0030]** Mature human chemerin has the amino acid sequence:
VGVAELTEAQRRGLQVALEEFHKHPPVQWAFQETSVESAVDTPFPAGIFVRLEFKLQQTSC
RKRDWKKPECKVRPNGRKRKCLACIKLGSEDKVLGRLVHCPIETQVLREAEEHQETQCLR
VQRAGEDPHSFYFPGQFAFSKALPRS.

**[0031]** Mouse prochemerin has the amino acid sequence:

**[0032]** MKCLLISLALWLGTVGTRGTEPELSETQRRSLQVALEEFHKHPPVQLAFQEIGVD
RAEEVLFSAGTFVRLEFKLQQTNCPKKDWKKPECTIKPNGRRRKCLACIKMDPKGKILGRI
VHCPILKQGPQDPQELQCIKIAQAGEDPHGYFLPGQFAFSRALRTK.

**[0033]** Mature mouse chemerin has the amino acid sequence:

**[0034]** TEPELSETQRRSLQVALEEFHKHPPVQLAFQEIGVDRAEEVLFSAGTFVRLEFKLQ
QTNCPKKDWKKPECTIKPNGRRRKCLACIKMDPKGKILGRIVHCPILKQGPQDPQELQCIKI
AQAGEDPHGYFLPGQFAFSRALRTK.

**[0035]** Rat prochemerin has the amino acid sequence:

**[0036]** TELELSETQRRGLQVALEEFHRHPPVQWAFQEIGVDSADDLFFSAGTFVRLEFKL
QQTSCLKKDWKKPECTIKPNGRKRKCLACIKLDPKGKVLGRMVHCPILKQGPQQEPQESQ
CSKIAQAGEDSRIYFFPGQFAFSRALQSK.

**[0037]** Mature mouse chemerin has the amino acid sequence:

**[0038]** MKCLLISLALWLGTADIHGTELELSETQRRGLQVALEEFHRHPPVQWAFQEIGVD
SADDLFFSAGTFVRLEFKLQQTSCLKKDWKKPECTIKPNGRKRKCLACIKLDPKGKVLGR
MVHCPILKQGPQQEPQESQCSKIAQAGEDSRIYFFPGQFAFSRALQSK.

**[0039]** Chemerin is a potent macrophage chemoattractant the acts via the G protein-coupled receptor ChemR23. Proteolyzed compositions of mouse chemerin inhibit macrophage activation and inhibition of inflammation in the presence of the Chem23 receptor. A 15 amino acid C-terminal peptide (mC15) of mouse chemerin (AGEDPHGYFLPGQFA) inhibits activation of macrophages and in the presence of ChemR23. As shown in the data provided herein, human chemerin C15 peptides (e.g. AGEDPHSFYFPGQFA) also are potent inflammatory inhibitors.

**[0040]** Accordingly, disclosed herein, in certain embodiments, are methods of modulating the activity of cells expressing the chemerin GPCR receptor, ChemR23. In some embodiments these cells are antigen presenting cells. In some embodiments, these cells include macrophages, dendritic cells, monocytes, neutrophils and NK cells among others which are a source of cytokines linked to

inflammatory skin disorders. In some embodiments, the chemerin C15 peptides act to reduce the secretion of cytokines by the ChemR23 expressing cells. In some embodiments, the chemerin C15 peptides decrease release of inflammatory cytokines such as IL-23, TNFα, IL-1β, IL-6, and RANTES. In some embodiments, the chemerin C15 peptides decrease release of IL-23. In some embodiments, the chemerin C15 peptides decrease release of TNFα. In some embodiments, the chemerin C15 peptides decrease release of IL-1β. In some embodiments, the chemerin C15 peptides decrease release of IL-6. In some embodiments, the chemerin C15 peptides decrease release of RANTES. In some embodiments, the chemerin C15 peptides prevent the recruitment of inflammatory immune cells. In some embodiments, the chemerin C15 peptides inhibit the transcription of inflammatory cytokines such as IL-23, TNFα, IL-1β, IL-6, and RANTES. In some embodiments, the chemerin C15 peptides inhibit the transcription of IL-23. In some embodiments, the chemerin C15 peptides inhibit the transcription of TNFα. In some embodiments, the chemerin C15 peptides inhibit the transcription of IL-1β. In some embodiments, the chemerin C15 peptides inhibit the transcription of IL-6. In some embodiments, the chemerin C15 peptides inhibit the transcription of RANTES. In some embodiments, the chemerin C15 peptides prevent the recruitment of inflammatory immune cells. In some embodiments, the chemerin C15 peptides prevent the activation of inflammatory immune cells. In some embodiments, the chemerin C15 peptides inhibit the activation of T cells.

**[0041]** As shown in the data provided herein, chemerin C15 peptides are not direct competitive inhibitors of chemerin binding to ChemR23. The chemerin C15 peptides thus exhibit properties of a dominant negative inhibitor, a biased ligand, or an allosteric antagonist. As such, they are capable of beneficially blocking inflammatory signals (e.g., cytokine release) via Chemerin/ChemR23 signaling and/or the signaling associated with accessory proteins to ChemR23 without inhibiting 'normal' Chemerin/ChemR23 and/or the signaling associated with accessory proteins to ChemR23 which lead to 'side effects'. Furthermore, the C15 peptides inhibit inflammatory processes stimulated by TNFα, IFNγ, LPS, Zymosan and other stimuli which do not signal directly through ChemR23. In this manner, the C15 peptides exhibit properties of an inhibitor of the NFκB pathway. As such, they are capable of beneficially blocking inflammatory signals (e.g., cytokine release) via prevention of NFκB activation, nuclear translocation, cytokine gene transcription and/or cytokine release without exhibiting adrenosuppression or other side effects associated with corticosteroids.

**[0042]** In addition, as shown in the data provided herein, chemerin C15 peptides contain an FYFP motif and lose the ability to inhibit inflammatory cytokine production in stimulated macrophages if the peptide is modified in the FYFP motif to FYAP or YFAP. In human C15, the

FYFP motif is embodied in its exact FYFP sequence, while in murine C15, the FYFP motif is embodied in the YFLP amino acid sequence. The FYFP motif is similar to the conserved FYFP motif of the PP2A regulatory B-subunit. Binding the B-subunit to PP2A core enzyme A and C subunits is dependent on the FYFP motif (Davis AJ, et al. *J Biol Chem.* 2008;283:16104-14). Under resting conditions, the protein phosphatase 2A (PP2A) core enzyme associates with IKK (IκB Kinase), the kinase which phosphorylates IκB and maintains it in an inactive unphosphorylated state. Additionally, PP2A core associates with NFκB of the NFκB/IκB complex, maintaining it in a resting unphosphorylated state. During activation of the NFκB pathway, NFκB and IκB are phosphorylated and PP2A association with the NFκB /IkB is diminished by association with the PP2A regulatory B-subunit. IκB also is released, thus allowing NFκB to translocate to the nucleus where it participates in cytokine transcription, including induction of IL-23 transcription. In some embodiments, binding of chemerin C15 peptide to PP2A interferes with binding of the regulatory B-subunit to the complex and thus stabilizes the NFκB/IκB in a resting state. In some embodiments, chemerin C15 peptides inhibit cytokine production by inhibiting the release of IκB from the NFκB, which prevents nuclear translocation and gene activation.

**[0043]** Described herein, in certain embodiments, are topical formulations comprising a chemerin C15 peptide for treating a inflammatory dermatological disorder. In some embodiments, the inflammatory dermatological disorder is a chronic blistering disorder, acne, psoriasis, dermatitis (e.g., contact or atopic), eczema, lichen planus, alopecia areata, urticaria, rosacea, scarring (i.e. the formation of a scar (e.g., a keloid scar or a hypertrophic scar)), and/or melanoma. In some embodiments, the inflammatory dermatological disorder is psoriasis. In some embodiments, the inflammatory dermatological disorder is dermatitis. In some embodiments, the inflammatory dermatological disorder is atopic dermatitis. In some embodiments, the inflammatory dermatological disorder is contact dermatitis. In some embodiments, a topical formulation disclosed herein comprises a therapeutically-effective amount of a chemerin C15 peptide. The topical formulations provided herein deliver therapeutic levels of the chemerin C15 peptide beneath the stratum corneum to the epidermis and dermis and offer an enhanced treatment of skin disorders, particularly inflammatory skin disorders.

**[0044]** Also described herein are methods for the administration of topical formulations comprising a chemerin C15 peptide. In one aspect, topical administration of a chemerin C15 peptide provides for local treatment of dermatological conditions. In one aspect, local treatment of dermal conditions with a chemerin C15 peptide reduces possible side effects associated with systemic administration of a chemerin C15 peptide. In one aspect, topical administration of a chemerin C15 peptide to a mammal minimizes systemic absorption of the chemerin C15 peptide.

In some embodiments, a topical formulation disclosed herein is administered before or after contact with an allergen and/or irritant.

**[0045]** In certain embodiments, chemerin C15 peptides applied locally for a skin disorder will have fewer or less severe side effect than currently approved topical agents for the treatment of skin disorders. These approved topical agents include steroids (e.g., corticosteroids) and calcineurin antagonists (e.g., Elidel) which carry known risks of thinning of the skin, cataracts, glaucoma and/ or neoplasms when used topically in the treatment of skin disorders. In certain embodiments, a chemerin C15 peptide applied locally for a skin disorder is a naturally occurring biological agent with fewer or less severe side effect than currently approved systemic biological agents for the treatment of skin disorders. These approved systemic biological agents include mono-clonal antibodies (e.g., Stelara) and fusion proteins (e.g., Enbrel) which carry known risks of antigenic response, infections and malignancies.

**[0046]** In certain embodiments, chemerin C15 peptides are formulated for topical administration to minimize systemic exposure of the chemerin C15 peptides. In certain embodiments, topical formulations of chemerin C15 peptides are designed to minimize systemic exposure of the chemerin C15 peptides (e.g., certain excipients are excluded which may result in the chemerin C15 peptides penetrating the skin and becoming systemically available). In some embodiments, minimizeing systemic exposure reduces unwanted side-effects (e.g., effects on non-targeted parts of the body) of administering a chemerin C15 peptide.

**[0047]** Disclosed herein is the use of chemerin C15 peptides in the manufacture of medicaments suitable for topical administration to a mammal for the treatment or prevention of dermatological diseases, disorders or conditions.

**[0048]** Described herein are pharmaceutical compositions suitable for topical administration, methods for treating, methods for formulating topical formulations, methods for producing, methods for manufacturing, treatment strategies, using chemerin C15 peptides.

**Chemerin C15 Peptides**

**[0049]** Disclosed herein, in certain embodiments, are chemerin C15 peptides. Further disclosed herein are topical formulations comprising a chemerin C15 peptide and optionally a pharmaceutically acceptable excipient. Additionally disclosed herein are methods of treating inflammatory dermatological disorders in an individual in need thereof comprising administering a chemerin C15 peptide disclosed herein or a topical formulation comprising a chemerin C15 peptide disclosed herein. Further disclosed herein are methods of inhibiting the activity of an inflammatory cytokine or chemokine in an individual in need thereof comprising administering a chemerin C15 peptide disclosed herein or a topical formulation comprising a chemerin C15 peptide disclosed

herein. Also disclosed herein, in certain embodiments, are method of inhibiting inhibits nuclear translocation or NFκB-mediated gene transcription of an inflammatory cytokine in an individual in need thereof comprising administering a chemerin C15 peptide disclosed herein or a topical formulation comprising a chemerin C15 peptide disclosed herein. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is a salt of a chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is carboxylated. In some embodiments, the chemerin C15 peptide is amidated. In some embodiments, the chemerin C15 peptide is cyclic. In some embodiments, the chemerin C15 peptide is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9% homologous to a naturally occurring chemerin C15 peptide.

**[0050]** The chemerin C15 peptides provided herein for administration exhibit one or more properties or activities useful as a topical treatment for an inflammatory disease or disorder. In some embodiments, a chemerin C15 peptide disclosed herein inhibits inflammation. In some embodiments, a chemerin C15 peptide disclosed herein inhibits inflammation associated with a dermatological disease or disorder. In some embodiments, a chemerin C15 peptide disclosed herein inhibits one or more cellular processes associated with inflammation. In some embodiments, a chemerin C15 peptide disclosed herein inhibits the release of one or more inflammatory cytokines. Exemplary inflammatory cytokine include, but are not limited to, IL-23, IL-12, TNFα, IL-1β, IL-6, or RANTES. In some embodiments, a chemerin C15 peptide disclosed herein inhibits the release of IL-23, IL-12, TNFα, IL-1β, IL-6, or RANTES. In some embodiments, a chemerin C15 peptide disclosed herein inhibits the transcription of one or more inflammatory cytokines. In some embodiments, a chemerin C15 peptide disclosed herein inhibits the transcription of IL-23, IL-12, TNFα, IL-1β, IL-6, or RANTES. In some embodiments, a chemerin C15 peptide disclosed herein inhibits the production of one or more inflammatory cytokines. In some embodiments, a chemerin C15 peptide disclosed herein inhibits the production and/or release of IL-23, IL-12, TNFα, IL-1β, IL-6, or RANTES. In some embodiments, a chemerin C15 peptide disclosed herein inhibits the production and/or release of one or more inflammatory cytokines by immune cells. In some embodiments, a chemerin C15 peptide disclosed herein inhibits the production and/or release of IL-23, IL-12, TNFα, IL-1β, IL-6, or RANTES by immune cells. In some embodiments, a chemerin C15 peptide disclosed herein inhibits the production and/or release of one or more inflammatory cytokines by antigen presenting cells. In some embodiments, a chemerin C15 peptide disclosed herein inhibits the production and/or release of IL-23, IL-12, TNFα, IL-1β, IL-6, or RANTES by antigen presenting cells. In some embodiments, a chemerin C15 peptide disclosed herein inhibits the production and/or release of one or more inflammatory

cytokines in myeloid dendritic cells (mDC), plasmacytoid dendritic cells (pDC) or macrophages. In some embodiments, a chemerin C15 peptide disclosed herein inhibits the production and/or release of IL-23, IL-12, TNFα, IL-1β, IL-6, or RANTES in myeloid dendritic cells (mDC), plasmacytoid dendritic cells (pDC) or macrophages. In some embodiments, a chemerin C15 peptide disclosed herein inhibits the production and/ or release of one or more inflammatory cytokines by immune cells expressing the ChemR23 receptor. In some embodiments, a chemerin C15 peptide disclosed herein inhibits the production and/ or release of IL-23, IL-12, TNFα, IL-1β, IL-6, or RANTES by immune cells expressing the ChemR23 receptor.

**[0051]** In some embodiments, a chemerin C15 peptide disclosed herein inhibits the activation of NF-κB. In some embodiments, a chemerin C15 peptide disclosed herein inhibits the activation of NF-κB associated with inflammation. In some embodiments, a chemerin C15 peptide disclosed herein inhibits the activation of NF-κB in cells expressing the ChemR23 receptor. In some embodiments, a chemerin C15 peptide disclosed herein binds to the protein phosphatase 2A core enzyme. In some embodiments, a chemerin C15 peptide disclosed herein prevents the release of IκB from NF-κB. In some embodiments, a chemerin C15 peptide disclosed herein prevents the nuclear translocation of NF-κB. In some embodiments, a chemerin C15 peptide disclosed herein inhibits Th1 and/or Th17 T-cell activation. In some embodiments, a chemerin C15 peptide disclosed herein inhibits Th1 and/or Th17 T-cell activation associated with inflammation.

**[0052]** In some embodiments, the chemerin C15 peptide is any suitable chemerin C15 peptide for topical administration. In some embodiments, the chemerin C15 peptide is human chemerin C15 peptide. In some embodiments, the chemerin C15 peptide comprises a sequence of amino acids AGEDPHSFYFPGQFA. In some embodiments, the chemerin C15 peptide has a sequence of amino acids consists essentially of the sequence of amino acids AGEDPHSFYFPGQFA.

**[0053]** In some embodiments, the chemerin C15 peptide is a mouse chemerin C15 peptide. In some embodiments, the chemerin C15 peptide comprises a sequence of amino acids AGEDPHGYFLPGQFA. In some embodiments, the chemerin C15 peptide has a sequence of amino acids consists essentially of the sequence of amino acids AGEDPHGYFLPGQFA.

**[0054]** In some embodiments, the chemerin C15 peptide is a chimeric chemerin C15 peptide comprising a sequence of amino acids derived from a human chemerin C15 peptide and a non-human chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is a chimeric chemerin C15 peptide comprising a sequence of amino acids derived from a human chemerin C15 peptide and a mouse chemerin C15 peptide. In some embodiments, the chemerin C15 peptide comprises a sequence of amino acids AGEDPHGYYFPGQFA. In some embodiments, the

chemerin C15 peptide has a sequence of amino acids consists essentially of the sequence of amino acids AGEDPHGYYFPGQFA.

**[0055]** In some embodiments, the chemerin C15 peptide is a peptide comprising the sequence of amino acids AGEDPHS$X_1X_2X_3$PGQFA, where $X_1$, $X_2$, and $X_3$ are hydrophobic amino acids. In some embodiments, the chemerin C15 peptide is a peptide comprising the sequence of amino acids AGEDPHS$X_1X_2X_3$PGQFA, where $X_1$, $X_2$, and $X_3$ are aromatic amino acids. In some embodiments, $X_1$ is tyrosine or phenyalanine. In some embodiments, $X_2$ is tyrosine or phenyalanine. In some embodiments, $X_2$ is tyrosine or phenyalanine.

**[0056]** In some embodiments, the chemerin C15 peptide comprises a sequence of amino acids derived from a chemerin C15 peptide and a regulatory B-subunit of PP2A. In some embodiments, the chemerin C15 peptide comprises a sequence of amino acids derived from a human chemerin C15 peptide and a human regulatory B-subunit of PP2A. In some embodiments, the chemerin C15 peptide comprises a sequence of amino acids PTFYFP. In some embodiments, the chemerin C15 peptide comprises a sequence of amino acids AGEDPTFYFPGQFA. In some embodiments, the chemerin C15 peptide consists essentially of a sequence of amino acids AGEDPTFYFPGQFA.

**[0057]** In some embodiments, the chemerin C15 peptide comprises the amino acid sequence AGEDPHSFYFPGQFA, where one or more amino acids of the sequence AGEDPHSFYFPGQFA is substituted. In some embodiments, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 amino acids are substituted.

**[0058]** In some embodiments, the chemerin C15 peptide comprises the amino acid sequence AGEDPHSFYFPGQFA, where one or more amino acids in the sequence PHSFYFP is substituted. In some embodiments, 1, 2, 3, 4, 5, 6, or 7 amino acids are substituted..

**[0059]** In some embodiments, the chemerin C15 peptide comprises L- amino acids. In some embodiments, the chemerin C15 peptide comprises a sequence of amino acids AGEDPHSFYFPGQFA, where the peptide comprises L- amino acids. In some embodiments, the chemerin C15 peptide has a sequence of amino acids consists essentially of the sequence of amino acids AGEDPHSFYFPGQFA, where the peptide comprises L- amino acids.

**[0060]** In some embodiments, the chemerin C15 peptide comprises D- and/or L- amino acids. In some embodiments, the chemerin C15 peptide comprises a sequence of amino acids AGEDPHSFYFPGQFA, where the peptide comprises D- and/or L- amino acids. In some embodiments, the chemerin C15 peptide has a sequence of amino acids consists essentially of the sequence of amino acids AGEDPHSFYFPGQFA, where the peptide comprises D- and/or L- amino acids.

**[0061]** In some embodiments, the chemerin C15 peptide comprises a sequence of amino acids AGEDPHSFYFPGQFA, where one or more amino acids of the sequence AGEDPHSFYFPGQFA is in the D-configuration. In some embodiments, the chemerin C15 peptide comprises a sequence of amino acids AGEDPHSFYFPGQFA, where each amino of the sequence AGEDPHSFYFPGQFA is in the D-configuration. In such examples, the sequence where each amino of the sequence is in the D-configuration is called a retroinverso peptide sequence. In such examples, the chemerin C15 peptide comprises a sequence of amino acids AFQGPFYFSHPDEGA.

**[0062]** In some embodiments, the chemerin C15 peptide comprises a sequence of amino acids comprising retroinverso sequences representing chemerin C-terminal fragments of human chemerin sequences (e.g., AGEDPHSFYFPGQFA. In some embodiments, the chemerin C15 peptide comprises a sequence of amino acids comprising retroinverso sequences representing chemerin C-terminal fragments of non-human chemerin sequences, such as for example, mouse chemerin C15 peptide (e.g., AGEDPHGYYFPGQFA).

**[0063]** In some embodiments, the chemerin C15 peptide comprises derivatives or analogs in which a substituted amino acid residue is not one encoded by the genetic code (i.e. an unnatural amino acid). In some embodiments, the chemerin C15 peptide comprises one or more unnatural amino acids. In some embodiments, the chemerin C15 peptide comprises a sequence of amino acids AGEDPHSFYFPGQFA, where one or more amino acids is a unnatural amino acid. In some embodiments, the chemerin C15 peptide has a sequence of amino acids consists essentially of the sequence of amino acids AGEDPHSFYFPGQFA, where one or more amino acids is a unnatural amino acid.

**[0064]** Examples of unnatural amino acids that can be incorporated into the chemerin C15 peptide provided include, but are not limited to, homoserine (hSer), homoserine lactone (hSerlac), homocysteine (Hcy), homoarginine (hArg), homocitrulline (Hci), penicillamine (Pen), Nα-methylarginine (N-MeArg), norleucine (Nle), norvaline (Nval), norisoleucine (NIle), N-methylisoleucine (N-MeIle), phenylglycine (PhG), t-butylglycine (Tle), hydroxyproline (Hyp), 3,4-dehydroproline (Δ-Pro), pyroglutamine (Pyr,Glp), ornithine (Orn), 1-aminoisobutyric acid (1-Aib), 2-aminoisobutyric acid (2-Aib), 2-aminobutyric acid (2-Abu), 4-aminobutyric acid (4-Abu), 2,4-diaminobutyric acid (A2bu), α-aminosuberic acid (Asu), albizzin (Abz), β-cyclohexylalanine (Cha), 3-(1-naphthyl)alanine (1-Nal), 3-(2-naphthyl)alanine (2-Nal), citrulline (Cit). pipecolinic acid (Pip), 4-chlorophenylalanine (4-ClPhe), 4-fluorophenylalanine (4-FPhe), sarcosine (Sar) and 1-aminopropanecarboxylic acid (1-NCPC). Additional unnatural amino acid include, but are not limited to those disclosed in U.S. Patent Application Pub. No. 2004/0121438 and U.S. Pat. No.

US5656727. Both natural and unnatural amino acids are commercially available from vendors such as NovaBiochem (San Diego, CA, USA) and Bachem (Torrance, CA, USA).

**[0065]** In some embodiments, the chemerin C15 peptide comprises a sequence of amino acids AGEDPHSFYFPGQFA, where 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 amino acids is a unnatural amino acid. In some embodiments, the chemerin C15 peptide has a sequence of amino acids consists essentially of the sequence of amino acids AGEDPHSFYFPGQFA, where 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 amino acids is a unnatural amino acid.

**[0066]** In some embodiments, the chemerin C15 peptide comprises a sequence of amino acids AGEDPH$X_1$FYFPGQFA, where $X_1$ is a unnatural amino acid. In some embodiments, the chemerin C15 peptide has a sequence of amino acids consists essentially of the sequence of amino acids AGEDPH$X_1$FYFPGQFA, where $X_1$ is a unnatural amino acid. In some embodiments, $X_1$ is a derivative of the amino acid serine. In some embodiments, $X_1$ is homoserine.

**[0067]** In some embodiments, the chemerin C15 peptide comprises a sequence of amino acids AGEDPHS$X_1$YFPGQFA, where $X_1$ is a unnatural amino acid. In some embodiments, the chemerin C15 peptide has a sequence of amino acids consists essentially of the sequence of amino acids AGEDPHS$X_1$YFPGQFA, where $X_1$ is a unnatural amino acid. In some embodiments, $X_1$ is a derivative of the amino acid phenylalanine or tyrosine. In some embodiments, $X_1$ is p-chlorophenylalanine. In some embodiments, $X_1$ is napthyl alanine.

**[0068]** In some embodiments, the chemerin C15 peptide comprises a sequence of amino acids AGEDPHS$X_1$Y$X_2$PGQFA, where $X_1$ and $X_2$ are unnatural amino acids. In some embodiments, $X_1$ and $X_2$ are the same unnatural amino acid. In some embodiments, $X_1$ and $X_2$ are different unnatural amino acids. In some embodiments, the chemerin C15 peptide has a sequence of amino acids consists essentially of the sequence of amino acids AGEDPHS$X_1$Y$X_2$PGQFA , where $X_1$ and $X_2$ are unnatural amino acids. In some embodiments, $X_1$ and $X_2$ are the same unnatural amino acid. In some embodiments, $X_1$ and $X_2$ are different unnatural amino acids. In some embodiments, $X_1$ is an aromatic unnatural amino acid. In some embodiments, $X_1$ is a derivative of the amino acid phenylalanine or tyrosine. In some embodiments, $X_1$ is p-chlorophenylalanine. In some embodiments, $X_1$ is napthyl alanine. In some embodiments, $X_2$ is an aromatic unnatural amino acid. In some embodiments, $X_2$ is p-chlorophenylalanine. In some embodiments, $X_2$ is napthyl alanine.

**[0069]** In some embodiments, the chemerin C15 peptide comprises a sequence of amino acids AGEDPHS$X_1X_2X_3$PGQFA, where $X_1$, $X_2$ and $X_3$ are unnatural amino acids. In some embodiments, $X_1$ and $X_2$ are the same unnatural amino acid. In some embodiments, $X_1$ and $X_2$ are different unnatural amino acids. In some embodiments, $X_1$ and $X_3$ are the same unnatural amino

acid. In some embodiments, $X_1$ and $X_3$ are different unnatural amino acids. In some embodiments, $X_2$ and $X_3$ are the same unnatural amino acid. In some embodiments, $X_2$ and $X_3$ are different unnatural amino acids. In some embodiments, $X_1$, $X_2$ and $X_3$ are the same unnatural amino acid. In some embodiments, $X_1$, $X_2$ and $X_3$ are different unnatural amino acids. In some embodiments, $X_1$ is an aromatic unnatural amino acid. In some embodiments, $X_1$ is a derivative of the amino acid phenylalanine or tyrosine. In some embodiments, $X_1$ is p-chlorophenylalanine. In some embodiments, $X_1$ is napthyl alanine. In some embodiments, $X_2$ is an aromatic unnatural amino acid. In some embodiments, $X_2$ is a derivative of the amino acid phenylalanine or tyrosine. In some embodiments, $X_2$ is p-chlorophenylalanine. In some embodiments, $X_2$ is napthyl alanine. In some embodiments, $X_3$ is an aromatic unnatural amino acid. In some embodiments, $X_3$ is a derivative of the amino acid phenylalanine or tyrosine. In some embodiments, $X_3$ is p-chlorophenylalanine. In some embodiments, $X_3$ is napthyl alanine.

**[0070]** In some embodiments, unnatural amino acids are selected from commercially available amino acids. In some embodiments, unnatural amino acids are selected from D-configuration, L-configuration or achiral amino acids which do not occur in nature (e.g. listed in the Accelrys Available Chemicals Directory (ACD), http://accelrys.com). In some embodiments, unnatural amino acids are selected for improvements to solubility, stability, potency, mechanism of action, and/or pharmaceutical properties of the peptide.

**[0071]** In some embodiments, the chemerin C15 peptide comprises a sequence of amino acids comprising chimeric sequences and retroinverso sequences containing one or more unnatural amino acids selected from commercially available unnatural amino acids (e.g. listed in the Accelrys Available Chemicals Directory (ACD), http://accelrys.com) and selected for improvements to solubility, stability, potency, mechanism of action, pharmaceutical properties of the peptide.

**[0072]** In some embodiments, the chemerin C15 peptide exhibits increased inhibition of cytokine production in stimulated macrophages compared to a human chemerin C16 peptide having the sequence of amino acids AGEDPHSFYFPGQFAF. In some embodiments, the chemerin C15 peptide exhibits increased inhibition of IL-23 production in stimulated macrophages compared to a human chemerin C16 peptide having the sequence of amino acids AGEDPHSFYFPGQFAF.

**[0073]** In some embodiments, the chemerin C15 peptide exhibits increased inhibition of cytokine production in stimulated macrophages compared to a human chemerin C17 peptide having the sequence of amino acids AGEDPHSFYFPGQFAFS. In some embodiments, the chemerin C15 peptide exhibits increased inhibition of IL-23 production in stimulated macrophages compared to a human chemerin C17 peptide having the sequence of amino acids AGEDPHSFYFPGQFAFS.

**[0074]** In some embodiments, the chemerin C15 peptide exhibits increased inhibition of cytokine production in stimulated macrophages compared to a mouse chemerin C15 peptide having the sequence of amino acids AGEDPHGYFLPGQFA. In some embodiments, the chemerin C15 peptide exhibits increased inhibition of IL-23 production in stimulated macrophages compared to a mouse chemerin C15 peptide having the sequence of amino acids AGEDPHGYFLPGQFA.

**[0075]** In some embodiments, the chemerin C15 peptide does not exhibit agonist activity toward the Chem23 receptor.

**[0076]** In some embodiments, the chemerin C15 peptide is a peptide salt such as pharmaceutically acceptable acid- or base addition salt. Salts of peptides or functional equivalents are prepared by known methods, which typically involve the mixing of the peptide with either a pharmaceutically acceptable acid to form an acid addition salt, or with a pharmaceutically acceptable base to form a base addition salt. Whether an acid or a base is pharmaceutically acceptable can be easily decided by a person skilled in the art after taking the specific intended use of the compound into consideration. Depending on the intended use, pharmaceutically acceptable acids include organic and inorganic acids such as formic acid, acetic acid, propionic acid, lactic acid, glycolic acid, oxalic acid, pyruvic acid, succinic acid, maleic acid, malonic acid, cinnamic acid, sulphuric acid, hydrochloric acid, hydrobromic acid, nitric acid, perchloric acid, phosphoric acid, and thiocyanic acid, which form ammonium salts with free amino groups of peptides and functional equivalents. Pharmaceutically acceptable bases, which form carboxylate salts with free carboxylic groups of peptides and functional equivalents, include ethylamine, methylamine, dimethylamine, triethylamine, isopropylamine, diisopropylamine, and other mono-, di- and trialkylamines, as well as arylamines. Moreover, also pharmaceutically acceptable solvates, complexes or adducts, such as hydrates or ethurates, alkali metal salt, such as lithium, sodium or potassium salts, or other salts such as, but not limited to calcium magnesium aluminum, zinc or iron salts, are encompassed.

**[0077]** In some embodiments, the chemerin C15 peptide is a multimer comprising one or more chemerin C15 peptides.

*Peptide Modifications*

**[0078]** In some embodiments, the chemerin C15 peptide is further modified to improve one or more properties of the chemerin C15 peptide. Exemplary properties include, but are not limited to, solubility, stability, potency, mechanism of action, ability to be detected and/or pharmaceutical properties of the chemerin C15 peptide. Generally, the modifications do not significantly reduce the therapeutic properties of the chemerin C15 peptide, such as the anti-inflammatory properties of the chemerin C15 peptide, including, for example, inhibition of NFκB and secretion and/or

production of one or more inflammatory cytokines (e.g. IL-23, IL-12, TNFα, IL-1β, IL-6, or RANTES).

**[0079]** In some embodiments, the chemerin C15 peptide is further modified by natural processes, such as processing and other known post-translational modifications, or by chemical or enzymatic techniques well-known in the art. Known modifications include, but are not limited to, acetylation, acylation, ADP-ribosylation, amidation, covalent attachment of flavin, covalent attachment of a heme moiety, covalent attachment of a nucleotide or nucleotide derivative, covalent attachment of a lipid or lipid derivative, covalent attachment of phosphotidylinositol, cross-linking, cyclization, disulfide bond formation, demethylation, formation of covalent crosslinks, formation of cysteine, formation of pyroglutamate, formylation, gamma carboxylation, glycosylation, GPI anchor formation, hydroxylation, iodination, methylation, myristoylation, oxidation, proteolytic processing, phosphorylation, prenylation, racemization, selenoylation, sulfation, transfer-RNA mediated addition of amino acids to proteins such as arginylation, and ubiquitination.

**[0080]** In some embodiments, the modification increases the solubility of the chemerin C15 peptide. In one example, amidation increases the solubility of the chemerin C15 peptide. In some embodiments, the modification renders that the chemerin C15 peptide less susceptible to protease degradation. In some embodiments, the modification increases the ability of the chemerin C15 peptide to penetrate the skin. In one example, lipidation increases the ability of the chemerin C15 peptide to penetrate the skin. In some embodiments, a hydrogen of the N-terminal amino group of the peptide is replaced. In some embodiments, the entire N-terminal amino group of the peptide is replaced. In some embodiments, the hydroxyl group (OH) of the C-terminal carboxylic group is replaced. In some embodiments, the entire C-terminal carboxylic group is replaced.

**[0081]** In some embodiments, functional groups of the chemerin C15 peptide that are modified include hydroxyl, amino, guanidinium, carboxyl, amide, phenol, imidizole rings or sulfhydryl. Exemplary non-limiting reaction of such groups, include acetylation of hydroxyl groups by alkyl halides; esterification, amidation or hydrogenization (i.e. reduction to alcohol) of carboxyl groups; deamidation, acylation, alkylation, arylation of amino groups (e.g. primary amino group of the peptide or the amino group of lysine residues); halogenation or nitration of tyrosine phenol groups.

**[0082]** Modification of peptides are well known to those of skill in the art and have been described in great detail in the scientific literature. Several particularly common modifications, glycosylation, lipid attachment, sulfation, gamma-carboxylation of glutamic acid residues, hydroxylation and ADP-ribosylation, for instance, are described in most basic texts, such as *Proteins-Structure & Molecular Properties* (2nd ed., T. E. Creighton, W. H. Freeman & Co., NY, 1993). Many detailed reviews are available on this subject, such as by Wold,

*Posttranslational Covalent Modification of Proteins*, 1-12 (Johnson, ed., Acad. Press, NY, 1983); Seifter et al., 182 Meth. Enzymol. 626-46 (1990); and Rattan et al., 663 Ann. N. Y. Acad. Sci. 48-62 (1992).

**[0083]** In some embodiments, the chemerin C15 peptide is conjugated to soluble or insoluble carrier molecule to modify their solubility properties as needed and to increase the local concentrations of peptides in targeted tissues. Examples of soluble carrier molecules include, but are not limited to, polymers of polyethyleneglycol (PEG) and polyvinylpyrrolidone; examples of insoluble polymers include silicates, polystyrene, and cellulose.

**[0084]** In some embodiments, the chemerin C15 peptides are micro-encapsulated to enhance their stability during and after therapeutic application. In some embodiments, polyester or PEG microspheres are used to encapsulate and stabilize the chemerin C15 peptides. Various methods of preparing microspheres for peptide encapsulation are known in art. The method selected depends upon the hydrophilic or hydrophobic nature of the peptide composition to be encapsulated. Examples of protocols for such methods are found in Wang HT et al. (1991, *J. Control. Release* 17:23-25) and U.S. Pat. No. 4,324,683, both of which are incorporated herein in their entirety. In some embodiments, i*n vitro* peptide release studies are performed to determine the relative availability of the peptide after it has been incorporated into a microsphere. In an exemplary method, microspheres (about 200 mg) are suspended in pH 7.2 phosphate-buffered saline (PBS) (2.5 ml) and agitated at 37 °C and 100 rpm in an environmental incubator shaker (G-24, New Brunswick Scientific Co., Edison, N.J.). At specific sampling times (each day for the first 4 days and every other day thereafter), the buffer solution is completely removed and replaced with fresh PBS. The peptide content of the PBS is measured using the Bradford method or other suitable quantitative assay typically used for protein analysis.

**[0085]** In some embodiments, the chemerin C15 peptide is further modified by attachment of detectable moiety, such for example, a fluorescent dye or a radiolabeled moiety. Exemplary detectable moieties are known in the art and include, but are not limited to, Rhodamine, Fluorescein, Cy3, Alexa Fluor 405, Alexa Fluor 488, Alexa Fluor 546, Alexa Fluor 555, Alexa Fluor 633, Alexa Fluor 647, Allophycocyanin (APC), APC-Cy7, fluorescein isothiocyanate (FITC), Pacific Blue, R-phycoerythrin (R-PE), PE-Cy5, PE-Cy7, Texas Red, PE-Texas Red, peridinin chlorophyll protein (PerCP), PerCP-Cy5.5.

**[0086]** In some embodiments, the peptide is conjugated to an immunogenic carrier peptide. In some embodiments, conjugation to an immunogenic carrier peptide allows for the production of C15 peptide specific antibodies. In some embodiments, the immunogenic peptide is Keyhole limpet hemocyanin (KLH).

**Production of chemerin C15 peptides**

**[0087]** Disclosed herein, in certain embodiments, are chemerin C15 peptides. Further disclosed herein are topical formulations comprising a chemerin C15 peptide and optionally a pharmaceutically acceptable excipient. Additionally disclosed herein are methods of treating inflammatory dermatological disorders in an individual in need thereof comprising administering a chemerin C15 peptide disclosed herein or a topical formulation comprising a chemerin C15 peptide disclosed herein. Further disclosed herein are methods of inhibiting the activity of an inflammatory cytokine or chemokine in an individual in need thereof comprising administering a chemerin C15 peptide disclosed herein or a topical formulation comprising a chemerin C15 peptide disclosed herein. Also disclosed herein, in certain embodiments, are method of inhibiting inhibits nuclear translocation or NFκB-mediated gene transcription of an inflammatory cytokine in an individual in need thereof comprising administering a chemerin C15 peptide disclosed herein or a topical formulation comprising a chemerin C15 peptide disclosed herein. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is a salt of a chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is carboxylated. In some embodiments, the chemerin C15 peptide is amidated. In some embodiments, the chemerin C15 peptide is cyclic. In some embodiments, the chemerin C15 peptide is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9% homologous to a naturally occurring chemerin C15 peptide.

**[0088]** The chemerin C15 peptides provided herein can be produced using any method known to those skilled in the art. In some embodiments, the peptides are produced using recombinant methods of expressing peptides in cells or in animals. In some embodiments, the peptides are produced *in vitro* using chemical synthesis.

**[0089]** In some examples, the chemerin C15 peptides are generated by protease cleavage of a chemerin polypeptide. In some embodiments, the chemerin C15 peptides are generated by an *in vitro* protease reaction where a chemerin polypeptide is incubated with a cysteine protease that cleaves the C-terminal end of the polypeptide to produce the 15 amino acid length chemerin C15 peptide. In some embodiments, the chemerin polypeptide employed in the reaction is a native protein. In some embodiments, the chemerin polypeptide employed in the reaction is a recombinant protein. In some embodiments, the chemerin C15 peptide is purified from the reaction by a suitable purification method, such as for example, HPLC or dialysis. In some embodiments, the purified chemerin C15 peptide is further modified as described elsewhere herein.

**[0090]** In some embodiments, the peptides are produced using chemical synthesis methods known to those skilled in the art such as those disclosed in Merrifield, R. B., Solid Phase Peptide

Synthesis I., *J. Am. Chem. Soc.* 85:2149-2154 (1963); Carpino, L. A. et al., [(9-Fluorenylmethyl)Oxy]Carbonyl (Fmoc) Amino Acid Chlorides: Synthesis, Characterization, And Application To The Rapid Synthesis Of Short Peptides, J. Org. Chem. 37:51:3732-3734; Merrifield, R. B. et al., Instrument For Automated Synthesis Of Peptides, Anal. Chem. 38:1905-1914 (1966); or Kent, S. B. H. et al., High Yield Chemical Synthesis Of Biologically Active Peptides On An Automated Peptide Synthesizer Of Novel Design, IN: Peptides 1984 (Ragnarsson U., ed.) Almqvist and Wiksell Int., Stockholm (Sweden), pp. 185-188, all of which are incorporated by reference herein in their entirety. In some embodiments, the peptides are produced by a machine capable of sequential addition of amino acids to a growing peptide chain. In some embodiments, the peptides are manufactured using standard solution phase methodology, which can be amenable to large-scale production efforts. In an exemplary method, the peptides are generated using solid phase synthesis by addition of FMOC-protected amino acids followed by final cleavage of the peptide using the trifluoroacetic acid (TFA). In some embodiments, the peptide is then purified. In some embodiments, the peptide is purified by HPLC purification. In some embodiments, the peptide is purified by HPLC purification on a C18 column with a gradient of water/acetronitrile.

**Dermatological Disorders (Dermatoses)**

**[0091]** Disclosed herein, in certain embodiments, are chemerin C15 peptides. Further disclosed herein are topical formulations comprising a chemerin C15 peptide and optionally a pharmaceutically acceptable excipient. Additionally disclosed herein are methods of treating inflammatory dermatological disorders in an individual in need thereof comprising administering a chemerin C15 peptide disclosed herein or a topical formulation comprising a chemerin C15 peptide disclosed herein. Further disclosed herein are methods of inhibiting the activity of an inflammatory cytokine or chemokine in an individual in need thereof comprising administering a chemerin C15 peptide disclosed herein or a topical formulation comprising a chemerin C15 peptide disclosed herein. Also disclosed herein, in certain embodiments, are method of inhibiting inhibits nuclear translocation or NFκB-mediated gene transcription of an inflammatory cytokine in an individual in need thereof comprising administering a chemerin C15 peptide disclosed herein or a topical formulation comprising a chemerin C15 peptide disclosed herein. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is a salt of a chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is carboxylated. In some embodiments, the chemerin C15 peptide is amidated. In some embodiments, the chemerin C15 peptide is cyclic. In some embodiments, the chemerin C15 peptide is at least

80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9% homologous to a naturally occurring chemerin C15 peptide.

**[0092]** As used herein, an inflammatory dermatological disorder includes a dermatological disorder is caused by (either partially or fully) an immune disorder, (e.g. an autoimmune disorder (e.g., eczema, psoriasis)); a proliferation disorder (e.g., melanoma); contact with an allergen and/or an irritant; an overproduction of sebum lipids (e.g., acne); a fibroblast disorder (e.g., scarring after a trauma (e.g., surgery)); or combinations thereof. Dermatological disorders include, but are not limited to, psoriasis, atopic dermatitis, irritant contact dermatitis, eczematous dermatitis, a chronic blistering (bullous) disorder, acne, seborrhoeic cutaneous manifestations of immunologically-mediated disorders, alopecia, alopecia areata, adult respiratory distress syndrome, pulmonary fibrosis, scleredoma, scar formation, (e.g., a keloid scar or a hypertrophic scar), urticaria, rosacea, melanoma, chronic obstructive pulmonary disease (COPD), inflammation from kidney transplant, asthma, hidradentis supporativa, rheumatoid arthritis, psoriatic arthritis, Sjogren's Syndrome, uveitis, Graft vs. Host disease (GVHD), Oral Lichen Planus, arthralgia or Islet Cell Transplant inflammation. In some embodiments, the dermatological disorder is psoriasis. In some embodiments, the dermatological disorder is dermatitis. In some embodiments, the dermatological disorder is atopic dermatitis. In some embodiments, the dermatological disorder is contact dermatitis.

*Psoriasis*

**[0093]** Disclosed herein are methods of treating psoriasis in an individual in need thereof comprising administering a chemerin C15 peptide disclosed herein or a topical formulation comprising a chemerin C15 peptide disclosed herein. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is a salt of a chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is carboxylated. In some embodiments, the chemerin C15 peptide is amidated. In some embodiments, the chemerin C15 peptide is cyclic. In some embodiments, the chemerin C15 peptide is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9% homologous to a naturally occurring chemerin C15 peptide.

**[0094]** In certain instances, the symptoms of psoriasis result from (either partially or fully) the exudation of plasma from vessels and capillaries into the epidermis, dermis, and/or subcutaneous tissues. T helper (Th) 17 cells are involved in the pathogenesis of psoriasis and other autoimmune inflammatory diseases. Interleukin (IL)-23 stimulates survival and proliferation of Th17 cells, and thus serves major cytokine regulator for these diseases. In psoriasis, IL-23 is overproduced by

dendritic cells and keratinocytes. IL-23 stimulates Th17 cells within dermis to make IL-17A and IL-22. IL-22, in particular, drives keratinocyte hyperproliferation in psoriasis (Fitch et al. (2007) *Curr Rheumatol Rep.* 9(6):461-7). Interleukin-12/23p40 and TNF-α monoclonal antibodies and inhibitors have been shown to be effective in the treatment of psoriasis in human patients (Krueger et al (2007) *N Engl J Med* 356:580-592; Koutrube et al (2010) *Therapeutics and Clinical Risk Management* 6:123-141; Mercuri and Naldi (2010) *Biologics: Targets and Therapy* 4:119-129).

**[0095]** Multiple genome-wide association studies also have indicated NFκB activation plays a major role in psoriasis (Stuart et al (2010) *Nat Gen* 42,1000–1004; Nair et al. (2009) *Nat. Genet.* 41(2): 199–204). In certain instances, impaired negative regulation of NFκB is due to loss of function of the inhibitory IKK (Perera et al (2012) *Annu Rev Pathol Mech Dis*). Many studies have shown that the NFκB signaling pathway is involved in the immune and inflammatory responses associated with psoriasis (Chen et al. (2000) *J. Invest. Dermatol.* 115, 1124-1133; Danning et al. (2000) *Arthritis Rheum.*, 43, 1244-1256; 3) Aronica et al. (1999) *J. Immunol.*, 163, 5116—5124; 4) Hawiger et al. (2001) *Immunol. Res.*, 23, 99-109). In addition, it has been shown that several antipsoriatic drugs such as acitretin and dimethylfumart (DMF) exert their action through inhibition of the NFκB signaling pathway (Zhang et al (2008) *Arch Dermatol Res.* 300(10):575-81; Mrowietz et al (2005) *Trend Mol Med* 11(1):43-48 . For example, acitretin and DMF inhibit NFκB translocation and decrease the concentration of NFκB in the nucleus of human keritinocytes. Rotterin, another potent NFκB inhibitor also possess antipsoriatic properties (Maioli et al (2010) *Curr. Drug Metab.* 11(5):425-30).

**[0096]** In some embodiments, a chemerin C15 peptide topical formulation is administered to treat psoriasis by inhibition of the production or secretion one or more cytokines involved in the pathogenesis of psoriasis. In some embodiments, a chemerin C15 peptide topical formulation is administered to treat psoriasis by inhibition of NFκB-mediated gene transcription of one or more cytokines involved in the pathogenesis of psoriasis. In some embodiments, a chemerin C15 peptide topical formulation is administered to treat inflammation associated with psoriasis.

*Dermatitis*

**[0097]** Disclosed herein are methods of treating dermatitis in an individual in need thereof comprising administering a chemerin C15 peptide disclosed herein or a topical formulation comprising a chemerin C15 peptide disclosed herein. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is a salt of a chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is carboxylated. In some embodiments, the chemerin C15 peptide is amidated. In some embodiments, the chemerin C15 peptide is cyclic. In some embodiments, the chemerin C15 peptide is at least 80%, 85%, 90%,

91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9% homologous to a naturally occurring chemerin C15 peptide.

**[0098]** As used herein, dermatitis means an inflammatory condition of the skin. In certain instances, dermatitis is acute and results (either partially or fully) from contact with an offending agent. In certain instances, dermatitis is chronic and results (either partially or fully) from hypersensitivity. In some embodiments, the dermatitis is atopic dermatitis. In some embodiments, the dermatitis is contact dermatitis. In one embodiment, the dermatitis is chronic. In one embodiment, the dermatitis is acute.

**[0099]** In certain instances, the symptoms of dermatitis (e.g., chronic or acute) result from (either partially or fully) a disorder of an immune system. The NFκB pathway has been shown to play a critical role in the disease severity of allergic disorders (Tanaka et al (2007) *J Invest Dermatol* 127(4):855-63). Topical treatment of an animal models of atopic dermatitis with an NFκB inhibitor reduced hyperplasia of keratinocytes and infiltration of inflammatory cells at the site of the lesion. In addition, NFκB inhibition suppressed proliferation of immunocompetent cells, IgE production form splenic B cells and IgE activation of mast cells *in vitro*. In addition, downregulation of NFκB pathway by inhibitors such as licochalcone E have been shown to reduce IL-12p40 expression resulting in suppression of chronic allergic contact dermatitis.

**[00100]** In some embodiments, a chemerin C15 peptide topical formulation is administered to treat dermatitis by inhibition of antigen presenting cells, such as dendritic cells or macrophages. In some embodiments, a chemerin C15 peptide topical formulation is administered to treat dermatitis by inhibition of the production of one or more inflammatory cytokines. In some embodiments, a chemerin C15 peptide topical formulation is administered to treat dermatitis by inhibition NFκB-mediated gene transcription of one or more cytokines involved in the pathogenesis of dermatitis. In some embodiments, a chemerin C15 peptide topical formulation is administered to treat inflammation associated with dermatitis.

*Bullous Disorders*

**[00101]** Disclosed herein are methods of treating bullous disorders in an individual in need thereof comprising administering a chemerin C15 peptide disclosed herein or a topical formulation comprising a chemerin C15 peptide disclosed herein. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is a salt of a chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is carboxylated. In some embodiments, the chemerin C15 peptide is amidated. In some embodiments, the chemerin C15 peptide is cyclic. In some embodiments, the chemerin C15 peptide is at least 80%, 85%, 90%,

91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9% homologous to a naturally occurring chemerin C15 peptide.

**[00102]** In certain instances, a bullous disorder is characterized by the formation of blisters (i.e., the accumulation of fluid between cells in the upper layers of the skin). In certain instances, bullous disorders are immune disorders in which the immune system attacks the skin and causes blistering. In certain instances, a bullous disorder is associated with the induction of an inflammatory response. High levels of cytokines such as IL-6 and TNF-α have been found in blister of patients with bullous pemphigoid (Rhodes et al. (1999) *Acta Dermato-Venereologica* 79(4):288).

**[00103]** Bullous disorders include, but are not limited to, bullous pemphigoid, pemphigus vulgaris, pemphigus vegetans, pemphigus foliaceous, paraneoplastic pemphigus, mucous membrane pemphigoid, linear IgA bullous disease, dermatitis herpeti-formis, and epidermolysis bullosa acquisita.

**[00104]** In some embodiments, a chemerin C15 peptide topical formulation is administered to treat inflammation associated with a bullous disorder. In some embodiments, a chemerin C15 peptide topical formulation is administered to treat a bullous disorder by inhibition of antigen presenting cells, such as dendritic cells or macrophages. In some embodiments, a chemerin C15 peptide topical formulation is administered to treat a bullous disorder through inhibition of the production of one or more inflammatory cytokines. In some embodiments, a chemerin C15 peptide topical formulation is administered to treat dermatitis through inhibition NFκB-mediated gene transcription of one or more cytokines involved in the pathogenesis of a bullous disorder.

*Eczema*

**[00105]** Disclosed herein are methods of treating eczema in an individual in need thereof comprising administering a chemerin C15 peptide disclosed herein or a topical formulation comprising a chemerin C15 peptide disclosed herein. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is a salt of a chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is carboxylated. In some embodiments, the chemerin C15 peptide is amidated. In some embodiments, the chemerin C15 peptide is cyclic. In some embodiments, the chemerin C15 peptide is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9% homologous to a naturally occurring chemerin C15 peptide.

**[00106]** . As used herein, eczema is a chronic inflammatory state of the skin. In some embodiments, a chemerin C15 peptide topical formulation is administered to treat inflammation associated with eczema. In some embodiments, a chemerin C15 peptide topical formulation is

administered to treat eczema by inhibition of antigen presenting cells, such as dendritic cells or macrophages. In some embodiments, a chemerin C15 peptide topical formulation is administered to treat eczema through inhibition of the production of one or more inflammatory cytokines. In some embodiments, a chemerin C15 peptide topical formulation is administered to treat eczema through inhibition NFκB-mediated gene transcription of one or more cytokines involved in the pathogenesis of eczema.

*Urticaria*

**[00107]** Disclosed herein are methods of treating urticaria in an individual in need thereof comprising administering a chemerin C15 peptide disclosed herein or a topical formulation comprising a chemerin C15 peptide disclosed herein. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is a salt of a chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is carboxylated. In some embodiments, the chemerin C15 peptide is amidated. In some embodiments, the chemerin C15 peptide is cyclic. In some embodiments, the chemerin C15 peptide is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9% homologous to a naturally occurring chemerin C15 peptide.

**[00108]** In certain instances, urticaria results from (either partially or fully) hypersensitivity or another immune disorder. Dermatographic urticaria is one of the most common types of urticaria in which the skin becomes raised and inflamed when scratched or rubbed.

**[00109]** In some embodiments, a chemerin C15 peptide topical formulation is administered to treat inflammation associated with urticaria. In some embodiments, a chemerin C15 peptide topical formulation is administered to treat urticaria by inhibition of antigen presenting cells, such as dendritic cells or macrophages. In some embodiments, a chemerin C15 peptide topical formulation is administered to treat urticaria through inhibition of the production of one or more inflammatory cytokines. In some embodiments, a chemerin C15 peptide topical formulation is administered to treat urticaria through inhibition NFκB-mediated gene transcription of one or more cytokines involved in the pathogenesis of inflammation associated with urticaria.

*Rosacea*

**[00110]** Disclosed herein are methods of treating rosacea in an individual in need thereof comprising administering a chemerin C15 peptide disclosed herein or a topical formulation comprising a chemerin C15 peptide disclosed herein. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is a salt of a chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is carboxylated. In some embodiments, the chemerin C15 peptide is amidated. In some embodiments, the chemerin

C15 peptide is cyclic. In some embodiments, the chemerin C15 peptide is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9% homologous to a naturally occurring chemerin C15 peptide.

**[00111]** As used herein, rosacea refers to any of erythematotelangiectatic rosacea (ETR), Papulopustular rosacea, and/or Phymatous rosacea. In some instances, rosacea is characterized by the release of release of cathelicidin antimicrobial peptides resulting in induction of proinflammatory cytokine release and an exacerbated innate immune response (Yamasaki et al. *Nature Medicine* 13, 975 - 980 (2007)).

**[00112]** In some embodiments, a chemerin C15 peptide topical formulation is administered to treat inflammation associated with rosacea. In some embodiments, a chemerin C15 peptide topical formulation is administered to treat rosacea by inhibition of antigen presenting cells, such as dendritic cells or macrophages. In some embodiments, a chemerin C15 peptide topical formulation is administered to treat rosacea through inhibition of the production of one or more inflammatory cytokines. In some embodiments, a chemerin C15 peptide topical formulation is administered to treat rosacea through inhibition NFκB-mediated gene transcription of one or more cytokines involved in the pathogenesis of rosacea.

*Skin ulcers*

**[00113]** Disclosed herein are methods of treating skin ulcers in an individual in need thereof comprising administering a chemerin C15 peptide disclosed herein or a topical formulation comprising a chemerin C15 peptide disclosed herein. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is a salt of a chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is carboxylated. In some embodiments, the chemerin C15 peptide is amidated. In some embodiments, the chemerin C15 peptide is cyclic. In some embodiments, the chemerin C15 peptide is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9% homologous to a naturally occurring chemerin C15 peptide.

**[00114]** As used herein, an ulcer is a disorder of the skin characterized by degradation of the epidermis and often portions of the dermis and even subcutaneous fat. In certain instances, ulcers are areas of necrotic tissue. In certain instances, ulcers result from immune system dysfunction (e.g., the improper functioning of neutrophils) and are associated with inflammation.

**[00115]** In some embodiments, a chemerin C15 peptide topical formulation is administered to treat inflammation associated with a skin ulcer. In some embodiments, a chemerin C15 peptide topical formulation is administered to treat a skin ulcer by inhibition of antigen presenting cells, such as dendritic cells or macrophages. In some embodiments, a chemerin C15 peptide topical formulation

is administered to treat a skin ulcer through inhibition of the production of one or more inflammatory cytokines. In some embodiments, a chemerin C15 peptide topical formulation is administered to treat a skin ulcer through inhibition NFκB-mediated gene transcription of one or more cytokines involved in the pathogenesis of a skin ulcer.

*Scarring*

**[00116]** Disclosed herein are methods of treating scarring in an individual in need thereof comprising administering a chemerin C15 peptide disclosed herein or a topical formulation comprising a chemerin C15 peptide disclosed herein. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is a salt of a chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is carboxylated. In some embodiments, the chemerin C15 peptide is amidated. In some embodiments, the chemerin C15 peptide is cyclic. In some embodiments, the chemerin C15 peptide is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9% homologous to a naturally occurring chemerin C15 peptide.

**[00117]** As used herein, scarring refers to the formation of a scar. In one aspect, the scar is a hypertrophic scar, or keloid scar, or a scar resulting from acne. In certain instances, a scar is an area of fibrous tissue that results from the overproduction of collagen. In certain instances, wound healing comprises the migration of fibroblasts to the site of injury. In certain instances, fibroblasts deposit collagen. In certain instances, fibroblasts deposit excess collagen at the wound site, resulting (either partially or fully) in a scar.

**Topical formulations**

**[00118]** Disclosed herein, in certain embodiments, are chemerin C15 peptides. Further disclosed herein are topical formulations comprising a chemerin C15 peptide and optionally a pharmaceutically acceptable excipient. Additionally disclosed herein are methods of treating inflammatory dermatological disorders in an individual in need thereof comprising administering a chemerin C15 peptide disclosed herein or a topical formulation comprising a chemerin C15 peptide disclosed herein. Further disclosed herein are methods of inhibiting the activity of an inflammatory cytokine or chemokine in an individual in need thereof comprising administering a chemerin C15 peptide disclosed herein or a topical formulation comprising a chemerin C15 peptide disclosed herein. Also disclosed herein, in certain embodiments, are method of inhibiting inhibits nuclear translocation or NFκB-mediated gene transcription of an inflammatory cytokine in an individual in need thereof comprising administering a chemerin C15 peptide disclosed herein or a topical formulation comprising a chemerin C15 peptide disclosed herein. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide. In some embodiments, the chemerin C15

peptide is a salt of a chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is carboxylated. In some embodiments, the chemerin C15 peptide is amidated. In some embodiments, the chemerin C15 peptide is cyclic. In some embodiments, the chemerin C15 peptide is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9% homologous to a naturally occurring chemerin C15 peptide.

**[00119]** In some embodiments, a topical formulation disclosed herein facilitates the delivery of a chemerin C15 peptide to the skin. In some embodiments, a topical formulation disclosed herein facilitates the delivery of a chemerin C15 peptide to the skin for a local effect (i.e., an effect that is limited to the skin). In certain instances, local administration of a chemerin C15 peptide reduces or eliminates side-effects that are associated with systemic administration of a chemerin C15 peptide. In some embodiments, a topical formulation of a chemerin C15 peptide disclosed herein does not result in a systemic effect, or substantially reduces the any systemic effect.

**[00120]** Topical formulations include, but are not limited to, aerosols, liquids, ointments, creams, lotions, solutions, suspensions, emulsions, pastes, gels, powders, salves, plasters, paints, foams, sticks, slow release nanoparticles, slow release microparticles, bioadhesives, patches, bandages and wound dressings. In some embodiments, the formulations comprise liposomes, micelles, and/or microspheres. In some embodiments, a pharmaceutically acceptable formulation includes any carrier suitable for use on human skin or mucosal surface.

*Ointments*

**[00121]** Disclosed herein are topical ointments comprising a chemerin C15 peptide and optionally a pharmaceutically acceptable excipient. Additionally disclosed herein are methods of treating inflammatory dermatological disorders in an individual in need thereof comprising administering a topical ointment comprising a chemerin C15 peptide disclosed herein. Further disclosed herein are methods of inhibiting the activity of an inflammatory cytokine or chemokine in an individual in need thereof comprising administering a topical ointment comprising a chemerin C15 peptide disclosed herein. Also disclosed herein, in certain embodiments, are method of inhibiting inhibits nuclear translocation or NFκB-mediated gene transcription of an inflammatory cytokine in an individual in need thereof comprising administering a topical ointment comprising a chemerin C15 peptide disclosed herein. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is a salt of a chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is carboxylated. In some embodiments, the chemerin C15 peptide is amidated. In some embodiments, the chemerin C15 peptide is cyclic. In some embodiments, the chemerin C15 peptide is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%,

95%, 96%, 97%, 98%, 99%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9% homologous to a naturally occurring chemerin C15 peptide.

**[00122]** Ointments, as is well known in the art of pharmaceutical formulation, are semi-solid preparations that are typically based on petrolatum or other petroleum derivatives. As an ointment, the composition has a consistency suitable for uniform dermal application. In some embodiments, the ointment is substantially viscous to remain in contact with the skin regardless of perspiration, excess moisture or environmental conditions. The specific ointment base to be used, as will be appreciated by those skilled in the art, is one that will provide for optimum drug delivery, and, will provide for other desired characteristics as well, e.g., emolliency or the like. As with other carriers or vehicles, an ointment base should be inert, stable, nonirritating and nonsensitizing. As explained in Remington: The Science and Practice of Pharmacy, 19th Ed. (Easton, Pa.: Mack Publishing Co., 1995), at pages 1399-1404, ointment bases are, for example, grouped in four classes: oleaginous bases; emulsifiable-bases; emulsion bases; and water-soluble bases. Oleaginous ointment bases include, for example, vegetable oils, fats obtained from animals, and semisolid hydrocarbons obtained from petroleum. Emulsifiable ointment bases, also known as absorbent ointment bases, contain little or no water and include, for example, hydroxystearin sulfate, anhydrous lanolin and hydrophilic petrolatum. Emulsion ointment bases are either water-in-oil (W/O) emulsions or oil-in-water (O/W) emulsions, and include, for example, cetyl alcohol, glyceryl monostearate, lanolin, and stearic acid. Some water-soluble ointment bases are prepared from polyethylene glycols of varying molecular weight; again, see Remington: The Science and Practice of Pharmacy for further information. In certain instances, ointments are semisolid preparations that soften or melt at body temperature. In certain instances, ointments re-hydrate the skin and are thus useful for dermatological disorders characterized by loss of moisture.

**[00123]** In some embodiments, the ointment comprises about 0.1-100 mg of chemerin C15 peptide per gram of ointment. In some embodiments, the ointment comprises about 1-10 mg of a chemerin C15 peptide per gram of ointment. In some embodiments, the ointment comprises about 1-100 mg of a chemerin C15 peptide per gram of ointment. In some embodiments, the ointment comprises about 1-10 mg of a chemerin C15 peptide per gram of ointment. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide.

**[00124]** In some embodiments, the ointment comprises petrolatum. In some embodiments, the ointment comprises about 50% petrolatum. In some embodiments, the ointment comprises caprylic capric triglyceride. In some embodiments, the ointment comprises about 45% caprylic capric triglyceride. In some embodiments, the ointment comprises beeswax. In some embodiments, the

ointment comprises about 5% beeswax. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide.

**[00125]** In some embodiments, the ointment comprises a chemerin C15 peptide and petrolatum. In some embodiments, the ointment comprises a chemerin C15 peptide and caprylic capric triglyceride. In some embodiments, the ointment comprises a chemerin C15 peptide and beeswax. In some embodiments, the ointment comprises a chemerin C15 peptide, petrolatum, caprylic capric triglyceride, and beeswax. In one example of an ointment, the ointment comprises about 1-10 mg of a chemerin C15 peptide per gram of ointment, about 50% petrolatum, about 45% caprylic triglyceride and about 5% beeswax. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide.

**[00126]** In some embodiments, the ointment comprises butylated hydroxytoluene. In some embodiments, the ointment comprises about 0.02% w/w butylated hydroxytoluene. In some embodiments, the ointment comprises PEG. In some embodiments, the ointment comprises PEG 400. In some embodiments, the ointment comprises about 15% w/w PEG 400. In some embodiments, the ointment comprises Span 80. In some embodiments, the ointment comprises about 2% w/w Span 80. In some embodiments, the ointment comprises white wax. In some embodiments, the ointment comprises about 10% white wax. In some embodiments, the ointment comprises white petrolatum. In some embodiments, the ointment comprises about 71.98% w/w white petrolatum.

**[00127]** In some embodiments, the ointment comprises a chemerin C15 peptide, white wax, and white petrolatum. In some embodiments, the ointment comprises a chemerin C15 peptide, butylated hydroxytoluene, PEG 400, Span 80, white wax, and white petrolatum. In an example of an ointment, the ointment comprises about 1-10 mg a chemerin C15 peptide per gram of ointment, about 0.02% w/w butylated hydroxytoluene, about 15% w/w PEG 400, about 2% w/w Span 80, about 10% w/w white wax, and about 71.98% w/w white petrolatum. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide.

**[00128]** In some embodiments, the ointment comprises dimethyl isosorbide. In some embodiments, the ointment comprises about 10% w/w dimethyl isosorbide. In some embodiments, the ointment comprises butylated hydroxytoluene. In some embodiments, the ointment comprises about 0.02% w/w butylated hydroxytoluene. In some embodiments, the ointment comprises Span 80. In some embodiments, the ointment comprises about 2% w/w. In some embodiments, the ointment comprises white wax. In some embodiments, the ointment comprises about 10% w/w white wax. In some embodiments, the ointment comprises white petrolatum. In some embodiments, the ointment comprises about 76.98% w/w white petrolatum.

**[00129]** In some embodiments, the ointment comprises a chemerin C15 peptide, butylated dimethyl isosorbide, butylated hydroxytoluene , Span 80, white wax, and white petrolatum. In an example of an ointment, the ointment comprises about 1-10 mg of a chemerin C15 peptide per mg ointment, about 10% w/w dimethyl isosorbide, about 0.02% w/w butylated hydroxytoluene , about 2% w/w Span 80, about 10% w/w white wax, and about 76.98% w/w white petrolatum. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide.

*Solutions*

**[00130]** Disclosed herein are topical solutions comprising a chemerin C15 peptide and optionally a pharmaceutically acceptable excipient. Additionally disclosed herein are methods of treating inflammatory dermatological disorders in an individual in need thereof comprising administering a topical solution comprising a chemerin C15 peptide disclosed herein. Further disclosed herein are methods of inhibiting the activity of an inflammatory cytokine or chemokine in an individual in need thereof comprising administering a topical solution comprising a chemerin C15 peptide disclosed herein. Also disclosed herein, in certain embodiments, are method of inhibiting inhibits nuclear translocation or NFκB-mediated gene transcription of an inflammatory cytokine in an individual in need thereof comprising administering a topical solution comprising a chemerin C15 peptide disclosed herein. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is a salt of a chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is carboxylated. In some embodiments, the chemerin C15 peptide is amidated. In some embodiments, the chemerin C15 peptide is cyclic. In some embodiments, the chemerin C15 peptide is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9% homologous to a naturally occurring chemerin C15 peptide.

**[00131]** Solutions, as well known in the art, are homogenous liquids comprising dissolved materials. In certain embodiments, solutions are water or organic solvent based. In certain embodiments, solutions comprise a chemerin C15 peptide along with additional components which enhance the penetration of a chemerin C15 peptide applied topically to the skin. In some embodiments, a solution comprising a chemerin C15 peptide is applied topically to the skin by painting with an applicator, as drops or as a spray. In some embodiments, the solution is applied from a pump spray bottle. In some embodiments, the solution is applied from an eye dropper.

**[00132]** In some embodiments, the solution comprises about 0.1-100 mg of a chemerin C15 peptide per mL of solution. In some embodiments, the solution comprises about 1-10 mg of a chemerin C15 peptide per mL of solution. In some embodiments, the solution comprises about 1-100 mg of a chemerin C15 peptide per mL of solution. In some embodiments, the solution

comprises about 1-10 mg of a chemerin C15 peptide per mL of solution. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide.

**[00133]** In some embodiments, the solution comprises isopropyl myristate. In some embodiments, the solution comprises alcohol. In some embodiments, the solution comprises undecylenic acid. In some embodiments, the solution comprises sodium lauryl sulfate.

**[00134]** In some embodiments, the solution comprises a chemerin C15 peptide, isopropyl myristate, alcohol, undecylenic acid and sodium lauryl sulfate. In one example of a solution, the solution contains about 1-10 mg of a chemerin C15 peptide per mL of solution, isopropyl myristate, alcohol, undecylenic acid and sodium lauryl sulfate. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide.

**[00135]** In some embodiments, the solution comprises isopropyl myristate. In some embodiments, the solution comprises about 45% isopropyl myristate. In some embodiments, the solution comprises isopropyl myristate alcohol. In some embodiments, the solution comprises about 45% isopropyl myristate alcohol. In some embodiments, the solution comprises undecylenic acid. In some embodiments, the solution comprises about 5% undecylenic acid. In some embodiments, the solution comprises sodium lauryl sulfate. In some embodiments, the solution comprises about 5% sodium lauryl sulfate.

**[00136]** In some embodiments, the solution comprises a chemerin C15 peptide, isopropyl myristate, alcohol, undecylenic acid, and sodium lauryl sulfate. In another example of a solution, the solution comprises about 1-10 mg of a chemerin C15 peptide per mL of solution, about 45% isopropyl myristate, about 45% alcohol, about 5% undecylenic acid and about 5% sodium lauryl sulfate. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide. In some embodiments, the solution is applied from a pump spray bottle.

**[00137]** In some embodiments, the solution comprises a chemerin C15 peptide, DMSO and water. In a another example of a solution, the solution comprises about 1-10 mg of a chemerin C15 peptide per mL of solution, about 50% DMSO, and about 50% water. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide. In some embodiments, the solution is applied from a pump spray bottle.

**[00138]** In another example of a solution, the solution comprises about 1-10 mg of a chemerin C15 peptide per ml solution in DMSO. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide. In some embodiments, the solution is applied from a pump spray bottle.

**[00139]** In some embodiments, the solution comprises dimethyl isosorbide. In some embodiments, the solution comprises about 15% w/w dimethyl isosorbide. In some embodiments, the solution comprises Transcutol. In some embodiments, the solution comprises about 25% w/w

Transcutol. In some embodiments, the solution comprises hexylene glycol. In some embodiments, the solution comprises about 12% w/w hexylene glycol. In some embodiments, the solution comprises propylene glycol. In some embodiments, the solution comprises about 5% w/w propylene glycol.

**[00140]** In some embodiments, the solution comprises dimethyl isosorbide, Transcutol, hexylene glycol, and propylene glycol. In another example of a solution, the solution comprises about 1-10 mg chemerin C15 peptide per ml solution, about 15% w/w dimethyl isosorbide, about 25% w/w Transcutol, about 12% w/w hexylene glycol, about 5% w/w propylene glycol, 25% Trolamine q.s. pH 4.5 and water to 100%. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide. In some embodiments, the solution is applied from a pump spray bottle.

**[00141]** In another example of a solution, the solution comprises about 1-10 mg chemerin C15 peptide per ml solution, about 15% w/w Dimethyl isosorbide, about 25% w/w Transcutol, about 12% w/w Hexylene glycol, about 5% w/w Propylene glycol, 25% Trolamine q.s. pH 6.0 and water to 100%. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide. In some embodiments, the solution is applied from a pump spray bottle.

*Creams and Lotions*

**[00142]** Disclosed herein are topical creams or lotions comprising a chemerin C15 peptide and optionally a pharmaceutically acceptable excipient. Additionally disclosed herein are methods of treating inflammatory dermatological disorders in an individual in need thereof comprising administering a topical creams or lotions comprising a chemerin C15 peptide disclosed herein. Further disclosed herein are methods of inhibiting the activity of an inflammatory cytokine or chemokine in an individual in need thereof comprising administering a topical creams or lotions comprising a chemerin C15 peptide disclosed herein. Also disclosed herein, in certain embodiments, are method of inhibiting inhibits nuclear translocation or NFκB-mediated gene transcription of an inflammatory cytokine in an individual in need thereof comprising administering a topical creams or lotions comprising a chemerin C15 peptide disclosed herein. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is a salt of a chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is carboxylated. In some embodiments, the chemerin C15 peptide is amidated. In some embodiments, the chemerin C15 peptide is cyclic. In some embodiments, the chemerin C15 peptide is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9% homologous to a naturally occurring chemerin C15 peptide.

**[00143]** Creams, as also well known in the art, are viscous liquids or semi-solid emulsions, either oil-in-water or water-in-oil. Cream bases are water-washable, and contain an oil phase, an

emulsifier, and an aqueous phase. The oil phase, also called the "internal" phase, is generally comprised of petrolatum and a fatty alcohol such as cetyl or stearyl alcohol. The aqueous phase usually, although not necessarily, exceeds the oil phase in volume, and generally contains a humectant. The emulsifier in a cream formulation is generally a nonionic, anionic, cationic, or amphoteric surfactant. In certain instances, creams are semisolid (e.g., soft solid or thick liquid) formulations that include a chemerin C15 peptide dispersed in an oil-in-water emulsion or a water-in-oil emulsion. Disclosed herein, in certain embodiments, is a topical formulation of a chemerin C15 peptide wherein the topical formulation is in the form of a lotion. In certain instances, lotions are fluid emulsions (e.g., oil-in-water emulsions or a water-in-oil emulsions). In some embodiments, the hydrophobic component of a lotion and/or cream is derived from an animal (e.g., lanolin, cod liver oil, and ambergris), plant (e.g., safflower oil, castor oil, coconut oil, cottonseed oil, menhaden oil, palm kernel oil, palm oil, peanut oil, soybean oil, rapeseed oil, linseed oil, rice bran oil, pine oil, sesame oil, or sunflower seed oil), or petroleum (e.g., mineral oil, or petroleum jelly).

**[00144]** In certain instances, lotions and creams have a "drying" effect on dermatological disorders (e.g., some or all fluid exuded from the disorder is miscible in the ointment) and are thus useful for dermatological disorders characterized by the exudation of fluids.

**[00145]** In some embodiments, the cream comprises about 0.1-100 mg of a chemerin C15 peptide per ml cream. In some embodiments, the cream comprises about 1-10 mg of a chemerin C15 peptide per ml cream. In some embodiments, the cream comprises about 1-100 mg of a chemerin C15 peptide per ml cream. In some embodiments, the cream comprises about 1-10 mg of a chemerin C15 peptide per ml cream. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide.

**[00146]** In some embodiments, the lotion comprises about 0.1-100 mg of a chemerin C15 peptide per ml lotion. In some embodiments, the lotion comprises about 1-10 mg of a chemerin C15 peptide per ml lotion. In some embodiments, the lotion comprises about 1-100 mg of a chemerin C15 peptide per ml lotion. In some embodiments, the lotion comprises about 1-10 mg of a chemerin C15 peptide per ml lotion. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide.

**[00147]** In some embodiments, the lotion comprises dimethyl isosorbide. In some embodiments, the lotion comprises about 13% w/w dimethyl isosorbide. In some embodiments, the lotion comprises Transcutol. In some embodiments, the lotion comprises about 20% w/w Transcutol. In some embodiments, the lotion comprises Hexylene glycol. In some embodiments, the lotion comprises about 10% w/w Hexylene glycol. In some embodiments, the lotion comprises Propylene

glycol. In some embodiments, the lotion comprises about 4% w/w Propylene glycol. In some embodiments, the lotion comprises Methylparaben. In some embodiments, the lotion comprises about 0.015% w/w Methylparaben. In some embodiments, the lotion comprises Propylparaben. In some embodiments, the lotion comprises about 0.05% w/w Propylparaben. In some embodiments, the lotion comprises EDTA. In some embodiments, the lotion comprises about 0.01% w/w EDTA. In some embodiments, the lotion comprises Carbopol Ultrez 10. In some embodiments, the lotion comprises about 0.5% w/w Carbopol Ultrez 10. In some embodiments, the lotion comprises Penmulen TR-1. In some embodiments, the lotion comprises about 0.2% w/w Penmulen TR-1. In some embodiments, the lotion comprises Isopropyl myristate. In some embodiments, the lotion comprises about 3% w/w Isopropyl myristate. In some embodiments, the lotion comprises Oleyl alcohol. In some embodiments, the lotion comprises about 5% w/w Oleyl alcohol. In some embodiments, the lotion comprises about 0.2% w/w Butylated hydroxytoluene. In some embodiments, the lotion comprises White petrolatum. In some embodiments, the lotion comprises about 5% w/w White petrolatum. In some embodiments, the pH of the lotion is adjusted to about 4.0 to 6.0. with Trolamine. In some embodiments, the pH of the lotion is adjusted to about 4.0 to 6.0 with Trolamine.

**[00148]** In some embodiments, the lotion comprises a chemerin C15 peptide, Dimethyl isosorbide, Transcutol, Hexylene glycol, Propylene glycol, Methylparaben, Propylparaben, EDTA, Carbopol Ultrez 10, Penmulen TR-1, and Butylated hydroxytoluene. In some embodiments, the lotion comprises a chemerin C15 peptide, Dimethyl isosorbide, Transcutol, Hexylene glycol, Propylene glycol, Methylparaben, Propylparaben, EDTA, Carbopol Ultrez 10, Penmulen TR-1, Isopropyl myristate, Oleyl alcohol, Butylated hydroxytoluene, and White petrolatum. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide.

**[00149]** In one example of a lotion, the lotion comprises about 1-10 mg of a chemerin C15 peptide per ml lotion, about 13% w/w Dimethyl isosorbide, about 20% w/w Transcutol, about 10% w/w Hexylene glycol, about 4% w/w Propylene glycol, about 0.015% w/w Methylparaben, about 0.05% w/w Propylparaben, about 0.01% w/w EDTA, about 0.5% w/w Carbopol Ultrez 10, about 0.2% w/w Penmulen TR-1, about 3% w/w Isopropyl myristate, about 5% w/w Oleyl alcohol, about 0.2% w/w Butylated hydroxytoluene, about 5% w/w White petrolatum, 25% Trolamine q.s. pH 6.0 and water to 100%. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide.

**[00150]** In some embodiments, the lotion comprises Cetyl alcohol. In some embodiments, the lotion comprises about 2% w/w Cetyl alcohol. In some embodiments, the lotion comprises Light mineral oil. In some embodiments, the lotion comprises about 5.5% w/w Light mineral oil. In

some embodiments, the lotion comprises Oleic acid. In some embodiments, the lotion comprises about 5% w/w Oleic acid.

**[00151]** In some embodiments, the lotion comprises a chemerin C15 peptide, Dimethyl isosorbide, Transcutol, Hexylene glycol, Propylene glycol, Methylparaben, Propylparaben, EDTA, Carbopol Ultrez 10, Penmulen TR-1, Cetyl alcohol, Light mineral oil, Oleic acid, Butylated hydroxytoluene. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide.

**[00152]** In another example of a lotion, the lotion comprises about 1-10 mg of a chemerin C15 peptide per ml lotion, about 13% w/w Dimethyl isosorbide, about 20% w/w Transcutol, about 10% w/w Hexylene glycol, about 4% w/w Propylene glycol, about 0.015% w/w Methylparaben, about 0.05% w/w Propylparaben, about 0.01% w/w EDTA, about 0.3% w/w Carbopol Ultrez 10, about 0.2% w/w Penmulen TR-1, about 2% w/w Cetyl alcohol, about 5.5% w/w Light mineral oil, about 5% w/w Oleic acid, 0.2% w/w Butylated hydroxytoluene, 25% Trolamine q.s. pH 6.0 and water to 100%. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide.

*Gels*

**[00153]** Disclosed herein are topical gels comprising a chemerin C15 peptide and optionally a pharmaceutically acceptable excipient. Additionally disclosed herein are methods of treating inflammatory dermatological disorders in an individual in need thereof comprising administering a topical gel comprising a chemerin C15 peptide disclosed herein. Further disclosed herein are methods of inhibiting the activity of an inflammatory cytokine or chemokine in an individual in need thereof comprising administering a topical gel comprising a chemerin C15 peptide disclosed herein. Also disclosed herein, in certain embodiments, are method of inhibiting inhibits nuclear translocation or NFκB-mediated gene transcription of an inflammatory cytokine in an individual in need thereof comprising administering a topical gel comprising a chemerin C15 peptide disclosed herein. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is a salt of a chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is carboxylated. In some embodiments, the chemerin C15 peptide is amidated. In some embodiments, the chemerin C15 peptide is cyclic. In some embodiments, the chemerin C15 peptide is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9% homologous to a naturally occurring chemerin C15 peptide.

**[00154]** Gels are semi-solid, suspension-type systems and are well known in the art. Gel forming agent for use herein can be any gelling agent typically used in the pharmaceutical art for topical semi solid dosage forms. Single-phase gels contain organic macromolecules distributed

substantially uniformly throughout the carrier liquid, which is typically aqueous, but also can contain an alcohol and optionally an oil. In order to prepare a uniform gel, dispersing agents such as alcohol or glycerin can be added, or the gelling agent can be dispersed by tritration, mechanical mixing or stirring, or combinations thereof. The amount of gelling agents varies widely and will ordinarily range from about 0.1% to about 2.0% by weight, based on the total weight of the composition. The gel forming agent also works by the principle of copolymerization. Under alkaline pH, carbomer in presence of water undergoes cross linking and forms a gel like structure. The degree of polymerization is dependent upon the pH. At a threshold pH, the viscosities achieved by the polymer grade are the maximum. In certain instances, gels are semisolid (or semi-rigid) systems consisting of dispersions of large organic molecules dispersed in a liquid. In certain instances, gels are water-soluble and are removed using warm water or saline. In certain instances, gels re-hydrate the skin and are thus useful for dermatological disorders characterized by loss of moisture.

**[00155]** In some embodiments, the gel comprises about 0.1-100 mg of a chemerin C15 peptide per ml gel. In some embodiments, the gel comprises about 1-10 mg of a chemerin C15 peptide per ml gel. In some embodiments, the gel comprises about 1-100 mg of a chemerin C15 peptide per ml gel. In some embodiments, the gel comprises about 1-10 mg of a chemerin C15 peptide per ml gel. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide.

**[00156]** In some embodiments, the lotion comprises dimethyl isosorbide. In some embodiments, the lotion comprises about 15% w/w dimethyl isosorbide. In some embodiments, the lotion comprises Transcutol. In some embodiments, the lotion comprises about 25% w/w Transcutol. In some embodiments, the lotion comprises Hexylene glycol. In some embodiments, the lotion comprises about 12% w/w Hexylene glycol. In some embodiments, the lotion comprises Propylene glycol. In some embodiments, the lotion comprises about 5% w/w Propylene glycol. In some embodiments, the lotion comprises Methylparaben. In some embodiments, the lotion comprises about 0.015% w/w Methylparaben. In some embodiments, the lotion comprises Propylparaben. In some embodiments, the lotion comprises about 0.05% w/w Propylparaben. In some embodiments, the gel comprises EDTA. In some embodiments, the gel comprises about 0.01% w/w EDTA. In some embodiments, the gel comprises Penmulen TR-1. In some embodiments, the gel comprises about 0.5% w/w Penmulen TR-1. In some embodiments, the gel comprises Hydroxyethyl cellulose. In some embodiments, the gel comprises about 1% w/w Hydroxyethyl cellulose.

**[00157]** In some embodiments, the gel comprises a chemerin C15 peptide, Dimethyl isosorbide, Transcutol, Hexylene glycol, Propylene glycol, Methylparaben, Propylparaben, and EDTA. In some embodiments, the gel comprises a chemerin C15 peptide, Dimethyl isosorbide, Transcutol,

Hexylene glycol, Propylene glycol, Methylparaben, Propylparaben, EDTA, and Penmulen TR-1. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide.

**[00158]** In one example of a gel, the gel comprises about 1-10 mg of a chemerin C15 peptide per ml gel, about 15% w/w Dimethyl isosorbide, about 25% w/w Transcutol, about 12% w/w Hexylene glycol, about 5% w/w Propylene glycol, about 0.015% w/w Methylparaben, about 0.05% w/w Propylparaben, about 0.01% w/w EDTA, about 0.5% w/w Penmulen TR-1, 25% Trolamine q.s. pH 6.0 and water to 100%. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide.

**[00159]** In some embodiments, the gel comprises a chemerin C15 peptide, Dimethyl isosorbide, Transcutol, Hexylene glycol, Propylene glycol, Methylparaben, Propylparaben, EDTA, and hydroxyethylcellulose. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide.

**[00160]** In another example of a gel, the gel comprises about 1-10 mg of a chemerin C15 peptide per ml gel, about 15% w/w Dimethyl isosorbide, about 25% w/w Transcutol, about 12% w/w Hexylene glycol, about 5% w/w Propylene glycol, about 0.015% w/w Methylparaben, about 0.05% w/w Propylparaben, about 0.01% w/w EDTA, about 1% w/w Hydroxyethyl cellulose, 25% Trolamine q.s. pH 4.5 and water to 100%. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide.

*Pastes*

**[00161]** Disclosed herein are topical pastes comprising a chemerin C15 peptide and optionally a pharmaceutically acceptable excipient. Additionally disclosed herein are methods of treating inflammatory dermatological disorders in an individual in need thereof comprising administering a topical paste comprising a chemerin C15 peptide disclosed herein. Further disclosed herein are methods of inhibiting the activity of an inflammatory cytokine or chemokine in an individual in need thereof comprising administering a topical paste comprising a chemerin C15 peptide disclosed herein. Also disclosed herein, in certain embodiments, are method of inhibiting inhibits nuclear translocation or NFκB-mediated gene transcription of an inflammatory cytokine in an individual in need thereof comprising administering a topical paste comprising a chemerin C15 peptide disclosed herein. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is a salt of a chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is carboxylated. In some embodiments, the chemerin C15 peptide is amidated. In some embodiments, the chemerin C15 peptide is cyclic. In some embodiments, the chemerin C15 peptide is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%,

99%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9% homologous to a naturally occurring chemerin C15 peptide.

**[00162]** Pastes are semi-solid dosage forms in which the active agent is suspended in a suitable base. Depending on the nature of the base, pastes are divided between fatty pastes or those made from a single-phase aqueous gels. The base in a fatty paste is generally petrolatum or hydrophilic petrolatum or the like. The pastes made from single-phase aqueous gels generally incorporate carboxymethylcellulose or the like as a base. In certain instances, pastes contain at least 20% solids. In certain instances, pastes are ointments that do not flow at body temperature. In certain instances, pastes re-hydrate the skin and are thus useful for dermatological disorders characterized by loss of moisture. In certain instances, pastes serve as protective coatings over areas to which they are applied.

**[00163]** In some embodiments, the solution comprises about 0.1-100 mg of a chemerin C15 peptide per gram paste. In some embodiments, the solution comprises about 1-10 mg of a chemerin C15 peptide per gram paste. In some embodiments, the solution comprises about 1-100 mg of a chemerin C15 peptide per gram paste. In some embodiments, the solution comprises about 1-10 mg of a chemerin C15 peptide per gram paste. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide.

*Plasters*

**[00164]** Disclosed herein are topical plasters comprising a chemerin C15 peptide and optionally a pharmaceutically acceptable excipient. Additionally disclosed herein are methods of treating inflammatory dermatological disorders in an individual in need thereof comprising administering a topical plaster comprising a chemerin C15 peptide disclosed herein. Further disclosed herein are methods of inhibiting the activity of an inflammatory cytokine or chemokine in an individual in need thereof comprising administering a topical plaster comprising a chemerin C15 peptide disclosed herein. Also disclosed herein, in certain embodiments, are method of inhibiting inhibits nuclear translocation or NFκB-mediated gene transcription of an inflammatory cytokine in an individual in need thereof comprising administering a topical plaster comprising a chemerin C15 peptide disclosed herein. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is a salt of a chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is carboxylated. In some embodiments, the chemerin C15 peptide is amidated. In some embodiments, the chemerin C15 peptide is cyclic. In some embodiments, the chemerin C15 peptide is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%,

95%, 96%, 97%, 98%, 99%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9% homologous to a naturally occurring chemerin C15 peptide.

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**[00165]** Plasters are comprised of a pasty mixture that is spread on the body, either directly or after being saturated into a base material such as cloth. In some embodiments, medications, including the pharmacologically active compositions of the invention, are dissolved or dispersed within the plaster to make a medicated plaster.

**[00166]** In some embodiments, the plaster comprises about 0.1-100 mg of a chemerin C15 peptide per gram plaster. In some embodiments, the plaster comprises about 1-10 mg of a chemerin C15 peptide per gram plaster. In some embodiments, the plaster comprises about 1-100 mg of a chemerin C15 peptide per gram plaster. In some embodiments, the plaster comprises about 1-10 mg of a chemerin C15 peptide per gram plaster. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide.

*Sticks*

**[00167]** Disclosed herein are topical sticks comprising a chemerin C15 peptide and optionally a pharmaceutically acceptable excipient. Additionally disclosed herein are methods of treating inflammatory dermatological disorders in an individual in need thereof comprising administering a topical stick comprising a chemerin C15 peptide disclosed herein. Further disclosed herein are methods of inhibiting the activity of an inflammatory cytokine or chemokine in an individual in need thereof comprising administering a topical stick comprising a chemerin C15 peptide disclosed herein. Also disclosed herein, in certain embodiments, are method of inhibiting inhibits nuclear translocation or NFκB-mediated gene transcription of an inflammatory cytokine in an individual in need thereof comprising administering a topical stick comprising a chemerin C15 peptide disclosed herein. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is a salt of a chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is carboxylated. In some embodiments, the chemerin C15 peptide is amidated. In some embodiments, the chemerin C15 peptide is cyclic. In some embodiments, the chemerin C15 peptide is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9% homologous to a naturally occurring chemerin C15 peptide.

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**[00168]** In certain instances, sticks are solid dosage forms that melt at body temperature. In some embodiments, a stick comprises a wax, a polymer, a resin, dry solids fused into a firm mass, and/or fused crystals. In some embodiments, a topical formulation of a chemerin C15 peptide is in the

form of a styptic pencil (i.e., a stick prepared by (1) heating crystals until they lose their water of crystallization and become molten, and (2) pouring the molten crystals into molds and allowing them to harden). In some embodiments, a topical formulation of a chemerin C15 peptide is in the form of stick wherein the stick comprises a wax (e.g., the wax is melted and poured into appropriate molds in which they solidify in stick form).

**[00169]** In some embodiments, a topical formulation of a chemerin C15 peptide is in the form of stick wherein the stick comprises a melting base (i.e., a base that softens at body temperature). Examples of melting bases include, but are not limited to, waxes, oils, polymers and gels. In some embodiments, a topical formulation of a chemerin C15 peptide is in the form of stick wherein the stick comprises a moisten base (i.e., a base that is activated by the addition of moisture).

**[00170]** In some embodiments, the solution comprises about 0.1-100 mg of a chemerin C15 peptide per gram of the stick. In some embodiments, the solution comprises about 1-10 mg of a chemerin C15 peptide per gram of the stick. In some embodiments, the solution comprises about 1-100 mg of a chemerin C15 peptide per gram of the stick. In some embodiments, the solution comprises about 1-10 mg of a chemerin C15 peptide per gram of the stick. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide.

*Bioadhesives*

**[00171]** Disclosed herein are topical bioadhesives comprising a chemerin C15 peptide and optionally a pharmaceutically acceptable excipient. Additionally disclosed herein are methods of treating inflammatory dermatological disorders in an individual in need thereof comprising administering a topical bioadhesive comprising a chemerin C15 peptide disclosed herein. Further disclosed herein are methods of inhibiting the activity of an inflammatory cytokine or chemokine in an individual in need thereof comprising administering a topical bioadhesive comprising a chemerin C15 peptide disclosed herein. Also disclosed herein, in certain embodiments, are method of inhibiting inhibits nuclear translocation or NFκB-mediated gene transcription of an inflammatory cytokine in an individual in need thereof comprising administering a topical bioadhesive comprising a chemerin C15 peptide disclosed herein. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is a salt of a chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is carboxylated. In some embodiments, the chemerin C15 peptide is amidated. In some embodiments, the chemerin C15 peptide is cyclic. In some embodiments, the chemerin C15 peptide is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9% homologous to a naturally occurring chemerin C15 peptide.

**[00172]** Bioadhesives are preparations that adhere to surfaces of body tissues. Polymeric bioadhesive formulations are well known in the art; see, for example, Heller et al., "Biodegradable polymers as drug delivery systems", in Chasin, M. and Langer, R., eds.: Dekker, N. Y., pp. 121-161 (1990); and U.S. Pat. No. 6,201,065. Suitable non-polymeric bioadhesives are also known in the art, including certain fatty acid esters (U.S. Pat. No. 6,228,383).

**[00173]** Disclosed herein, in certain embodiments, is a topical formulation of a chemerin C15 peptide wherein the topical formulation is administered via a patch. In some embodiments, a topical formulation disclosed herein is dissolved and/or dispersed in a polymer or an adhesive. In some embodiments, a patch disclosed herein is constructed for continuous, pulsatile, or on demand delivery of a chemerin C15 peptide .

**[00174]** In some embodiments, the bioadhesive comprises about 0.1-100 mg of a chemerin C15 peptide. In some embodiments, the bioadhesive comprises about 1-10 mg of a chemerin C15 peptide. In some embodiments, the bioadhesive comprises about 1-100 mg of a chemerin C15 peptide. In some embodiments, the bioadhesive comprises about 1-10 mg of a chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide.

*Patches, Wound Dressings, and Bandages*

**[00175]** Disclosed herein are patches, wound dressings or bandages comprising a chemerin C15 peptide and optionally a pharmaceutically acceptable excipient. Additionally disclosed herein are methods of treating inflammatory dermatological disorders in an individual in need thereof comprising administering a patch, would dressing or bandage comprising a chemerin C15 peptide disclosed herein. Further disclosed herein are methods of inhibiting the activity of an inflammatory cytokine or chemokine in an individual in need thereof comprising administering a patch, would dressing or bandage comprising a chemerin C15 peptide disclosed herein. Also disclosed herein, in certain embodiments, are method of inhibiting inhibits nuclear translocation or NFκB-mediated gene transcription of an inflammatory cytokine in an individual in need thereof comprising administering a patch, would dressing or bandage comprising a chemerin C15 peptide disclosed herein. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is a salt of a chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is carboxylated. In some embodiments, the chemerin C15 peptide is amidated. In some embodiments, the chemerin C15 peptide is cyclic. In some embodiments, the chemerin C15 peptide is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9% homologous to a naturally occurring chemerin C15 peptide.

**[00176]** Wound dressings, patches and bandages include, but are not limited to gauzes, transparent film dressings, hydrogels, polyurethane foam dressings, hydrocolloids and alginates. In certain instances, wound dressings (1) maintain moisture in the wound, (2) are semipermeable, (3) are semiocclusive, (4) allow for autolytic debridement, (5) protect from external contaminants, (6) absorb exuded fluids, and/or (7) allow for wound visualization.

**[00177]** In some embodiments, the patch, wound dressing, or bandage comprises about 0.1-100 mg of a chemerin C15 peptide. In some embodiments, the patch, wound dressing, or bandage comprises about 1-10 mg of a chemerin C15 peptide. In some embodiments, the patch, wound dressing, or bandage comprises about 1-100 mg of a chemerin C15 peptide. In some embodiments, the patch, wound dressing, or bandage comprises about 1-10 mg of a chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide.

*Dermatological Excipients*

**[00178]** Disclosed herein are topical formulations comprising a chemerin C15 peptide and a pharmaceutically acceptable excipient. Additionally disclosed herein are methods of treating inflammatory dermatological disorders in an individual in need thereof comprising administering a chemerin C15 peptide disclosed herein or a topical formulation comprising a chemerin C15 peptide disclosed herein and a pharmaceutically acceptable excipient. Further disclosed herein are methods of inhibiting the activity of an inflammatory cytokine or chemokine in an individual in need thereof comprising administering a chemerin C15 peptide disclosed herein or a topical formulation comprising a chemerin C15 peptide disclosed herein and a pharmaceutically acceptable excipient. Also disclosed herein, in certain embodiments, are method of inhibiting inhibits nuclear translocation or NFκB-mediated gene transcription of an inflammatory cytokine in an individual in need thereof comprising administering a chemerin C15 peptide disclosed herein or a topical formulation comprising a chemerin C15 peptide disclosed herein and a pharmaceutically acceptable excipient. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is a salt of a chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is carboxylated. In some embodiments, the chemerin C15 peptide is amidated. In some embodiments, the chemerin C15 peptide is cyclic. In some embodiments, the chemerin C15 peptide is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9% homologous to a naturally occurring chemerin C15 peptide.

**[00179]** In some embodiments, the topical formulations described herein comprise one or more inert excipients, which include, but are not limited to, water, buffered aqueous solutions, surfactants, volatile liquids, starches, polyols, granulating agents, microcrystalline cellulose,

diluents, lubricants, acids, bases, salts, emulsions, such as oil/water emulsions, oils such as mineral oil and vegetable oil, wetting agents, chelating agents, antioxidants, sterile solutions, complexing agents, and disintegrating agents.

**[00180]** In some embodiments, the topical formulations described herein comprise one or more cosmetic or pharmaceutical agents commonly used in the skin care industry. Examples of such agents are described in, for example, CTFA Cosmetic Ingredient Handbook, Seventh Edition, 1997 and the Eighth Edition, 2000, which is incorporated by reference herein in its entirety. Examples of classes of such agents include, but are not limited to: abrasives, absorbents, aesthetic components such as fragrances, pigments, colorings/colorants, essential oils, skin sensates, astringents, etc. (e.g. clove oil, menthol, camphor, eucalyptus oil, eugenol, menthyl lactate, witch hazel distillate), anti-acne agents, anti-caking agents, antifoaming agents, antimicrobial agents (e.g., iodopropyl butylcarbamate), antioxidants, binders, biological additives, buffering agents, bulking agents, chelating agents, chemical additives, cosmetic biocides, denaturants, drug astringents, external analgesics, film formers or materials, opacifying agents, pH adjusters, propellants, reducing agents, sequestrants, skin bleaching and lightening agents (e.g. hydroquinone, kojic acid, ascorbic acid, magnesium ascorbyl phosphate, ascorbyl glucosamine), skin-conditioning agents (e.g. humectants), skin soothing and/or healing agents (e.g. panthenol and its derivatives, aloe vera, pantothenic acid and its derivatives, allantoin, bisabolol, and dipotassium glycyrrhizinate), skin protectants (e.g., sunscreens, or ultraviolet light absorbers or scattering agents), skin treating agents, thickeners, and vitamins and derivatives thereof. In some embodiments, a topical formulation of a chemerin C15 peptide comprises one or more of such agents.

**[00181]** In some embodiments, the topical formulations described herein comprise a gelling (or thickening) agent. In some embodiments, a topical formulation disclosed herein further comprises from about 0.1% to about 5%, more preferably from about 0.1% to about 3%, and most preferably from about 0.25% to about 2%, of a gelling agent. In certain embodiments, the viscosity of a topical formulation disclosed herein is in the range from about 100 to about 500,000 cP, about 100 cP to about 1,000 cP, about 500 cP to about 1500 cP, about 1000 cP to about 3000 cP, about 2000 cP to about 8,000 cP, about 4,000 cP to about 10,000 cP, about 10,000 cP to about 50,000 cP.

**[00182]** Suitable gelling agents for use in preparation of the gel topical formulation include, but are not limited to, celluloses, cellulose derivatives, cellulose ethers (e.g., carboxymethylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxymethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, methylcellulose), guar gum, xanthan gum, locust bean gum, alginates (e.g., alginic acid), silicates, starch, tragacanth, carboxyvinyl polymers, carrageenan, paraffin, petrolatum, acacia (gum arabic), agar, aluminum magnesium silicate, sodium alginate, sodium

stearate, bladderwrack, bentonite, carbomer, carrageenan, carbopol, xanthan, cellulose, microcrystalline cellulose (MCC), ceratonia, chondrus, dextrose, furcellaran, gelatin, ghatti gum, guar gum, hectorite, lactose, sucrose, maltodextrin, mannitol, sorbitol, honey, maize starch, wheat starch, rice starch, potato starch, gelatin, sterculia gum, polyethylene glycol (e.g. PEG 200-4500), gum tragacanth, ethyl cellulose, ethylhydroxyethyl cellulose, ethylmethyl cellulose, methyl cellulose, hydroxyethyl cellulose, hydroxyethylmethyl cellulose, hydroxypropyl cellulose, poly(hydroxyethyl methacrylate), oxypolygelatin, pectin, polygeline, povidone, propylene carbonate, methyl vinyl ether/maleic anhydride copolymer (PVM/MA), poly(methoxyethyl methacrylate), poly(methoxyethoxyethyl methacrylate), hydroxypropyl cellulose, hydroxypropylmethyl-cellulose (HPMC), sodium carboxymethyl-cellulose (CMC), silicon dioxide, polyvinylpyrrolidone (PVP: povidone), or combinations thereof.

**[00183]** In some embodiments, the topical formulations described herein comprise an emollient. Emollients include, but are not limited to, castor oil esters, cocoa butter esters, safflower oil esters, cottonseed oil esters, corn oil esters, olive oil esters, cod liver oil esters, almond oil esters, avocado oil esters, palm oil esters, sesame oil esters, squalene esters, kikui oil esters, soybean oil esters, acetylated monoglycerides, ethoxylated glyceryl monostearate, hexyl laurate, isohexyl laurate, isohexyl palmitate, isopropyl palmitate, methyl palmitate, decyloleate, isodecyl oleate, hexadecyl stearate decyl stearate, isopropyl isostearate, methyl isostearate, diisopropyl adipate, diisohexyl adipate, dihexyldecyl adipate, diisopropyl sebacate, lauryl lactate, myristyl lactate, and cetyl lactate, oleyl myristate, oleyl stearate, and oleyl oleate, pelargonic acid, lauric acid, myristic acid, palmitic acid, stearic acid, isostearic acid, hydroxystearic acid, oleic acid, linoleic acid, ricinoleic acid, arachidic acid, behenic acid, erucic acid, lauryl alcohol, myristyl alcohol, cetyl alcohol, hexadecyl alcohol, stearyl alcohol, isostearyl alcohol, hydroxystearyl alcohol, oleyl alcohol, ricinoleyl alcohol, behenyl alcohol, erucyl alcohol, 2-octyl dodecanyl alcohol, lanolin and lanolin derivatives, beeswax, spermaceti, myristyl myristate, stearyl stearate, carnauba wax, candelilla wax, lecithin, and cholesterol.

**[00184]** In some embodiments, the topical formulations described herein comprise an anti-oxidant. Anti-oxidants include, but are not limited to, propyl, octyl and dodecyl esters of gallic acid, butylated hydroxyanisole (BHA, usually purchased as a mixture of ortho and meta isomers), green tea extract, uric acid, cysteine, pyruvate, nordihydroguaiaretic acid, ascorbic acid, salts of ascorbic acid such as ascorbyl palmitate and sodium ascorbate, ascorbyl glucosamine, vitamin E (i.e., tocopherols such as a-tocopherol), derivatives of vitamin E (e.g., tocopheryl acetate), retinoids such as retinoic acid, retinol, trans-retinol, cis-retinol, mixtures of trans-retinol and cis-retinol, 3-dehydroretinol and derivatives of vitamin A (e.g., retinyl acetate, retinal and retinyl palmitate, also

known as tetinyl palmitate), sodium citrate, sodium sulfite, lycopene, anthocyanids, bioflavinoids (e.g., hesperitin, naringen, rutin and quercetin), superoxide dismutase, glutathione peroxidase, butylated hydroxytoluene (BHT), indole-3-carbinol, pycnogenol, melatonin, sulforaphane, pregnenolone, lipoic acid and 4-hydroxy-5-methyl-3[2H]-furanone.

**[00185]** In some embodiments, the topical formulations described herein comprise a skin protecting agent. Exemplary skin protecting agent include, but are not limited to, sunscreens, anti-acne additives, anti-wrinkle and anti-skin atrophy agents. Suitable sunscreens as skin protecting agents include 2-ethylhexyl p-methoxycinnamate, 2-ethylhexyl N,N-dimethyl-p-aminobenzoate, p-aminobenzoic acid, 2-phenylbenzimidazole-5-sulfonic acid, octocrylene, oxybenzone, homomethyl salicylate, octyl salicylate, 4,4'-methoxy-t-butyldibenzoylmethane, 4-isopropy dibenzoylmethane, 3-benzylidene camphor, 3-(4-methylbenzylidene) camphor, anthanilates, ultrafine titanium dioxide, zinc oxide, iron oxide, silica, 4-N,N-(2-ethylhexyl)methylaminobenzoic acid ester of 2,4-dihydroxybenzophenone, 4-N,N-(2-ethylhexyl)-methylaminobenzoic acid ester with 4-hydroxydibenzoylmethane, 4-N,N-(2-ethylhexyl)-methylaminobenzoic acid ester of 2-hydroxy-4-(2-hydroxyethoxy)benzophenone and 4-N,N(2-ethylhexyl)-methylaminobenzoic acid ester of 4-(2-hydroxyethoxy)dibenzoylmethane. Suitable anti-acne agents include salicylic acid; 5-octanoyl salicylic acid; resorcinol; retinoids such as retinoic acid and its derivatives; sulfur-containing D and L amino acids other than cysteine; lipoic acid; antibiotics and antimicrobials such as benzoyl peroxide, octopirox, tetracycline, 2,4,4'-trichloro-2'-hydroxydiphenyl ether, 3,4,4'-trichlorobanilide, azelaic acid, phenoxyethanol, phenoxypropanol, phenoxisopropanol, ethyl acetate, clindamycin and melclocycline; flavonoids; and bile salts such as scymnol sulfate, deoxycholate and cholate. Examples of anti-wrinkle and anti-skin atrophy agents are retinoic acid and its derivatives, retinol, retinyl esters, salicylic acid and its derivatives, sulfur-containing D and L amino acids except cysteine, alpha-hydroxy acids (e.g., glycolic acid and lactic acid), phytic acid, lipoic acid and lysophosphatidic acid.

**[00186]** In some embodiments, the topical formulations described herein comprise irritation-mitigating additives to minimize or eliminate the possibility of skin irritation or skin damage resulting from the permeation-enhancing base or other components of the composition. Exemplary irritation-mitigating additives include, but are not limited to, alpha-tocopherol; monoamine oxidase inhibitors, particularly phenyl alcohols such as 2-phenyl-1-ethanol; glycerin; salicylic acids and salicylates; ascorbic acids and ascorbates; ionophores such as monensin; amphiphilic amines; ammonium chloride; N-acetylcysteine; cis-urocanic acid; capsaicin; and chloroquine.

**[00187]** In some embodiments, the topical formulations described herein comprise a dry-feel modifier, which is an agent which when added to an emulsion, imparts a "dry feel" to the skin when

the emulsion dries. Exemplary dry-feel modifiers include, but are not limited to, talc, kaolin, chalk, zinc oxide, silicone fluids, inorganic salts such as barium sulfate, surface treated silica, precipitated silica, fumed silica such as an Aerosil available from Degussa Inc. of New York, N.Y. U.S.A. Another dry feel modifier is an epichlorohydrin cross-linked glyceryl starch of the type that is disclosed in U.S. Pat. No. 6,488,916.

**[00188]** In some embodiments, the topical formulations described herein comprise an antimicrobial agent to prevent spoilage upon storage, i.e., to inhibit growth of microbes such as yeasts and molds. Suitable antimicrobial agents are typically selected from the group consisting of the methyl and propyl esters of p-hydroxybenzoic acid (i.e., methyl and propyl paraben), sodium benzoate, sorbic acid, imidurea, purite, peroxides, perborates and combinations thereof.

**[00189]** In some embodiments, the topical formulations described herein comprise an aesthetic agent. Examples of aesthetic agents include fragrances, pigments, colorants, essential oils, skin sensates and astringents. Suitable aesthetic agents include clove oil, menthol, camphor, eucalyptus oil, eugenol, methyl lactate, bisabolol, witch hazel distillate and green tea extract.

**[00190]** In some embodiments, the topical formulations described herein comprise a fragrance. Fragrances are aromatic substances which can impart an aesthetically pleasing aroma. Typical fragrances include aromatic materials extracted from botanical sources (i.e., rose petals, gardenia blossoms, jasmine flowers, etc.) which can be used alone or in any combination to create essential oils. In some embodiment, alcoholic extracts are prepared for compounding fragrances. In some examples, the fragrance is a synthetically prepared fragrance. One or more fragrances can optionally be included in the sunscreen composition in an amount ranging from about 0.001 to about 5 weight percent, p or about 0.01 to about 0.5 percent by weight. In some embodiments, additional preservatives are used if desired and include, for example, well known preservative compositions such as benzyl alcohol, phenyl ethyl alcohol and benzoic acid, diazolydinyl, urea, chlorphenesin, iodopropynyl and butyl carbamate, among others.

**[00191]** In some embodiments, the topical formulations described herein comprise a surfactant. Surfactants which can be used to form pharmaceutical compositions and dosage forms provides herein include, but are not limited to, hydrophilic surfactants, lipophilic surfactants, and mixtures thereof. In some embodiments, a mixture of hydrophilic surfactants is employed. In some embodiments, a mixture of lipophilic surfactants is employed. In some embodiments, a mixture of at least one hydrophilic surfactant and at least one lipophilic surfactant is employed.

**[00192]** In certain embodiments, the surfactant is any suitable, non-toxic compound that is non-reactive with the medicament and that substantially reduces the surface tension between the medicament, the excipient and the site of administration. Exemplary surfactants include but are not

limited to: oleic acid available under the tradenames Mednique 6322 and Emersol 6321 (from Cognis Corp., Cincinnati, Ohio); cetylpyridinium chloride (from Arrow Chemical, Inc. Westwood, N. J.); soya lecithin available under the tradename Epikuron 200 (from Lucas Meyer Decatur, Ill.); polyoxyethylene(20) sorbitan monolaurate available under the tradename Tween 20 (from ICI Specialty Chemicals, Wilmington, Del.); polyoxyethylene(20) sorbitan monostearate available under the tradename Tween 60 (from ICI); polyoxyethylene(20) sorbitan monooleate available under the tradename Tween 80 (from ICI); polyoxyethylene (10) stearyl ether available under the tradename Brij 76 (from ICI); polyoxyethylene (2) oleyl ether available under the tradename Brij 92 (frown ICI); Polyoxyethylene-polyoxypropylene-ethylenediamine block copolymer available under the tradename Tetronic 150 R1 (from BASF); polyoxypropylene-polyoxyethylene block copolymers available under the tradenames Pluronic L-92, Pluronic L-121 end Pluronic F 68 (from BASF); castor oil ethoxylate available under the tradename Alkasurf CO-40 (from Rhone-Poulenc Mississauga Ontario, Canada); and mixtures thereof.

**[00193]** In some embodiment a suitable hydrophilic surfactant has an HLB value of at least 10, while suitable lipophilic surfactants have an HLB value of or less than about 10. An empirical parameter used to characterize the relative hydrophilicity and hydrophobicity of non-ionic amphiphilic compounds is the hydrophilic-lipophilic balance ("HLB" value). Surfactants with lower HLB values are more lipophilic or hydrophobic, and have greater solubility in oils, while surfactants with higher HLB values are more hydrophilic, and have greater solubility in aqueous solutions. Hydrophilic surfactants are generally considered to be those compounds having an HLB value greater than about 10, as well as anionic, cationic, or zwitterionic compounds for which the HLB scale is not generally applicable. Similarly, lipophilic (i.e., hydrophobic) surfactants are compounds having an HLB value equal to or less than about 10. An HLB value of a surfactant is guide generally used to enable formulation of industrial, pharmaceutical and cosmetic emulsions.

**[00194]** Hydrophilic surfactants for use in the topical formulations provided are either ionic or non-ionic. Suitable ionic surfactants include, but are not limited to, alkylammonium salts; fusidic acid salts; fatty acid derivatives of amino acids, oligopeptides, and polypeptides; glyceride derivatives of amino acids, oligopeptides, and polypeptides; lecithins and hydrogenated lecithins; lysolecithins and hydrogenated lysolecithins; phospholipids and derivatives thereof; lysophospholipids and derivatives thereof; carnitine fatty acid ester salts; salts of alkylsulfates; fatty acid salts; sodium docusate; acyl lactylates; mono- and di-acetylated tartaric acid esters of mono- and di-glycerides; succinylated mono- and di-glycerides; citric acid esters of mono- and di-glycerides; and mixtures thereof.

**[00195]** Exemplary ionic surfactants include lecithins, lysolecithin, phospholipids, lysophospholipids and derivatives thereof; carnitine fatty acid ester salts; salts of alkylsulfates; fatty acid salts; sodium docusate; acyl lactylates; mono- and di-acetylated tartaric acid esters of mono- and di-glycerides; succinylated mono- and di-glycerides; citric acid esters of mono- and di-glycerides; and mixtures thereof.

**[00196]** In some embodiments, ionic surfactants are ionized forms of lecithin, lysolecithin, phosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, phosphatidic acid, phosphatidylserine, lysophosphatidylcholine, lysophosphatidylethanolamine, lysophosphatidylglycerol, lysophosphatidic acid, lysophosphatidylserine, PEG-phosphatidylethanolamine, PVP-phosphatidylethanolamine, lactylic esters of fatty acids, stearoyl-2-lactylate, stearoyl lactylate, succinylated monoglycerides, mono/diacetylated tartaric acid esters of mono/diglycerides, citric acid esters of mono/diglycerides, cholylsarcosine, caproate, caprylate, caprate, laurate, myristate, palmitate, oleate, ricinoleate, linoleate, linolenate, stearate, lauryl sulfate, teracecyl sulfate, docusate, lauroyl carnitines, palmitoyl carnitines, myristoyl carnitines, and salts and mixtures thereof.

**[00197]** Exemplary hydrophilic non-ionic surfactants include, but are not limited to, alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl macrogolglycerides; polyoxyalkylene alkyl ethers such as polyethylene glycol alkyl ethers; polyoxyalkylene alkylphenols such as polyethylene glycol alkyl phenols; polyoxyalkylene alkyl phenol fatty acid esters such as polyethylene glycol fatty acids monoesters and polyethylene glycol fatty acids diesters; polyethylene glycol glycerol fatty acid esters; polyglycerol fatty acid esters; polyoxyalkylene sorbitan fatty acid esters such as polyethylene glycol sorbitan fatty acid esters; hydrophilic transesterification products of a polyol with at least one member of the group consisting of glycerides, vegetable oils, hydrogenated vegetable oils, fatty acids, and sterols; polyoxyethylene sterols, derivatives, and analogues thereof; polyoxyethylated vitamins and derivatives thereof; polyoxyethylene-polyoxypropylene block copolymers; and mixtures thereof; polyethylene glycol sorbitan fatty acid esters and hydrophilic transesterification products of a polyol with at least one member of the group consisting of triglycerides, vegetable oils, and hydrogenated vegetable oils. In some embodiments, the polyol is glycerol, ethylene glycol, polyethylene glycol, sorbitol, propylene glycol, pentaerythritol, or a saccharide.

**[00198]** Other exemplary hydrophilic-non-ionic surfactants include, without limitation, PEG-10 laurate, PEG-12 laurate, PEG-20 laurate, PEG-32 laurate, PEG-32 dilaurate, PEG-12 oleate, PEG-15 oleate, PEG-20 oleate, PEG-20 dioleate, PEG-32 oleate, PEG-200 oleate, PEG-400 oleate, PEG-15 stearate, PEG-32 distearate, PEG-40 stearate, PEG-100 stearate, PEG-20 dilaurate, PEG-25

glyceryl trioleate, PEG-32 dioleate, PEG-20 glyceryl laurate, PEG-30 glyceryl laurate, PEG-20 glyceryl stearate, PEG-20 glyceryl oleate, PEG-30 glyceryl oleate, PEG-30 glyceryl laurate, PEG-40 glyceryl laurate, PEG-40 palm kernel oil, PEG-50 hydrogenated castor oil, PEG-40 castor oil, PEG-35 castor oil, PEG-60 castor oil, PEG-40 hydrogenated castor oil, PEG-60 hydrogenated castor oil, PEG-60 corn oil, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, polyglyceryl-10 laurate, PEG-30 cholesterol, PEG-25 phyto sterol, PEG-30 soya sterol, PEG-20 trioleate, PEG-40 sorbitan oleate, PEG-80 sorbitan laurate, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, POE-20 oleyl ether, POE-20 stearyl ether, tocopheryl PEG-100 succinate, PEG-24 cholesterol, polyglyceryl-10oleate, Tween 40, Tween 60, sucrose monostearate, sucrose monolaurate, sucrose monopalmitate, PEG 10-100 nonyl phenol series, PEG 15-100 octyl phenol series, and poloxamers.

**[00199]** Exemplary suitable lipophilic surfactants include, but are not limited to fatty alcohols; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lower alcohol fatty acids esters; propylene glycol fatty acid esters; sorbitan fatty acid esters; polyethylene glycol sorbitan fatty acid esters; sterols and sterol derivatives; polyoxyethylated sterols and sterol derivatives; polyethylene glycol alkyl ethers; sugar esters; sugar ethers; lactic acid derivatives of mono- and di-glycerides; hydrophobic transesterification products of a polyol with at least one member of the group consisting of glycerides, vegetable oils, hydrogenated vegetable oils, fatty acids and sterols; oil-soluble vitamins/vitamin derivatives; and mixtures thereof. Within this group, lipophilic surfactants include glycerol fatty acid esters, propylene glycol fatty acid esters, and mixtures thereof, or are hydrophobic transesterification products of a polyol with at least one member of the group consisting of vegetable oils, hydrogenated vegetable oils, and triglycerides.

**[00200]** In some embodiments, surfactants are used in any formulation provided herein where its use is not otherwise contradicted. In some embodiments, the surfactant is in an amount of about 0.0001 to 1% by weight, in particular about 0.001 to 0.1% by weight, based on the total weight of the formulation. In some embodiments, the use of no surfactants or limited classes of surfactants is desirable. In some embodiments, the topical formulations provided can contain no, or substantially no surfactant, i.e. contain less than approximately 0.0001% by weight of surface-active agents. This is particularly the case if one employs a cromone as described above. Other suitable surfactant/emulsifying agents would be known to one of skill in the art and are listed in the CTFA International Cosmetic Ingredient Dictionary and Handbook, Vol. 2, 7th Edition (1997).

**[00201]** Other exemplary suitable aqueous vehicles include, but are not limited to, Ringer's solution and isotonic sodium chloride. In some embodiments, aqueous suspensions include suspending agents such as cellulose derivatives, sodium alginate, polyvinyl-pyrrolidone and gum

tragacanth, and a wetting agent such as lecithin. Suitable preservatives for aqueous suspensions include ethyl and n-propyl p-hydroxybenzoate.

**[00202]** Exemplary chelating agents which can be used to form pharmaceutical compositions and dosage forms provide herein include, but are not limited to, ethylene diaminetetraacetic acid (EDTA), EDTA disodium, calcium disodium edetate, EDTA trisodium, albumin, transferrin, desferoxamine, desferal, desferoxamine mesylate, EDTA tetrasodium and EDTA dipotassium, sodium metasilicate or combinations of any of these. In some embodiments, up to about 0.1% W/V of a chelating agent, such as EDTA or its salts, is added to the formulations of the invention.

**[00203]** Exemplary preservatives which can be used to form pharmaceutical compositions and dosage forms provided herein include, but are not limited to, purite, peroxides, perborates, imidazolidinyl urea, diazolidinyl urea, phenoxyethanol, alkonium chlorides including benzalkonium chlorides, methylparaben, ethylparaben and propylparaben. In other embodiments, suitable preservatives for the compositions of the invention include: benzalkonium chloride, purite, peroxides, perborates, thimerosal, chlorobutanol, methyl paraben, propyl paraben, phenylethyl alcohol, edetate disodium, sorbic acid, Onamer M, or other agents known to those skilled in the art. In some embodiments of the invention, such preservatives are employed at a level of from 0.004% to 0.02% W/V.

**[00204]** Exemplary lubricants which can be used to form pharmaceutical compositions and dosage forms provided include, but are not limited to, calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, talc, hydrogenated vegetable oil (e.g., peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil, and soybean oil), zinc stearate, ethyl oleate, ethyl laureate, agar, or mixtures thereof.

**[00205]** Exemplary thickening agents which can be used to form pharmaceutical compositions and dosage forms provided include, but are not limited to, isopropyl myristate, isopropyl palmitate, isodecyl neopentanoate, squalene, mineral oil, $C_{12}$-$C_{15}$ benzoate and hydrogenated polyisobutene. In some embodiments, agents which would not disrupt other compounds of the final product, such as non-ionic thickening agents are desirable. The selection of additional thickening agents is well within the skill of one in the art.

**[00206]** Pharmaceutical topical formulations disclosed herein are formulated in any suitable manner. Any suitable technique, carrier, and/or excipient is contemplated for use with the chemerin C15 peptides disclosed herein. For a summary of pharmaceutical topical formulations described herein *see Remington: The Science and Practice of Pharmacy*, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*,

Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms*, Marcel Decker, New York, N.Y., 1980; and *Pharmaceutical Dosage Fo*rms *and* Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins1999), which are herein incorporated by reference for such disclosures.

*Topical Penetration Enhancers*

**[00207]** In some embodiments, the topical formulations described herein comprise a topical penetration enhancer. The delivery of drugs topically to the skin provides many advantages. For the patient, it is comfortable, convenient, and noninvasive. The variable rates of absorption and metabolism possibly encountered in oral treatment are avoided, and other inherent inconveniences (e.g., gastrointestinal irritation, the need for administration with food in some cases or without food in other cases) are eliminated. Such localized treatment avoids incurring high systemic drug levels and possible adverse effects that could follow, i.e. inhibition of cytokine release or NF-κB activity in other biological processes.

**[00208]** The topical delivery of drugs into the skin, however, is commonly challenging. Skin is a structurally complex, relatively thick membrane. Molecules moving from the environment into and through intact skin must first penetrate the stratum corneum and any material on its surface. The stratum corneum is a layer approximately 10-15 micrometers thick over most of the body that consists of dense, highly keratinized cells. The high degree of keratinization within these cells, as well as their dense packing, are believed to be the factors most responsible for creating, in most cases, a substantially impermeable barrier to drug penetration. With many drugs, the rate of penetration through the skin is extremely low without the use of some means to enhance the skin's permeability. As the stratum corneum of many inflammatory dermatoses is commonly thicker than that of normal skin, the penetration of topical drugs into the affected areas of skin is particularly difficult to achieve.

**[00209]** In order to increase the degree and rate at which a drug penetrates the skin, various approaches have been followed, each of which involves the use of either a chemical penetration enhancer or a physical penetration enhancer. Physical enhancements of skin permeation include, for example, electrophoretic techniques such as iontophoresis. The use of ultrasound (or "phonophoresis") as a physical penetration enhancer has also been researched. Chemical penetration enhancers are more commonly used. These are compounds that are topically administered along with a drug (or, in some cases, prior to drug administration) in order to increase the permeability of the stratum corneum, and thereby provide for enhanced penetration of the drug through the skin. Ideally, such chemical penetration enhancers (or "permeation enhancers," as the

compounds are referred to herein) are compounds that are innocuous and serve merely to facilitate diffusion of the drug through the stratum corneum.

**[00210]** Various compounds for enhancing the permeability of skin are known in the art and are described in the pertinent texts and literature. Compounds that have been used to enhance skin permeability include: sulfoxides such as dimethylsulfoxide (DMSO) and decylmethylsulfoxide ($C_{10}$MSO); ethers such as diethylene glycol monoethyl ether (available commercially as Transcutol.RTM.) and diethylene glycol monomethyl ether; surfactants such as sodium laurate, sodium lauryl sulfate, cetyltrimethylammonium bromide, benzalkonium chloride, Poloxamer (231, 182, 184), Tween (20, 40, 60, 80), and lecithin (U.S. Pat. No. 4,783,450); the 1-substituted azacycloheptan-2-ones, particularly 1-n-dodecylcyclazacycloheptan-2-one (available under the trademark Azone.RTM. from Nelson Research & Development Co., Irvine, Calif.; see U.S. Pat. Nos. 3,989,816, 4,316,893, 4,405,616, and 4,557,934); alcohols such as ethanol, propanol, octanol, benzyl alcohol, and the like; fatty acids such as lauric acid, oleic acid and valeric acid; fatty acid esters such as isopropyl myristate, isopropyl palmitate, methylpropionate, and ethyl oleate; polyols and esters thereof such as propylene glycol, ethylene glycol, glycerol, butanediol, polyethylene glycol, and polyethylene glycol monolaurate (PEGML; see, e.g., U.S. Pat. No. 4,568,343); amides and other nitrogenous compounds such as urea, dimethylacetamide (DMA), dimethylformamide (DMF), 2-pyrrolidone, 1-methyl-2-pyrrolidone, ethanolamine, diethanolamine and triethanolamine; terpenes; alkanones; and organic acids, particularly salicylic acid and salicylates, citric acid, and succinic acid. The book Percutaneous Penetration Enhancers (Smith et al., editors, CRC Press, 1995) provides an excellent overview of the field and further background information on a number of chemical and physical enhancers.

**[00211]** It has long been thought that strong bases, such as NaOH, were not suitable as permeation enhancers because they would damage skin. It has been now been discovered that the skin permeability of various drugs could be enhanced without skin damage by exposing the skin to a base or basic solution, in a skin contacting formulation or patch. The desired pH of the solution on the skin can be obtained using a variety of bases or base concentrations. Accordingly, the pH is selected so as to be low enough so as to not cause skin damage, but high enough to enhance skin permeation to various active agents. As such, it is important that the amount of base in any patch or formulation is optimized so as to increase the flux of the drug through the body surface while minimizing any possibility of skin damage. In some embodiments, this means that the pH at the body surface in contact with a formulation or drug delivery system of the invention is in the range of approximately pH 8.0 to about pH 13.0, about pH 8.0 to about pH 11.5, about pH 8.5 to about

pH 11.5, or about pH 8.5 to about pH 10.5. In some embodiments, the pH is in the range of about pH 9.5 to about pH 11.5, or about pH 10.0 to about pH 11.5.

**[00212]** In one embodiment, the pH at the skin surface is the primary design consideration, i.e., the composition or system is designed so as to provide the desired pH at the skin surface. In certain instances, anhydrous formulations and transdermal systems do not have a measurable pH, and the formulation or system is designed so as to provide a target pH at the skin surface. Moisture from the body surface can migrate into the formulation or system, dissolve the base and thus release the base into solution, which will then provide the desired target pH at body surface. In certain instances, a hydrophilic composition is desirable. In addition, when using aqueous formulations, the pH of the formulation in certain instances changes over time after it is applied on the skin. For example, gels, solutions, ointments, etc., in certain instances, experience a net loss of moisture after being applied to the body surface, i.e., the amount of water lost is greater than the amount of water received from the body surface. In that case, the pH of the formulation in certain instance is different than its pH when manufactured. In some embodiments, this problem is easily remedied by designing the aqueous formulations to provide a target pH at the body surface.

**[00213]** In other embodiments, the pH of the formulation or the drug composition contained within a delivery system will be in the range of approximately pH 8.0 to about pH 13.0, about pH 8.0 to about pH 11.5, about pH 8.5 to about pH 11.5, or about pH 8.5 to about pH 10.5. In some embodiments, the pH will be in the range of about pH 9.5 to about pH 11.5, or about pH 10.0 to about pH 11.5. In one embodiment of the invention the pH of the formulation is higher than the pH at the body surface. For example, if an aqueous formulation is used, moisture from the body surface can dilute the formulation, and thus provide for a different pH at the body surface, which will typically be lower than that of the formulation itself.

**[00214]** In one embodiment, the body surface is exposed to a base or basic solution for a sufficient period of time so as to provide a high pH at the skin surface, thus creating channels in the skin or mucosa for the drug to go through. It is expected that drug flux is proportional to the strength of the solution and the duration of exposure. However, it is desirable to balance the maximization of drug flux with the minimization of skin damage. This can be done in numerous ways. For example, in some embodiments, the skin damage is minimized by selecting a lower pH within the 8.0 to 13.0 range, by exposing the skin to the formulation or system for a shorter period of time, or by including at least one irritation-mitigating additive. Alternatively, the patient can be advised to change the location of application with each subsequent administration.

**[00215]** While certain amounts are set forth below, it is understood that, for all of the inorganic and organic bases described herein, the optimum amount of any such base will depend on the

strength or weakness of the base and its molecular weight, and other factors such as the number of ionizable sites in the active agent being administered and whether there are any acidic species present in the formulation or patch. One skilled in the art can readily determine the optimum amount for any particular base such that the degree of enhancement is optimized while the possibility of damage to the body surface is eliminated or at least substantially minimized.

**[00216]** Exemplary inorganic bases are inorganic hydroxides, inorganic oxides, inorganic salts of weak acids, and combinations thereof. Some inorganic bases are those whose aqueous solutions have a high pH, and are acceptable as food or pharmaceutical additives. Examples of such inorganic bases include ammonium hydroxide, sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide, magnesium oxide, calcium oxide, $Ca(OH)_2$, sodium acetate, sodium borate, sodium metaborate, sodium carbonate, sodium bicarbonate, sodium phosphate, potassium carbonate, potassium bicarbonate, potassium citrate, potassium acetate, potassium phosphate and ammonium phosphate and combinations thereof.

**[00217]** Inorganic hydroxides include, for example, ammonium hydroxide, alkali metal hydroxide and alkaline earth metal hydroxides, and mixtures thereof. Some inorganic hydroxides include ammonium hydroxide; monovalent alkali metal hydroxides such as sodium hydroxide and potassium hydroxide; divalent alkali earth metal hydroxides such as calcium hydroxide and magnesium hydroxide; and combinations thereof.

**[00218]** The amount of inorganic hydroxide included in the compositions and systems of the invention will typically represent about 0.3-7.0 W/V %, about 0.5-4.0 W/V %, about 0.5-3.0 W/V %, or about 0.75-2.0 W/V % of a topically applied formulation or of a drug reservoir of a drug delivery system, or patch.

**[00219]** Inorganic oxides include, for example, magnesium oxide, calcium oxide, and the like.

**[00220]** In some embodiments, the amount of inorganic oxide included in the compositions and systems of the invention is substantially higher than the numbers set forth above for the inorganic hydroxide. In some instance, it is as high as 20 wt %, in some cases as high as 25 wt % or higher, but will generally be in the range of about 2-20 wt %. In some embodiments, these amounts are adjusted to take into consideration the presence of any base-neutralizable species.

**[00221]** Inorganic salts of weak acids include, ammonium phosphate (dibasic); alkali metal salts of weak acids such as sodium acetate, sodium borate, sodium metaborate, sodium carbonate, sodium bicarbonate, sodium phosphate (tribasic), sodium phosphate (dibasic), potassium carbonate, potassium bicarbonate, potassium citrate, potassium acetate, potassium phosphate (dibasic), potassium phosphate (tribasic); alkaline earth metal salts of weak acids such as magnesium phosphate and calcium phosphate; and the like, and combinations thereof.

**[00222]** Organic bases suitable for use in the invention are compounds having an amino group, amido group, an oxime, a cyano group, an aromatic or non-aromatic nitrogen-containing heterocycle, a urea group, and combinations thereof. More specifically, examples of suitable organic bases are nitrogenous bases, which include, but are not limited to, primary amines, secondary amines, tertiary amines, amidines, guanidines, hydroxylamines, cyano guanidines, cyanoamidines, oximes, cyano (--CN) containing groups, aromatic and non-aromatic nitrogen-containing heterocycles, urea, and mixtures thereof. In some embodiments, the organic bases are primary amines, secondary amines, tertiary amines, aromatic and non-aromatic nitrogen-containing heterocycles, and mixtures thereof.

**[00223]** For all permeation-enhancing bases herein, the optimum amount of any particular agent will depend on the strength or weakness of the base, the molecular weight of the base, and other factors such as the number of ionizable sites in the drug administered and any other acidic species in the formulation or patch. One skilled in the art can readily determine the optimum amount for any particular agent by ensuring that a formulation is effective to provide a pH at the skin surface, upon application of the formulation, in the range of about pH 7.5 to about pH 13.0, about pH 8.0 to about pH 11.5, or about pH 8.5 to about pH 10.5. In some embodiments, the pH will be in the range of about pH 9.5 to about pH 11.5, or about pH 10.0 to about pH 11.5. This in turn ensures that the degree of treatment is maximized while the possibility of damage to the body surface is eliminated or at least substantially minimized.

**[00224]** In the case of intranasal administration, such solutions or suspensions, in some embodiments, are isotonic relative to nasal secretions and of about the same pH, ranging e.g., from about pH 4.0 to about pH 7.4 or from about pH 6.0 to about pH 7.0. Buffers should be physiologically compatible and include, simply by way of example, phosphate buffers. For example, a representative nasal decongestant is described as being buffered to a pH of about 6.2 (Remington's Pharmaceutical Sciences 16th edition, Ed. Arthur Osol, page 1445 (1980)). One skilled in the art can readily determine a suitable saline content and pH for an innocuous aqueous solution for nasal and/or upper respiratory administration. An example of a suitable formulation for intranasal administration, is an aqueous solution buffered to a pH of about 6.0 to about 8.0 with Sodium Phosphate, Monobasic, comprising about 1% W/V of the LFA-1 antagonist, up to about 0.1% W/V EDTA, and, optionally, up to about 0.4% w/w Methylparaben and up to about 0.02% w/w Propylparaben.

**[00225]** Additional permeation enhancers will be known to those of ordinary skill in the art of topical drug delivery, and/or are described in the pertinent texts and literature. See, e.g., Percutaneous Penetration Enhancers, Smith et al., eds. (CRC Press, 1995).

**[00226]** Disclosed herein, in certain embodiments, is a topical formulation of a chemerin C15 peptide wherein the topical formulation comprises a penetration enhancer. Penetration enhancers include, but are not limited to, sodium lauryl sulfate, sodium laurate, polyoxyethylene-20-cetyl ether, laureth-9, sodium dodecylsulfate, dioctyl sodium sulfosuccinate, polyoxyethylene-9-lauryl ether (PLE), Tween 80, nonylphenoxypolyethylene (NP-POE), polysorbates, sodium glycocholate, sodium deoxycholate, sodium taurocholate, sodium taurodihydrofusidate, sodium glycodihydrofusidate, oleic acid, caprylic acid, mono- and di-glycerides, lauric acids, acylcholines, caprylic acids, acylcarnitines, sodium caprates, EDTA, citric acid, salicylates, DMSO, decylmethyl sulfoxide, ethanol, isopropanol, propylene glycol, polyethylene glycol, glycerol, propanediol, and diethylene glycol monoethyl ether. In some embodiments, the topical formulation of a chemerin C15 contains a penetration enhancer. In some embodiments, the topical formulation of a chemerin C15 does not contain a penetration enhancer. In some embodiments, the topical formulation of a chemerin C15 contains DMSO. In some embodiments, the topical formulation of a chemerin C15 does not contain DMSO.

*Combination Therapies*

**[00227]** In some embodiments, the topical formulation comprises at least one additional therapeutic agent in addition to the chemerin C15 peptide. In some embodiments, the additional therapeutic agent is an antioxidant, anti-inflammatory agent, antimicrobial agent, antiangiogenic agent, anti-apoptotic agent, vascular endothelial growth factor inhibitor, antiviral agent, calcineurin inhibitor, corticosteroid, or immunomodulator. In some embodiments, the topical formulation comprising a chemerin C15 peptide is a corticosteroid. In some embodiments, the corticosteroid is a topical corticosteroid. Agents for use with the chemerin C15 peptides are further described in the Combination Therapies section herein.

**Administration and Dosages**

**[00228]** Disclosed herein, in certain embodiments, are chemerin C15 peptides. Further disclosed herein are topical formulations comprising a chemerin C15 peptide and optionally a pharmaceutically acceptable excipient. Additionally disclosed herein are methods of treating inflammatory dermatological disorders in an individual in need thereof comprising administering a chemerin C15 peptide disclosed herein or a topical formulation comprising a chemerin C15 peptide disclosed herein. Further disclosed herein are methods of inhibiting the activity of an inflammatory cytokine or chemokine in an individual in need thereof comprising administering a chemerin C15 peptide disclosed herein or a topical formulation comprising a chemerin C15 peptide disclosed herein. Also disclosed herein, in certain embodiments, are method of inhibiting inhibits nuclear translocation or NFκB-mediated gene transcription of an inflammatory cytokine in an individual in

need thereof comprising administering a chemerin C15 peptide disclosed herein or a topical formulation comprising a chemerin C15 peptide disclosed herein. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is a salt of a chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is carboxylated. In some embodiments, the chemerin C15 peptide is amidated. In some embodiments, the chemerin C15 peptide is cyclic. In some embodiments, the chemerin C15 peptide is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9% homologous to a naturally occurring chemerin C15 peptide.

**[00229]** The benefits of topical administration include localized delivery of the therapeutic agent directly to the affected tissue and minimal systemic side effects due to low systemic bioavailability. For example, in some embodiments, topical formulations provided herein are administered directly to the skin, eye, mouth, nose, vaginal mucosa or anal mucosa. The methods of topical delivery provided herein are particularly well suited for localized administration of the formulation. Suitable formulations and additional carriers are discussed herein and, additionally, described in Remington "The Science and Practice of Pharmacy" (20.sup.th Ed., Lippincott Williams & Wilkins, Baltimore Md.), the teachings of which are incorporated by reference in their entirety herein.

**[00230]** One advantage of the therapeutic composition according to the invention is that topical application is particularly convenient for treating and preventing a variety of dermal conditions. In some embodiments, therapeutic compositions are noninvasively applied directly to the site of interest. Other disorders conveniently addressed by topical administration include allergic conditions of the nasal passageway, eye, and oral cavity. In some embodiments, chemerin C15 peptides provided have a rapid systemic clearance such that any drug that gets absorbed systemically is quickly cleared.

**[00231]** In some embodiments, the local concentration of the chemerin C15 peptide is about 2 times, 3 times, 4 times, 5 times, 10 times, 25 times, 50 times, or 100 times greater than the systemic concentration. In another embodiment, local concentration of chemerin C15 peptide is 100 times greater than the systemic concentration. In another embodiment, local concentration of chemerin C15 peptide is 1000 times greater than the systemic concentration. In one embodiment, the local concentration is about 10,000 times or more greater than the systemic concentration at the same time point. In some embodiments, the concentration of therapeutic agent is measured using any known method in the art (e.g. ELISA and/or LCMS/MS).

**[00232]** In certain instances, the method of delivery of the pharmaceutically active composition selected involves application of a formulation of the invention to an area of body surface affected

with an inflammatory or immune related condition or symptom thereof. In embodiments of the methods provided, the formulation is topically applied to skin, eyes, mouth, nose, vaginal mucosa or anal mucosa. In some embodiments, a cream, ointment, paste, plaster, or lotion is spread on the affected area of skin and gently rubbed in. In some embodiments, a polymeric or other bioadhesive formulation is spread or dabbed on the affected area of skin. In some embodiments, a solution is applied in the same ways, but more typically will be applied with a dropper, spray, swab, or the like, and carefully applied to the affected area of skin. In some embodiments, petrolatum is spread on the skin surrounding the affected area of skin to protect it from possible irritation during treatment.

**[00233]** In some embodiments, topical delivery is achieved by use of a delivery device that facilitates the delivery of the agent directly into the skin tissue, e.g. micro-needle injection devices, or a delivery device comprised of a covering for the skin whereby the agent is held between the affected skin and covering for prolonged periods by means of an adhesive property of the covering.

*Dosing*

**[00234]** Disclosed herein, in certain embodiments, is a topical formulation of a chemerin C15 peptide wherein the topical formulation administered for prophylactic and/or therapeutic treatments. In certain instances, amounts effective for this use will depend on the severity and course of the disease, disorder or condition, previous therapy, the individual's health status and response to the drugs, and the judgment of the treating physician

**[00235]** The compositions are delivered with a pharmacokinetic profile that results in the delivery of an effective dose of the chemerin C15 peptide. The actual effective amounts of drug can vary according to the specific drug or combination thereof being utilized, the particular composition formulated, the mode of administration, and the age, weight, condition of the patient, and severity of the symptoms or condition being treated. Dosages for a particular patient can be determined by one of ordinary skill in the art using conventional considerations, (e.g. by means of an appropriate, conventional pharmacological protocol). The total daily doses of the medicaments contemplated for administration, and consequently the concentrations by weight of the medicaments in the respective compositions, can vary widely, but are within the typical skill of the routine practitioner.

**[00236]** In some embodiments, a topical formulation of a chemerin C15 peptide is delivered such that a local therapeutically effective concentration is achieved. For example, in some embodiments, the local therapeutically effective concentration is achieved with a local tissue concentration of the chemerin C15 peptide sufficient to inhibit cellular process associated with inflammation by at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% in an *in vitro* dose titration study. In some embodiments, the local therapeutically effective concentration is

achieved with a local tissue concentration of the chemerin C15 peptide sufficient to inhibit cellular process associated with inflammation by at least about 50% in an *in vitro* dose titration study. For example, in some embodiments, the local therapeutically effective concentration is achieved with a local tissue concentration of the chemerin C15 peptide sufficient to inhibit cellular process associated with inflammation by at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% *in vitro* in an antigen presenting cell, such as a macrophage or a dendritic cell. In some embodiments, the local therapeutically effective concentration is achieved with a local tissue concentration of the chemerin C15 peptide sufficient to inhibit cellular process associated with inflammation by at least about 50% *in vitro* in an antigen presenting cell, such as a macrophage or a dendritic cell. In some embodiments, the antigen presenting cell is stimulated, such as, for example, by contacting the cell with IFNγ and/or LPS prior to, during or following addition of the chemerin C15 peptide.

**[00237]** In some embodiments, the local therapeutically effective concentration is achieved with a local tissue concentration of the chemerin C15 peptide sufficient to inhibit secretion of one or more inflammatory cytokines by at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% *in vitro* in an antigen presenting cell, such as a macrophage or a dendritic cell. In some embodiments, the local therapeutically effective concentration is achieved with a local tissue concentration of the chemerin C15 peptide sufficient to inhibit secretion of one or more inflammatory cytokines by at least about 50% *in vitro* in an antigen presenting cell, such as a macrophage or a dendritic cell. In some embodiments, the antigen presenting cell is stimulated, such as, for example, by contacting the cell with IFNγ and/or LPS. In some embodiments, the antigen presenting cell is stimulated, such as, for example, by contacting the cell with IFNγ and/or LPS prior to, during or following addition of the chemerin C15 peptide.

**[00238]** In some embodiments, the local therapeutically effective concentration is achieved with a local tissue concentration of the chemerin C15 peptide sufficient to inhibit transcription of one or more inflammatory cytokines by at least about 10%, 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% *in vitro* in an antigen presenting cell, such as a macrophage or a dendritic cell. In some embodiments, the local therapeutically effective concentration is achieved with a local tissue concentration of the chemerin C15 peptide sufficient to inhibit transcription of one or more inflammatory cytokines by at least about 50% *in vitro* in an antigen presenting cell, such as a macrophage or a dendritic cell. In some embodiments, the antigen presenting cell is stimulated, such as, for example, by contacting the cell with IFNγ and/or LPS prior to, during or following addition of the chemerin C15 peptide. In some embodiments, the inflammatory cytokine is IL-23, IL-12, TNFα, IL-1β, IL-6, or RANTES.

**[00239]** In some embodiments, the local therapeutically effective concentration is achieved with a local tissue concentration of the chemerin C15 peptide of greater than about 0.1 pM-100 nM. In some embodiments, the local therapeutically effective concentration is achieved with a local tissue concentration of the chemerin C15 peptide of greater than about 1 pM-10 nM. In some embodiments, the local therapeutically effective concentration is achieved with a local tissue concentration of the chemerin C15 peptide of greater than about 1pM-1 nM. In some embodiments, the local therapeutically effective concentration is achieved with a local tissue concentration of the chemerin C15 peptide of greater than about 1-100 pM. In some embodiments, the local therapeutically effective concentration is achieved with a local tissue concentration of the chemerin C15 peptide of greater than about 1-10 pM. In some embodiments, chemerin C15 peptide achieves a local tissue concentration of greater than about 1 nM within about 1-12 hours following administration to a subject. In some embodiments, chemerin C15 peptide achieves a local tissue concentration of greater than about 10 pM within about 1-12 hours following administration to a subject. In some embodiments, chemerin C15 peptide achieves a local tissue concentration of greater than about 10 pM within about 1-12 hours following administration to a subject. In some embodiments, chemerin C15 peptide achieves a local tissue concentration of greater than about 1 pM within about 1-12 hours following administration to a subject.

**[00240]** In some embodiments, the local therapeutically effective concentration of the chemerin C15 peptide is achieved while maintaining a low systemic level. For example, in some embodiments, a local therapeutically effective concentration of about 1 pM-10 nM is achieved while maintaining a systemic drug concentration of less than 1-100 pM. For example, in some embodiments, a local therapeutically effective concentration of about 1 pM-1 nM is achieved while maintaining a systemic drug concentration of less than 1-100 pM. For example, in some embodiments, a local therapeutically effective concentration of about 1-100 pM is achieved while maintaining a systemic drug concentration of less than 1-100 pM.

**[00241]** For example, in some embodiments, a local therapeutically effective concentration of about 1 pM-10 nM is achieved while maintaining a systemic drug concentration of less than 10-100 pM. For example, in some embodiments, a local therapeutically effective concentration of about 1 pM-1 nM is achieved while maintaining a systemic drug concentration of less than 10-100 pM. For example, in some embodiments, a local therapeutically effective concentration of about 1-100 pM is achieved while maintaining a systemic drug concentration of less than 10-100 pM.

**[00242]** In other embodiments, a local therapeutically effective concentration of about 1 pM-10 nM is achieved while maintaining a systemic drug concentration of less than 1000 pM. In other embodiments, a local therapeutically effective concentration of about 1 pM-10 nM is achieved

while maintaining a systemic drug concentration of less than 10 pM. In other embodiments, a local therapeutically effective concentration of about 1 pM-1 nM is achieved while maintaining a systemic drug concentration of less than 1000 pM. In other embodiments, a local therapeutically effective concentration of about 1 pM-1 nM is achieved while maintaining a systemic drug concentration of less than 10 pM. In other embodiments, a local therapeutically effective concentration of about 1-100 pM is achieved while maintaining a systemic drug concentration of less than 1000 pM. In other embodiments, a local therapeutically effective concentration of about 1-100 pM is achieved while maintaining a systemic drug concentration of less than 10 pM.

**[00243]** In some embodiments, the systemic concentration of the peptide is measured by blood plasma concentration using any of a variety of methods known in the art and as disclosed above, such as for example an ELISA and/or LCMS/MS.

**[00244]** In some embodiments, an effective amount of the chemerin C15 peptide is a dose of about 0.01-100 milligrams per square inch. In some embodiments, an effective amount of the chemerin C15 peptide is a dose of about 0.01-10 milligrams per square inch. In some embodiments, an effective amount of the chemerin C15 peptide is a dose of about 0.1-100 milligrams per square inch. In some embodiments, an effective amount of the chemerin C15 peptide is a dose of about 0.1-10 milligrams per square inch.

**[00245]** In some embodiments, the dosing regimen depends on a number of factors that are readily be determined, such as the size of the affected area, the severity of the dermatosis, and the responsiveness of the inflammatory dermatosis to treatment, but will normally be one or more doses per day, with a course of treatment lasting from several days to several months, or until a cure is effected or a significant diminution in the size and/or severity of the inflammatory dermatosis is achieved. In some embodiments, another dosing regimen favors the use of a systemic biologic agent and/or potent topical agent to cure or significantly diminish the size and/or severity of the inflammatory dermatosis and then dose the site of the dermatosis with chemerin C15 peptide to prevent remission or return of the dermatosis. Local administration of topical formulation of a chemerin C15 peptide that is rapidly cleared from the systemic circulation has a particular benefit for patients with inflammatory diseases affecting large areas. In some embodiments, patients are able to treat large areas without significant immunosuppression and risk of side effects due to systemic exposure to drug. One of ordinary skill can readily-determine optimum dosages, dosing methodologies, and repetition rates. In general, it is contemplated that the formulation will be applied one to four times daily. With a skin patch, the device is generally maintained in place on the body surface throughout a drug delivery period, typically in the range of 8 to 72 hours, and replaced as necessary.

**[00246]** In some embodiments, the topical formulation of a chemerin C15 peptide is present in an amount sufficient to exert a therapeutic effect to reduce symptoms of an immune related or inflammatory disease or disorder by an average of at least about 5, 10, 15, 20, 25, 30, 40, 50, 60, 70, 80, 90, more than 90%, or substantially eliminate symptoms of the immune related or inflammatory disease or disorder. For many inflammatory diseases, there are well recognized clinical assessments of therapeutic effect (e.g. PASI and/or PGA score for psoriasis and EASI score for eczema)

**[00247]** In some embodiments, the topical formulation of a chemerin C15 peptide is administered in a single dose. In some embodiments, a single dose of a chemerin C15 peptide is administered for treatment of an acute condition. In some embodiments, a single dose of a chemerin C15 peptide is administered is used when it is co-administered with an additional therapeutic agent for treatment of an acute condition.

**[00248]** In some embodiments, the topical formulation of a chemerin C15 peptide (by itself or in combination with one or more additional therapeutic agents) is administered in multiple doses. In some embodiments, dosing is about once, twice, three times, four times, five times, six times, seven times, eight times, nine times, ten times or more than ten times per day. In some embodiments, dosing is about once a year, twice a year, every six months, every 4 months, every 3 months, every 60 days, once a month, once every two weeks, once a week, or once every other day.

**[00249]** In some embodiments, the topical formulation of a chemerin C15 peptide and another therapeutic agent are administered together about once per day to about 10 times per day. In another embodiment, an additional therapeutic agent is administered concurrent with, prior to, or subsequent to administering the topical formulation of a chemerin C15 peptide. In another embodiment the administration of the topical formulation of a chemerin C15 peptide and another therapeutic agent continues for less than about 7 days. In yet another embodiment the co-administration continues for more than about 6, 10, 14, 28 days, two months, six months, or one year. In some cases, co-administered dosing is maintained as long as necessary, e.g., dosing for chronic inflammation.

**[00250]** In some embodiments, a topical formulation of a chemerin C15 peptide is administered once per day. In some embodiments, a topical formulation of a chemerin C15 peptide is administered twice per day. In some embodiments, a topical formulation of a chemerin C15 peptide is administered three times per day. In some embodiments, a topical formulation of a chemerin C15 peptide is administered any time. In some embodiments, a topical formulation of a chemerin C15 peptide is administered in the morning. In some embodiments, a topical formulation of a chemerin C15 peptide is administered during the day. In some embodiments, a topical

formulation of a chemerin C15 peptide is administered in the evening. In some embodiments, a topical formulation of a chemerin C15 peptide is administered at night.

**[00251]** In another aspect of the invention, the local tissue concentration of the chemerin C15 peptide is maintained at therapeutically effective levels for an extended period of time. In some embodiments, the local tissue concentrations of the chemerin C15 peptide is maintained at therapeutically effective levels for a certain amount of time or between doses. In some examples, a chemerin C15 peptide selected for local administration maintains local therapeutically effective levels for extended periods such the subject achieves a therapeutic effect without administration of multiple doses per day.

**[00252]** In some embodiments, the chemerin C15 peptide has a local tissue concentration of greater than about 1-1000 pM for at least about 2 hours, about 4 hours, about 6 hours, about 8 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, or about 24 hours following administration to a subject. In some embodiments, the chemerin C15 peptide has a local tissue concentration of greater than about 1-100 pM for at least about 2 hours, about 4 hours, about 6 hours, about 8 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, or about 24 hours following administration to a subject. In some embodiments, the chemerin C15 peptide has a local tissue concentration of greater than about 1-100 pM for at least about 2 hours, about 4 hours, about 6 hours, about 8 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, or about 24 hours following administration to a subject. In some embodiments, the chemerin C15 peptide has a local tissue concentration of greater than about 10-100 pM for at least about 2 hours, about 4 hours, about 6 hours, about 8 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, or about 24 hours following administration to a subject. In some embodiments, the chemerin C15 peptide has a local tissue concentration of greater than about 1-10 pM for at least about 2 hours, about 4 hours, about 6 hours, about 8 hours, about 10 hours, about 12 hours, about 14 hours, about 16 hours, about 18 hours, about 20 hours, about 22 hours, or about 24 hours following administration to a subject.

**[00253]** In some embodiments, administration of the topical formulation continues as long as necessary to treat the disease or disorder. In some embodiments, a composition of the invention is administered for more than 1, 2, 3, 4, 5, 6, 7, 14, or 28 days. In some embodiments, a composition of the invention is administered for less than 28, 14, 7, 6, 5, 4, 3, 2, or 1 day. In some embodiments, a composition of the invention is administered chronically on an ongoing basis, e.g., for the treatment of chronic inflammation.

**[00254]** In some embodiments, where a dermatological disorder does not improve, a topical formulation disclosed herein is administered chronically (i.e., for an extended period of time, including throughout the duration of the individual's life). In some embodiments, where a dermatological disorder does improve, a topical formulation disclosed herein is given continuously. In some embodiments, the dose of active agent being administered is temporarily reduced or temporarily suspended for a certain length of time *(i.e.*, a "drug holiday"). In some embodiments, a drug holiday lasts between 2 days and 1 year, including all integers in between. In some embodiments, the dose reduction during a drug holiday is from about 10% to about 100%, including all integers in between.

**[00255]** In some embodiments, where a dermatological disorder does improve, a topical formulation disclosed herein is administered as a maintenance dose. In some embodiments, where a dermatological disorder does improve, a topical formulation disclosed herein is administered with reduced frequency or at a reduced dose.

**[00256]** In some embodiments, a topical formulation disclosed herein is formulated for controlled release of a chemerin C15 peptide. In some embodiments, a chemerin C15 peptide is released over a time period exceeding 15 minutes, or 30 minutes, or 1 hour, or 4 hours, or 6 hours, or 12 hours, or 18 hours, or 1 day, or 2 days, or 3 days, or 4 days, or 5 days, or 6 days, or 7 days, or 10 days, or 12 days, or 14 days, or 18 days, or 21 days, or 25 days, or 30 days, or 45 days, or 2 months or 3 months or 4 months or 5 months or 6 months or 9 months or 1 year.

## Combination Therapies

**[00257]** Disclosed herein, in certain embodiments, are chemerin C15 peptides. Further disclosed herein are topical formulations comprising a chemerin C15 peptide and optionally a pharmaceutically acceptable excipient. Additionally disclosed herein are methods of treating inflammatory dermatological disorders in an individual in need thereof comprising administering a chemerin C15 peptide disclosed herein or a topical formulation comprising a chemerin C15 peptide disclosed herein. Further disclosed herein are methods of inhibiting the activity of an inflammatory cytokine or chemokine in an individual in need thereof comprising administering a chemerin C15 peptide disclosed herein or a topical formulation comprising a chemerin C15 peptide disclosed herein. Also disclosed herein, in certain embodiments, are method of inhibiting inhibits nuclear translocation or NFκB-mediated gene transcription of an inflammatory cytokine in an individual in need thereof comprising administering a chemerin C15 peptide disclosed herein or a topical formulation comprising a chemerin C15 peptide disclosed herein. In some embodiments, the chemerin C15 peptide is a human chemerin C15 peptide. In some embodiments, the chemerin C15

peptide is a salt of a chemerin C15 peptide. In some embodiments, the chemerin C15 peptide is carboxylated. In some embodiments, the chemerin C15 peptide is amidated. In some embodiments, the chemerin C15 peptide is cyclic. In some embodiments, the chemerin C15 peptide is at least 80%, 85%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.6%, 99.7%, 99.8%, or 99.9% homologous to a naturally occurring chemerin C15 peptide. In some embodiments, the aforementioned methods or formulations further comprise an additional therapeutic agent.

**[00258]** In some embodiments, the additional therapeutic agent treats the inflammatory dermatological disorder. In some embodiments, the additional therapeutic agent modulates side-effects of the chemerin C15 peptide. In some instances, pathological events in this disease state are marked by a combination of impaired autoregulation, apoptosis, ischemia, neovascularization, and inflammatory stimuli. In some embodiments, the combination of a chemerin C15 peptide and an additional therapeutic produces additive or synergistic effects.

**[00259]** In some embodiments, the additional therapeutic agent is an antioxidant, antiinflammatory agent, antimicrobial including antibacterial, antihistamine, mast cell stabilizer, antiviral and antifungal agents, antiangiogenic agent, anti-apoptotic agent, lubricant, and/or secretagogue.

**[00260]** Inflammation is induced by the process of leukocyte adhesion and neovascularization. In some embodiments, anti-inflammatory agents are administered in combination, prior to, after, or concomitantly with a chemerin C15 peptide. In some embodiments, the anti-inflammatory agents are chosen from corticosteroid related drugs including, but not limited to, adexamethasone, fluoromethalone, medrysone, betamethasone, triamcinolone, triamcinolone acetonide, prednisone, prednisolone, hydrocortisone, rimexolone, and pharmaceutically acceptable salts thereof, prednicarbate, deflazacort, halomethasone, tixocortol, prednylidene, prednival, paramethasone, methylprednisolone, meprednisone, mazipredone, isoflupredone, halopredone acetate, halcinonide, formocortal, flurandrenolide, fluprednisolone, fluprednidine acetate, fluperolone acetate, fluocortolone, fluocortin butyl, fluocinonide, fluocinolone acetonide, flunisolide, flumethasone, fludrocortisone, fluclorinide, enoxolone, difluprednate, diflucortolone, diflorasone diacetate, desoximetasone (desoxymethasone), desonide, descinolone, cortivazol, corticosterone, cortisone, cloprednol, clocortolone, clobetasone, clobetasol, chloroprednisone, cafestol, budesonide, beclomethasone, amcinonide, allopregnane acetonide, alclometasone, 21-acetoxypregnenolone, tralonide, diflorasone acetate, deacylcortivazol, RU-26988, budesonide, deacylcortivazol, and the like. In some embodiments, the anti-inflammatory agents are chosen from 5-aminosalicylate (5-ASA) compounds, such as sulfasalzine (Azulfidine), osalazine (Dipentum), and mesalamine (examples include Pentasa, Asacol, Dipentum, Colazal, Rowasa enema, and Canasa suppository).

In some embodiments, the anti-inflammatory agents are chosen from cyclosporine related drugs (e.g. calcineurin antagonist) including but not limited to members of the cyclosporine family, and other related calcineurin antagonists including sirolimus, tacorlimus and pimecrolimus. In some embodiments, the anti-inflammatory agents are chosen from the group of NSAIDs including but not limited to acetaminophen, acemetacin, aceclofenac, alminoprofen, amfenac, bendazac, benoxaprofen, bromfenac, bucloxic acid, butibufen, carprofen, celecoxib, cinmetacin, clopirac, diclofenac, etodolac, etoricoxib, felbinac, fenclozic acid, fenbufen, fenoprofen, fentiazac, flunoxaprofen, flurbiprofen, ibufenac, ibuprofen, indomethacin, isofezolac, isoxicam, isoxepac, indoprofen, ketoprofen, lonazolac, loxoprofen, mefenamic acid, meclofenamic acid, meloxicam, metiazinic acid, mofezolac, miroprofen, naproxen, niflumic, oxaprozin, pirozolac, pirprofen, pranoprofen, protizinic acid, rofecoxib, salicylic acid and its derivatives (i.e. for example, aspirin), sulindac, suprofen, suxibuzone, triaprofenic acid, tolmetin, valdecoxib, xenbucin, ximoprofen, zaltoprofen, zomepirac, aspirin, acemetcin, bumadizon, carprofenac, clidanac, diflunisal, enfenamic acid, fendosal, flufenamic acid, flunixin, gentisic acid, ketorolac, mesalamine, prodrugs thereof, and the like. In some embodiments, immunomodulators such as 6-mercaptopurine (6-MP), azathioprine (Imuran), methotrexate (Rheumatrex, Trexall), Stelara, infliximab (Remicade), and adalimumab (Humira) are used.

**[00261]** In some embodiments, the additional therapeutic agent is a Vascular Endothelial Growth Factor (VEGF) inhibitor such as, for example 1) neutralizing monoclonal antibodies against VEGF or its receptor, 2) small molecule tyrosine kinase inhibitors of VEGF receptors, 3) soluble VEGF receptors which act as decoy receptors for VEGF, and 4) ribozymes which specifically target VEGF. Some examples of antibodies which are active against VEGF are, for example, Lucentis (ranibizumab), and Avastin (bevacizumab). An example of an oligonucleotide drug is, e.g., Macugen (pegaptanib sodium injection). Small molecule tyrosine kinase inhibitors include, for example, pazopanib, sorafenib, sutent, and the like.

**[00262]** A class of therapeutic agents useful for administration in combination, prior to, after, or concomitantly with a chemerin C15 peptide are antihistamines, including alkylamine, ethanolamine and phenothiazine classes, such as, for example, chlorpheniramine maleate, chlorphenamiramine tannate, diphenhydramine hydrochloride, promethazine hydrochloride, acrivastine, azatadine maleate, azelastine hydrochloride, brompheniramine maleate, carbinoxamine maleate, cetirizine hydrochloride, clemastine fumarate, cyproheptadine hydrochloride, desloratadine, dexbrompheniramine maleate, dexchlorpheniramine maleate, dimenhydriunate, diphenhydramine hydrochloride, emedastine difumarate, fexofenadine hydrochloride, hydroxyzine hydrochloride, ketotifen fumarate, loratadine, meclizine hydrochloride, olopatadine hydrochloride, phenindamine

tartrate, quetiapine, tripelennamine citrate, tripelennamine hydrochloride, and triprolidine hydrochloride.

**[00263]** A class of therapeutic agents useful for administration in combination, prior to, after, or concomitantly with a chemerin C15 peptide are mast cell stabilizers such as cromolyn sodium and nedocromil.

**[00264]** Oxidative stress, in certain instances, is induced in cells with impaired autoregulatory and ischemic processes induced by immune or inflammatory disorders. In some embodiments, anti-oxidants useful for administration in combination, prior to, after, or concomitantly with a chemerin C15 peptide. Examples of suitable anti-oxidants useful in the methods of the invention include, but are not limited to, ascorbic acid, tocopherols, tocotrienols, carotinoids, glutathione, alpha-lipoic acid, ubiquinols, bioflavonoids, carnitine, and superoxide dismutase mimetics, such as, for example, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO), DOXYL, PROXYL nitroxide compounds; 4-hydroxy-2,2,6,6-tetramethyl-1-piperidinyloxy (Tempol), M-40401, M-40403, M-40407, M-40419, M-40484, M-40587, M-40588, and the like.

**[00265]** In some embodiments, methods are provided wherein anti-apoptotic therapeutic agents are administered in combination, prior to, after, or concomitantly with a chemerin C15 peptide. Examples of suitable anti-apoptotic agents are, for example, inhibitors of caspases, cathepsins, and TNF-α.

**[00266]** A class of therapeutic agents useful for administration in combination, prior to, after, or concomitantly with a chemerin C15 peptide are antimicrobial agents. Suitable antimicrobial compounds, include, but are not limited to, penicillins, such as, for example, amoxicillin, ampicillin, azlocillin, carbenicillin, cloxacillin, dicloxacillin, flucloxacillin, mezlocillin, nafcillin, penicillin, piperacillin, ticarcillin, and the like; beta-lactamase inhibitors; carbapenems, such as, for example, ertapenem, imipenem, meropenem, and the like; cephalosporins, such as, for example, cefaclor, cefamandole, cefoxitin, cefprozil, ceftiroxime, cefixime, cefdinir, cefditoren, cefoperazone, cefotaxime, cefpodoxime, cefadroxil, ceftazidime, ceftibuten, ceftizoxime, ceffiriaxone, cefazolin, cefixime, cephalexin, cefepime, and the like; quinolones, such as, for example, ciprofloxacin, enoxacin, gatifloxacin, levofloxacin, lomefloxacin, morifloxacin, norfloxacin, ofloxacin, trovafloxacin, and the like; macrolides, such as, for example, azithromycin, clarithromycin, dirithromycin, erythromycin, milbemycin, troleandomycin, and the like; monbactams, such as, for example, an LFA-1 antagonist, and the like; tetracyclins, such as, for example, demeclocyclin, doxycycline, minocycline, oxytetracyclin, tetracycline, and the like; aminoglycosides, such as, for example, amikacin, gentamicin, kanamycin, neomycin, netilmicin, paromomycin, streptomycin, tobramycin, and the like; carbacephem, such as, for example,

loracarbef, and the like; streptogramins; sulfonamides, such as, for example, mefanide, prontosil, sulfacetamide, sulfamethizole, sulfanilamide, sulfasalazine, sulfisoxazole, trimethoprim, trimethoprim-sultamethoxazole, and the like; other antimicrobials such as metronidazole; and the combination drugs such as for example, sulfamethoxazole and trimethoprim, and the like.

**[00267]** Other antimicrobial agents include the class of antiviral agents. Antiviral agents include, but are not limited to therapeutic agents such as entry inhibitors, reverse transcriptase inhibitors, nucleoside or nucleotide analogs, protease inhibitors, and inhibitors of viral release from host cells. Some illustrative therapeutic agents of this group, include, but are not limited to abacavir, acyclovir, adefovir, amantadine, amprenavir, arbidol, atazanavir, atripla, brivudine, cidofovir, combivir, darunavir, delavirdine, didanosine, docosanol, edoxudine, efavirenz, emtricitabine, enfuvirtide, entecavir, famciclovir, fomivirsen, foscarnet, fosfonet, ganciclovir, gardasil, ibacitabine, immunovir, idoxuridine, imiquimod, indinavir, inosine, interferon type III, interferon type II, interferon type I, interferon, lamivudine, lopinavir, loviride, maraviroc, moroxydine, nelfinavir, neviapine, nexavir, oseltamivir, penciclovir, peramivir, pleconaril, podophyllotoxin, raltegravir, ribavirin, rimantadine, ritonavir, saquinavir, stavudine, tenofovir, tenofovir disoproxil, tipranavir, trifluridine, trizivir, tromantadine, truvada, valaciclovir, valganciclovir, vicriviroc, vidarabine, viramidine, zalcitabine, zanamivir, zidovudine, and the like.

**[00268]** In some of the embodiments, the formulations administered to the skin comprise one or more antimicrobial or antibiotic agents.

**[00269]** In some of the embodiments, secretagogues are administered in combination, prior to, concomitantly with, or subsequent to administration of a chemerin C15 peptide. In some embodiments, increasing mucin or other fluid production in the eye is beneficial. Examples include but are not limited to Diquafasol, Rebamipide, and Eicosanoid 15-(S)-HETE.

## Examples

**[00270]** The following examples are illustrative and non-limiting to the scope of the formulations and methods described herein.

### Example 1: Effect of hC-15 on cytokine secretion by human macrophages

**[00271]** In this example, the ability of human chemerin C15 to inhibit secretion of cytokines from activated human macrophages was examined. For this experiment, the activity of the human chemerin C15 peptide AGEDPHSFYFPGQFA was compared to that of the human chemerin C17 peptide AGEDPHSFYFPGQFAFS. The C15 and C17 peptides were synthesized by solid phase synthesis using BOP coupling of FMOC protected amino acids with final cleavage from the resin with TFA. Peptides were purified by reverse phase C18 chromatography using a water/acetonitrile gradient.

**[00272]** Human macrophages were derived from human CD14+ monocytes obtained from 3 donors. On Day 1, the isolated monocytes were thawed and seeded in triplicate for each group in 1 ml RPMI 1640 GlutaMAX™ media (supplemented with 10% FBS, 100 U/ml penicillin, 100 µg/ml streptomycin, 0.05 µM mercaptoethanol, 1% NEAA and 1% sodium pyruvate) per well of a 24 well cell culture dish at a cell concentration of $5\times10^5$ cells/ml. M-CSF was added to each well to give a final concentration of 25 ng/ml. Cells were grown for 7 days at 37°C with 5% $CO_2$ to differentiate the cells into macrophages. Media and M-CSF were replaced after 4 days.

**[00273]** Following differentiation, the media containing M-CSF was removed. The cells were washed and vehicle control, dexamethasone, C15 or C17 were added to the appropriate wells. The test peptides were dissolved in 50% DMSO/water prior to addition. C-15 (MW 1669; 16.7 mg/ml) was added to a final concentration of 1 pM, 10 pM or 100 and C17 (MW 1904; 19.0 mg/ml) was added to a final concentration of 1 µM. Dexamethasone was added to a final concentration of 1 µM. Following addition to the wells, the plates were incubated at 37°C with 5% $CO_2$ for 1 hour. An equal volume of complete media was added to the non-treated wells. Control or test treatments were maintained at the correct concentration throughout the assay.

**[00274]** IFNγ (final concentration 20ng/ml) was then added to the appropriate wells. Following IFNγ addition, the plates were incubated at 37°C with 5% $CO_2$ for 4 hours. The concentration of vehicle control, test treatments or dexamethasone was maintained during IFNγ stimulation. LPS (final concentration 10ng/ml) was then added to the appropriate wells. Following LPS addition, the plates were incubated at 37°C with 5% $CO_2$ for 15 hours. After 6 hours, ~60µl of culture supernatant was removed from all wells and stored at -80°C for analysis. The concentration of vehicle control, test treatments or dexamethasone was maintained during LPS stimulation.

**[00275]** At 15 hours post LPS stimulation, the remaining cell culture supernatant was harvested and stored at -80°C until assayed. The concentration of vehicle control, test treatments or dexamethasone was maintained until culture termination.

**[00276]** Cell culture supernatants taken at 6 hours and 15 hours post LPS addition were assayed for the production of RANTES, TNFα, IL-1β, IL-6, IL-10, IL-12p40 (subunit common to IL-12 and IL-23) and IL-15 (negative control) using Luminex® technology (Procarta human cytokine kit; Panomics) following the manufacturer's instructions.

**[00277]** The results for the concentration of IL-1β and RANTES at 16 hours post-stimulation is shown in Figures 1A and 1B. Figure 1C shows the difference in RANTES expression between the 6 hour and 15 hours time points. Figure 1D shows the IL-10 expression at 16 hours. No inhibition of IL-15 was observed as expected.

**[00278]** At a dose as low as 1 pM, the human chemerin C15 peptide showed strong inhibition of human macrophage secretion of IL-1β and RANTES at 16 hours post-stimulation (approximately 45% and 65%, respectively) (Fig. 1A and 1B). For newly synthesized RANTES (i.e. the difference between the 6 and 15 hour time points), the inhibition was approximately 90%. The human chemerin C15 peptide also showed strong inhibition of human macrophage secretion of IL-12p40 at 16 hours post-stimulation (approximately 55%) (Fig. 1D). Dexamethasone also exhibited inhibition of IL-1β and RANTES secretion (approximately 30% and 50%, respectively for the 1 μM dosage), but the effect was less than that of C15. Dexamethasone inhibition of IL-12p40 secretion was slightly stronger than that of C15 (Fig. 1D). Dexamethasone also potently inhibited (~70%) the production of IL-10 which is an anti-inflammatory cytokine, whereas C15 only produced a modest decrease (~25%) in IL-10 (Fig. 1D). Since IL-10 is naturally anti-inflammatory, it is not desirable to inhibit IL-10. The human chemerin C17 peptide did not exhibit any significant inhibition of cytokine production even at 1 μM. Overall, the human chemerin peptide exhibited superior in potency to dexamethasone by showing similar effect on inflammatory cytokine levels at one millionth the dose.

## Example 2: Assay for ChemR23 or GPR1 Agonist or Antagonist Activity

**[00279]** Chemerin binds to two G protein-coupled receptors, ChemR23 (CMKLR1), and GPR1 in addition to CCRL2 which is not a G protein-coupled receptor. In order to determine the mode of action of chemerin C15 peptides, the ability of the chemerin peptides to act as antagonists or agonists of GCPRs was examined.

**[00280]** In this experiment, the agonist and/or antagonist activity of human chemerin C15 peptide AGEDPHSFYFPGQFA was compared to that of a mouse chemerin C15 peptide

AGEDPHGYFLPGQFA, human chemerin C16 peptide AGEDPHSFYFPGQFAF and human chemerin C17 peptide AGEDPHSFYFPGQFAFS.

**[00281]** The DiscoveRx PathHunter™ eXpress GPCR activity assay was employed to test agonist and antagonist activities of the chemerin peptides against the GPCRs ChemR23 and GPR1. Two assay formats were tested, the PathHunter β-Arrestin assay and the Hit Hunter cAMP Hunter assay.

*PathHunter β-Arrestin assay*

**[00282]** The PathHunter β-Arrestin assay monitors the activation of a GPCR in a homogenous, non-imaging assay format using a technology developed by DiscoveRx called complementation, which utilizes an enzyme fragment complementation (EFC) assay with β-galactosidase (β-Gal) as the functional reporter. The enzyme is split into two complementary portions expressed as fusion proteins in the cell. The Enzyme Acceptor (EA) is fused to β-Arrestin and the ProLink donor peptide is fused to the GPCR of interest. Upon GPCR stimulation, β-Arrestin is recruited to the receptor for desensitization, bringing the two fragments of β-Gal together and allowing complementation to occur. This will generate an active enzyme that can convert a chemiluminescent substrate and generate an output signal detectable on a standard microplate reader.

**[00283]** The assay involves CHO cell lines that express 1) a GPCR of interest (e.g. ChemR23 or GPR1) that has a fragment of the β-gal enzyme fused to the C-terminus of the receptor and 2) a β-arrestin fused to the main β-gal enzyme. When the agonist binds to the receptor, β-arrestin is recruited to the receptor and the β-gal enzyme is complemented by the fragment from the GPCR thus forming a functional β-gal enzyme. A substrate is then added and luminescence is generated to detect β-arrestin recruitment.

**[00284]** The protocol used was a standard protocol employed by DiscoveRx PathHunter™ profiling service. Briefly, PathHunter cell lines were expanded from freezer stocks in T25 flasks according to standard procedures and maintained in selective growth media prior to assay. Once it was established that the cells were healthy and growing normally, cells were passaged from flasks using cell dissociation reagent and seeded into white walled clear bottom 384-well microplates for compound profiling. For profiling, cells were seeded at a density of 5000 cells per well in a total volume of 20 μL and were allowed to adhere and recover overnight prior to compound addition.

**[00285]** For the agonist assay, intermediate dilution of compound stocks were generated such that 5 μL of 5X compound could be added to each well with a final DMSO concentration of 1 % of total volume. For profiling compound in agonist mode, the cells were incubated in the presence of compound at 37°C for 90 minutes.

**[00286]** For the antagonist assay, agonist dose curves were performed the morning of profiling to determine the EC80 value for the following antagonist testing with compounds. 5μL of 5X agonist (i.e. chemerin) was added to each well with an equal concentration of vehicle present. EC80 agonist concentration was determined directly from agonist dose curve. For antagonist determination, cells were preincubated with antagonist followed by agonist challenge at the EC80 concentration: 4. 5 μL of 5X compound added to cells and incubated at 37 °C for 30 minutes. 5. 5 μL of 6X EC80 agonist added to cells and incubated at 37 °C for 90 minutes.

**[00287]** Assay signal was generated through a single addition of 12.5 or 15 μL (50 % v/v) of PathHunter Detection reagent cocktail for agonist and antagonist assays respectively followed by one hour incubation at room temperature. Microplates were read following signal generation with a PerkinElmer Envision™ instrument for chemiluminescent signal detection

**[00288]** Dose curves in the presence and absence of compound were plotted using GraphPad Prism or Activity Base. For agonist mode assays, percentage activity was calculated using the following formula: % Activity =100% x (Mean RLU of test sample — mean RLU of vehicle control) / (mean MAX RLU control ligand — mean RLU of vehicle control)). For antagonist mode assays, percentage inhibition was calculated using the following formula: % Inhibition =100% x (1 — (Mean RLU of test sample — mean RLU of vehicle control) / (mean RLU of EC80 control — mean RLU of vehicle control)).

*Hit Hunter cAMP Hunter assay*

**[00289]** DiscoveRx have developed a panel of cell lines stably expressing non-tagged GPCRs that signal through cAMP. The Hit Hunter cAMP Hunter assay monitors the activation of a GPCR via Gi and Gs secondary messenger signaling in a homogenous, non-imaging assay format using a technology developed by DiscoveRx called complementation. This utilizes an enzyme frag ment complementation (EFC) assay with β-galactosidase (β-Gal) as the functional reporter. The enzyme is split into two complementary portions. Pro-Label donor peptide is fused to cAMP and in the assay competes with cAMP generated by cells for binding to a cAMP-specific antibody. Active β-Gal is formed by complementation with EA to any unbound ED-cAMP. The active enzyme can convert a chemiluminescent substrate to generate an output signal detectable on a standard microplate reader.

**[00290]** The protocol used was a standard protocol employed by DiscoveRx PathHunter™ profiling service. Briefly, cAMP Hunter cell lines were expanded from freezer stocks in T25 flasks according to standard procedures and maintained in selective growth media prior to assay. Once it was established that the cells were healthy and growing normally, cells were passaged from flasks using cell dissociation reagent buffer and seeded into white walled clear bottom 384-well

microplates for compound profiling. For profiling, cells were seeded at a density of 10000 cells per well in a total volume of 20 μL and were allowed to adhere and recover overnight prior to compound addition. Cells were treated the following day using the protocols shown below. cAMP modulation was determined using the DiscoveRx HitHunter cAMP XS+ assay.

**[00291]** For the agonist assay, media was aspirated from cells and replaced with 15 μL 2:1 HBSS/Hepes : cAMP XS+ Ab reagent. Intermediate dilution of compound stocks were generated such that 5 μL of 4X compound could be added to each well with a final vehicle concentration of 1 % of total volume. For profiling compound in agonist mode, the cells were incubated in the presence of compound at 37°C for 30 minutes.

**[00292]** For the antagonist assay, media was aspirated from cells and replaced with 10 μL 1:1 HBSS/Hepes : cAMP XS+ Ab reagent. Agonist dose curves were performed to determine the EC80 value for the following antagonist testing with compounds. 5 μL of 4X agonist (i.e. chemerin) was added to each well with an equal concentration of vehicle present. EC80 agonist concentration was determined directly from agonist dose curve. For antagonist determination, cells were pre-incubated with antagonist followed by agonist challenge at the EC80 concentration. 5 μL of 4X compound was added to cells and incubated at 37 °C for 30 minutes. 5 μL of 4X EC80 agonist was added to cells and incubated at 37 °C for 30 minutes.

**[00293]** Assay signal was generated through incubation with 20 μL cAMP XS+ ED/CL lysis cocktail for one hour followed by incubation with 20 μL cAMP XS+ EA reagent for three hours at room temperature. Microplates were read following signal generation with a PerkinElmer Envision™ instrument for chemiluminescent signal detection.

**[00294]** Dose curves in the presence and absence of compound were plotted using GraphPad Prism or Activity Base. For agonist mode assays, percentage activity is calculated using the following formula: % Activity =100% x (mean RLU of test sample — mean RLU of vehicle control) / (mean RLU of MAX control — mean RLU of vehicle control). For antagonist mode assays, percentage inhibition is calculated using the following formula: % Inhibition =100% x (1 — (mean RLU of test sample — mean RLU of vehicle control) / (mean RLU of EC80 control — mean RLU of vehicle control)).

**[00295]** A summary of the data is provided in Table 1 below for the GPR1 and CMKLR1 PathHunter Biosensor cell lines.

**Table 1. GPR1 and CMKLR1 PathHunter Biosensor Data**

| GPCR | Compound ID | [EC50] (M) | % Max Activity | Rank Order | [IC50] (M) | % Max Inhibition |
|---|---|---|---|---|---|---|
| GPR1 | mC15 | 3.7E-06 | 27.8% | 4 | >1.0E-5 | 0% |
| | C15 (human) | 1.7E-02 | 10.6% | 3 | >1.0E-5 | 0% |

| | | | | | | |
|---|---|---|---|---|---|---|
| | C16 (human) | 2.1E-09 | 87.9% | 2 | >1.0E-5 | 0% |
| | C17 (human) | 1.5E-09 | 80.9% | 1 | >1.0E-5 | 0% |
| **GPCR** | **Compound ID** | **[EC50] (M)** | **% Max Activity** | **Rank Order** | **[IC50] (M)** | **% Max Inhibition** |
| ChemR23 | mC15 | >1.0E-5 | 0.4% | 3 | >1.0E-5 | 0% |
| | C15 (human) | >1.0E-5 | 0.8% | 3 | >1.0E-5 | 0% |
| | C16 (human) | 2.9E-08 | 98.6% | 1 | >1.0E-5 | 0% |
| | C17 (human) | 4.8E-07 | 67.5% | 2 | >1.0E-5 | 0% |

**[00296]** A summary of the data is provided in Table 2 below for the mouse ChemR23 PathHunter and human ChemR23 cAMP Hunter Biosensor cell lines. PathHunter Biosensor cell lines.

**Table 2. ChemR23 PathHunter and human ChemR23 cAMP Hunter Biosensor Data**

| Compound Name | AssayName | AssayFormat | AssayTarget | ResultType | RC50(uM) |
|---|---|---|---|---|---|
| hrChemerin | Arrestin | Agonist | mChemR23 | EC50 | 0.0015405 |
| hrChemerin | cAMP | Agonist | ChemR23 | EC50 | 0.0040557 |
| mC15 | Arrestin | Agonist | ChemR23 | EC50 | >10 |
| mC15 | Arrestin | Antagonist | m ChemR23 | IC50 | >10 |
| mC15 | cAMP | Antagonist | ChemR23 | IC50 | >10 |
| C15 (human) | Arrestin | Agonist | m ChemR23 | EC50 | >10 |
| C15 (human) | Arrestin | Antagonist | m ChemR23 | IC50 | 9.6635 |
| C15 (human) | cAMP | Antagonist | ChemR23 | IC50 | >10 |
| C16 (human) | Arrestin | Agonist | m ChemR23 | EC50 | 0.038472 |
| C16 (human) | Arrestin | Antagonist | m ChemR23 | IC50 | >10 |
| C16 (human) | cAMP | Antagonist | ChemR23 | IC50 | >10 |
| C17 (human) | Arrestin | Agonist | m ChemR23 | EC50 | 0.84015 |
| C17 (human) | Arrestin | Antagonist | m ChemR23 | IC50 | >10 |
| C17 (human) | cAMP | Antagonist | ChemR23 | IC50 | >10 |

**[00297]** Agonist dose response curves for ChemR23 and GPR1 receptors are shown in Figures 2A and 2B. As shown in the table above and in the figure, neither human nor mouse chemerin C15 peptides acted as agonists for human ChemR23 or GPR1. Chemerin exhibited potent agonist activity for both receptors as expected. In addition, both human chemerin C16 and C17 peptides exhibited agonist activity.

**[00298]** For the antagonist assays, chemerin was stimulated to 80% maximum signal and antagonized with the chemerin peptides. Antagonist dose response curves for ChemR23 and GPR1 receptors are shown in Figures 2C and 2D. As shown in the table above and in the figure, neither human nor mouse chemerin C15 peptides acted as antagonists for human ChemR23 or GPR1.

**Example 3: Effect of Alanine Substitution in FYFP motif on C15 Anti-inflammatory activity**

**[00299]** The B-subunit of protein phosphatase 2A contains a FYFP motif that is similar to the FYFP motif in the human chemerin C15 peptide. This FYFP motif is conserved across species and

is critical for binding to the PP2A core enzyme (Davis AJ, et al. *J Biol Chem.* 2008;283:16104-14). The human wild-type PP2A B-subunit PR70 comprises the amino acid sequence IPTFYFPRGRP.

**[00300]** In this experiment, the importance of the FYFP motif in the human chemerin C15 peptide on anti-inflammatory activity was examined. The ability of the human chemerin C15 peptide AGEDPHSFYFPGQFA was compared to that of a substituted chemerin C15 peptide having the amino acid sequence AGEDPHGYFAPGQFA, where the second phenylalanine in the peptide is modified to alanine. The experiment was performed as described in Example 1. 0.1 pM 0.5 pM and 1 pM concentrations of the C15 and C15 mutant peptides were tested. Cytokine expression was determined as described in Example 1.

**[00301]** Figure 3 shows the percent inhibition of TNFα and RANTES expression in the presence of the C15 or C15 alanine substituted peptides. As shown in the figure, the C15 peptide was able to inhibit TNFα and RANTES expression by 61% and 47% respectively. In contrast, the mutant C15 polypeptide was unable to inhibit expression of either cytokine. This data demonstrates that the FYFP motif is important for the anti-inflammatory properties of the chemerin C15 peptide.

## Example 4: Ointment formulation of human chemerin C15 peptide

**[00302]** In this example, Human chemerin C15 peptide was formulated as an ointment follows:

**Table 3**

| Component | Amount |
|---|---|
| Human chemerin C15 peptide | 2.6 +/- 0.8 mg/g ointment |
| White Petroleum | 50% |
| Caprylic Capric Triglyceride | 45% |
| Beeswax | 5% |

**[00303]** In additional examples of an ointment, human chemerin C15 peptide is formulated as follows:

**Table 4**

| Component (% w/w) | Ointment 2728-74 | Ointment 2728-75 |
|---|---|---|
| Human chemerin C15 peptide | 2.6 +/- 0.8 mg/g ointment | 2.6 +/- 0.8 mg/g ointment |
| Dimethyl isosorbide | - | 10% |
| Butylated hydroxytoluene | 0.02% | 0.02% |
| PEG 400 | 15% | - |
| Span 80 | 2% | 2% |
| White wax | 10% | 10% |
| White petrolatum | 71.98% | 76.98$ |

## Example 5: Gel formulation of human chemerin C15 peptide

**[00304]** In this example, human chemerin C15 peptide is formulated as an gel follows:

**Table 5**

| Component (% w/w) | Gel 2728-60 | Gel 2728-76 |
|---|---|---|
| Human chemerin C15 peptide | 2.6 +/- 0.8 mg/ml gel | 2.6 +/- 0.8 mg/ml gel |
| Dimethyl isosorbide | 15% | 15% |
| Transcutol | 25% | 25% |
| Hexylene glycol | 12% | 12% |
| Propylene glycol | 5% | 5% |
| Methylparaben | 0.15% | 0.15% |
| Propylparaben | 0.05% | 0.05% |
| EDTA | 0.01% | 0.01% |
| Hydroxyethyl cellulose | - | 1% |
| Penmulen TR-1 | 0.5% | - |
| 25% Trolamine | q.s. pH 6.0 | q.s. pH 4.5 |
| Water | q.s. 100% | q.s. 100% |

## Example 6: Lotion formulation of human chemerin C15 peptide

**[00305]** In this example, human chemerin C15 peptide is formulated as an lotion follows:

**Table 6**

| Component (% w/w) | Lotion 2728-77 | Lotion 2728-72 |
|---|---|---|
| Human chemerin C15 peptide | 2.6 +/- 0.8 mg/ml lotion | 2.6 +/- 0.8 mg/ml lotion |
| Dimethyl isosorbide | 13% | 13% |
| Transcutol | 20% | 20% |
| Hexylene glycol | 10% | 10% |
| Propylene glycol | 4% | 4% |
| Methylparaben | 0.15% | 0.15% |
| Propylparaben | 0.05% | 0.05% |
| EDTA | 0.01% | 0.01% |
| Carbopol Ultrez 10 | 0.5% | 0.3% |
| Penmulen TR-1 | 0.2% | 0.2% |
| Isopropyl myristate | 3% | - |
| Oleyl alcohol | 5% | - |
| Cetyl alcohol | - | 2% |
| Light mineral oil | - | 5.5% |
| Oleic acid | - | 5% |
| Butylated hydroxytoluene | 0.2% | 0.2% |
| White petrolatum | 5% | - |
| 25% Trolamine | q.s. pH 6.0 | q.s. pH 6.0 |
| Water | q.s. 100% | q.s. 100% |

## Example 7: Solution formulation of human chemerin C15 peptide

**[00306]** In this example, human chemerin C15 peptide is formulated as a solution follows:

**Table 7**

| Component (% w/w) | Solution 2728-79 | Solution 2728-81 | Solution 2728-80 | Solution A |
|---|---|---|---|---|
| Human chemerin C15 peptide | 2.6 +/- 0.8 mg/ml solution | 2.6 +/- 0.8 mg/ml solution | 2.6 +/- 0.8 mg/ml solution | 2.6 +/- 0.8 mg/ml solution |
| Dimethyl isosorbide | 15% | 15% | - | |
| Transcutol | 25% | 25% | - | |
| Hexylene glycol | 12% | 12% | - | |
| Propylene glycol | 5% | 5% | - | |

| | | | | |
|---|---|---|---|---|
| DMSO | - | - | 99% | |
| 25% Trolamine | q.s. pH 4.5 | q.s. pH 6.0 | - | |
| Isopropyl myristate | | | | 45% |
| Alcohol | | | | 45% |
| Undecylenic acid | | | | 5% |
| Sodium lauryl sulfate | | | | 5% |
| Water | q.s. 100% | q.s. 100% | - | |

**Example 8: Skin Stability and Penetration of human chemerin C15 peptide**

**[00307]** In this example, the ability of the human C15 peptide to remain stable in and to penetrate human skin was examined. A DMSO form and an ointment comprising the C15 peptide were tested.

*Chemerin C15 peptide ointment*

**[00308]** The objective of the study was to determine whether human chemerin C15 peptide would diffuse through *in vitro* human skin maintained under flow-through conditions in Franz cells where the C15 peptide is administered as an ointment. Human chemerin C15 peptide was prepared as an ointment as described in Example 4. A 10% solution of the C15 ointment was prepare immediately prior to skin application. Female human skin obtained from abdominoplasty was maintained in tissue media and antibiotics and used within 3 days.

**[00309]** A standard Franz diffusion cell (LGA, Berkeley, CA) was used under static conditions (n=3). Approximately 200 µl of the 10% ointment solution was transferred to the surface of the skin and distributed on the surface by spatula. A thin liner was then applied for light pressure to the skin surface for 5 min after which the diffusion cell was occluded and maintained for 24 hours. After this time, the ointment was recovered by scraping a spatula over the skin surface and transferring the retained material to a 50/50 water-chloroform solution. The epidermis and dermis were then separated by heat and the epidermis extracted with a 50/50 water-chloroform solution. The epidermis was then transferred to a second tube and homogenized in PBS containing 0.1% protease inhibitor. The dermis was minced and homogenized in PBS containing 0.1% protease inhibitor. The receptor fluid was recovered and concentrated under vacuum. Ointment without C15 was applied to skin and the skin sampled in the same manner as a control (n=2).

**[00310]** C15 recovery from the dosing material, epidermis, and receptor fluid was determined by HPLC. C15 concentration in the dermis was determine by LC/MS. The skin surface and epidermis recoveries and epidermis homogenate samples were analyzed using the following reversed phase HPLC conditions:

**Table 8**

| | |
|---|---|
| HPLC | Shimadzu 20A system |
| Mobile phase | A-0.1% formic acid in water |

| | |
|---|---|
| | B-0.1% formic acid in acetonitrile |
| Column | Phenomenex Gemini™ C18 column (Cat. No. 00B-4439-E0, 4.6 × 50 mm, 3 μm) |
| Injection Volume | 5 μl |
| Gradient | 80% A + 20% B to 10% A + 90 % B (0-3 min) and 10% A + 90% B (3-3.5 min) |
| Flow rate | 800 μl/min |
| Detection | peak height at 275 nm at 1.92 min |
| LLQ | 150 ng/ml |

The dermis samples were analyzed using the following LC/MS/MS conditions:

**Table 9**

| | |
|---|---|
| HPLC | Shimadzu VP system with Shimadzu SIL-HTc autosampler |
| Mobil phase | A-0.2% formic acid in water<br>B-0.2% formic acid in acetonitrile |
| Column | 2.1 × 10 mm Peeke Scientific Duragel G C18 guard cartridge |
| Injection Volume | 100 μl |
| Gradient | 5% B (0.5 min) then 5-95% B (2 min) |
| Flow rate | 400 μl/min |
| Mass Spectrometer | Applied Biosystems/MDS SCIEC API 3000 |
| Interface | TurboIonSpray (ESI) at 400°C |
| Software | Analyst v1.4.1 |
| Polarity | Positive Ion |
| Q1/Q3 Ions | 803.7/120.4 for C15<br>256.2/167.2 for diphenyhydramine (I.S.)<br>272.1/215.2 for dextromethorphan (I.S.) |
| LLQ | 10 ng/ml |

**[00311]** Good mass balance was achieved with the sample recovery and extraction methods. Chloroform may have removed some C15 that had initially penetrated the epidermis. Low amounts of C15 were measured in the epidermis and dermis. Combined, both compartment accounted for less the 1% of the applied dose.

**Table 10**

| C15 applied mg | Skin Surface mg | % | Epidermis mg | % | Dermis homogenate ng | % | Receptor fluid | Total % |
|---|---|---|---|---|---|---|---|---|
| 2.19 | 0.74 | 33.6 | 1.53 | 70.2 | 0 | 0.00 | <LLQ | 103.8 |
| 3.52 | 1.17 | 33.3 | 2.25 | 64.1 | 77.4 | 0.02 | <LLQ | 97.4 |
| 2.06 | 0.83 | 40.6 | 1.45 | 71.2 | 238.2 | 0.12 | <LLQ | 111.8 |

*50% DMSO Solution Study*

**[00312]** The objective of the study was to determine whether human C15 peptide would diffuse through *in vitro* human skin maintained under flow-through conditions in Franz cells with 50% DMSO in water. 50% DMSO is considered an acceptable maximum for penetration enhancement.

**[00313]** The samples used in the study were mouse and human chemerin C15 peptides stored at -20 C°. The skin sample used was female human skin obtained from mammoplasty. A frozen sample was stored at -20 C° for 30 days. A fresh sample was obtained in tissue media and antibiotics and used within 3 days.

*Stability Study:*

**[00314]** An initial study was performed comparing stability of human C15 versus Mouse C15. Homogenates of frozen and fresh human skin were prepared to evaluate the degradation of C15 in skin. Frozen or fresh human skin were separately minced and homogenized in 3 ml water and the supernatant isolated. Supernatant was mixed with solutions of mouse or human C15 to yield a 0.5 mg/ml C15 solution. Each solution was incubated at 37°C and samples were taken at 0, 1, 2 and 24 hours for analysis of C15 (Fig. 3).

**[00315]** Human C15 was more stable than mouse C15 in this assay. Degradation of C15 was substantially lower in homogenates of frozen than of fresh skin. After 24 hours, C15 degradation in homogenate from frozen and fresh skin was 25% and 98%, respectively. Based on these findings, a 2% solution of human C15 was prepared for the diffusion cell tests.

*Franz cell Studies:*

**[00316]** Two studies of the dermal penetration of C15 were conducted with Franz cells:

1. A 1% solution of mouse C15 in 50% DMSO in water was applied to previously frozen human skin to develop the HPLC method for subsequent tests with human C15. This was done in triplicate.
2. A 2% solution of human C15 in 50% DMSO in water was applied to fresh human skin and epidermis, dermis, and receptor fluid were analyzed for C15.

**[00317]** Skin was rinsed, blotted dry, cut into circular pieces and conditioned in the Franz cell for 2 hours prior to C15 application. Flow-through, water-jacketed diffusion cells that exposed a skin area of 2.54 cm2 were used. The cells were maintained at 37°C, operated under static conditions and stirred at 700 rpm for 24 hr. PBS (pH = 7.0) was used as the receptor fluid. C15 solutions in 50% DMSO in water was prepared on the day of the experiments.

**[00318]** 400 µl of each C15 solution was pipetted in aliquots of 100 µl onto the skin surface and the diffusion cell sealed with parafilm. Diffusion cells were run in triplicate with a single control consisting of skin treated with vehicle only. Receptor fluid (≈5 mL) was collected at the end of 24

hours and concentrated by evaporation prior to analysis. The skin was blotted dry, tape-stripped three times to remove residual C15 and heat-separated at 50°C into epidermis and dermis. Epidermis was sonicated in 5% TCA for 10 minutes and the supernatant analyzed. Dermis was minced and homogenized in 5% TCA and the supernatant concentrated and analyzed.

**[00319]** For the mouse C15 experiment only the receptor fluid was analyzed.

**[00320]** A reverse-phase HPLC method was developed to quantify Human C15 (Shimamura et al., 2009). The separation was achieved using a Phenomenex Gemini™ C18 column (Cat. No. 00B-4439-E0, 4.6 × 50 mm, 3 μm) at 40°C in the Shimadzu 20A system. The mobile phase was mixed with (A) 0.1% formic in water and (B) 0.1% formic acid in acetonitrile. The separation was conducted using a gradient system of 80% A + 20% B to 10% A + 90% B (0-3 min) and 10% A + 90% B (3-3.5 min) at a flow rate of 0.8 ml/min. The injection volume was 5 μl. The eluent was monitored at 275 nm. Human C 15 was observed as a single peak in the chromatogram with retention time at about 1.8 min. The quantification of Human C 15 was achieved by external standard calibration. Results for human C15 are presented as % absorbed of the applied dose. See Table 11.

**[00321]** Very low levels of C15 were measured in the receptor fluid from each study. C15 receptor fluid levels were highest using frozen human skin and mouse C15 (0.3%). Human C15 was detected in the receptor fluid and epidermis. A broad peak at 1.8 min was observed with the dermis samples but could not be distinguished from a background peak. (Table 11). HPLC results and % absorbed for human C15 in fresh human skin (n=3).

**Table 11**

| Sample | Peak area 1.7-1.8 min | Net C15(ug) | Total C15 passaged through skin (ug) | % C15 in skin compartment |
|---|---|---|---|---|
| Skin 1 receptor fluid | 255 | 0.0053 | 1.26 | 0.02% |
| Skin 2 receptor fluid | 1587 | 0.0332 | 7.34 | 0.09% |
| Skin 3 receptor fluid | 84 ND | 0.0018 | 0.42 | 0.01% |
| Control receptor fluid | | | | |
| Skin 1 epidermis | 165899 | 3.50 | 700.72 | 8.76% |
| Skin 2 epidermis | 139517 | 2.95 | 590.32 | 7.38% |
| Skin 3 epidermis | 49493 | 1.07 | 213.58 | 2.67% |
| Control epidermis | ND | | | |
| Skin 1 dermis | Broad peak | | | |
| Skin 2 dermis | Broad peak | | | |
| Skin 3 dermis | Broad peak | | | |
| Control dermis | Broad peak | | | |

**[00322]** Human C15 does penetrate through human skin under *in vitro* flow-through conditions using penetration enhancement of 50% DMSO in water. Low levels are detected in the receptor fluid however higher levels are detected in the epidermis and most likely in the dermis.

**[00323]** The results from the two Frnz cell studies described above are summarized in the table below. The studies demonstrated that therapeutically relevant levels of C15 (e.g., >1 nM) can be delivered across the stratum corneum to the dermis or beyond. Penetration enhancers (e.g. DMSO) may not be necessary to achieve delivery to the dermis.

**Table 12**

| Sample | DMSO (50%) [C15] | Ointment [C15] |
|---|---|---|
| Skin1 Epidermis (2.54 $cm^2$)<br>Skin2 Epidermis (2.54 $cm^2$)<br>Skin3 Epidermis (2.54 $cm^2$) | 419,400 nM<br>353,500 nM<br>127,000 nM | 953,000 nM<br>1,406,000 nM<br>906,000 nM |
| Skin1 Dermis (2.54 $cm^2$)<br>Skin2 Dermis (2.54 $cm^2$)<br>Skin3 Dermis (2.54 $cm^2$) | NA*<br>NA*<br>NA* | 48 nM<br>149 nM<br>NS* |
| Skin1 Receptor Fluid (5 mL)<br>Skin2 Receptor Fluid (5 mL)<br>Skin3 Receptor Fluid (5 mL) | 151 nM<br>888 nM<br>50 nM | <10 nM<br><10 nM<br><10 nM |
| *NA no analysis possible, interference with HPLC detection.<br>*NS no sample<br>Study Outline: Formulated huC15 in DMSO (50% in water) or Ointment (50% Petrolatum, 45% coconut oil, 5% beeswax, no penetration enhancer) applied to fresh human skin. Epidermis, dermis and receptor fluid analyzed by HPLC or LCMS/MS (Ointment) for C15 after 24hrs. | | |

**Example 9: Microplaque Assay in Psoriasis patients**

**[00324]** The microplaque assay has been used successfully in evaluating topical treatments for psoriasis. The microplaque assay enables the direct comparison of different topical treatments and dosing's directly on psoriatic lesions. A template with 6 holes is adhered to a lesion. Patients visit the clinic daily to have a specific drug dose applied to a metal disk, each disk is then applied to a specific spot, and the arm is then wrapped and kept under occlusion until the next dosing occurs. Multiple formulations, control, and if desired, active comparator, can all be accommodated on one plaque. A typical microplaque assay involves 12-15 patients for 2 weeks.

**[00325]** In order to establish the clinical efficacy and bioavailability of C15 as a topical treatment for psoriasis, a Phase 0 microdosing study of two prototypical topical formulations of C15 is performed in patients with stable plaque psoriasis. In an exemplary microdosing study, a microplaque assay is performed wherein formulated drug is applied daily for 10 to 21 days to one of six test spots (2 cm diameter) on a single stable plaque on each of 15 test subjects. This format allows for the testing of C15 at 2 formulations and 3 concentrations with controls for each formulation and a medium strength steroid (Dexamethasone) or betamethasone Valorate as an active comparator.

**[00326]** In the study, all patients in each cohort will receive daily 0.2 ml applications of each test article applied to one of six uniform test sites cut into a hydrocolloid dressing which is placed over the study plaque on each patient. The test articles are applied by an investigator in a clinical setting during clinic hours. After application of each dose, the study plaque is occluded with an additional dressing until the next clinic visit. Delivering drug in excess and under occlusion greatly enhances the performance of the formulation and drug efficacy relative to more typical Phase 2/3 study designs in psoriasis. Even drugs such as Vitamin D analogs with slow onset (4-6 weeks in self-dosing patients) and very modest efficacy have demonstrated measurable improvement in the microplaque assay. Subjects are seen in the clinic for assessment of condition following treatment. The hydrocolloid dressing is removed, a digital image of the treated plaque is obtained, the treated sites is clinically scored, physical examination is performed, and samples for safety labs are collected. Total Clinical Score (TCS) of each treatment site is recorded at baseline, at pre-determined time period(s) during the study and following the last dosing. The TCS is the sum of erythema (0-3), scaling (0-3) and thickness (0-3). For each sign: 0= none; 1= mild; 2=moderate; 3=severe. The possible range for TCS is 0 to 9. In addition a Dynamic Severity Score (DSS) comparing each site to adjacent untreated area of the psoriasis plaque is recorded at baseline, at pre-determined time period(s) during the study and following the last dosing. The DDS is a 5-point system: -1 = worsened; 0=unchanged; 1= slight improvement; 2=clear improvement but not completely clear; 3= completely cleared. Efficacy measures of TCS and DSS are evaluated using descriptive statistics including mean, standard deviations, median, minimum, maximum, and percent change from baseline. All adverse events, including local and systemic events, reported during the study are listed, documenting course, severity, and outcome. All non-solicited adverse events are summarized by treatment group, severity, and relationship to study drug.

**[00327]** Additional microdosing studies can be designed to provide further exploration of additional formulations for informing Phase 2 studies or can be extended in length to address modest activity or slow onset of efficacy.

**[00328]** C15 *in vitro* inhibits cytokine production/secretion 40-60% within 15 hours. C15 appears to also inhibit cytokine message production. A recent study of the levels of IL-23 in involved and uninvolved skin from psoriasis patients demonstrates that IL-23 levels are 2-fold higher in the plaque than in non-involved skin. Our expectation that the onset of C15 effect will be observable in a microplaque time course is based on results obtained in a Phase 1 study of Stelara in which psoriasis patients showed a 50% improvement in PASI score within two weeks after a single dose. This same cohort of patients achieved maximal serum concentrations at 5 days post-injection. Stelara appears to achieve its therapeutic effect by clearing IL-23 via antibody-antigen binding and by inhibiting IL23p19 message.

**Example 10: Activity of C15 in a Mouse Model of Psoriasis**

**[00329]** In this example, the therapeutic activity of a human chemerin C15 peptide is tested in a mouse model of psoriasis. K5.Stat3C recombinant mice resemble human psoriasis based on clinical, histological, immunophenotypic, and biochemical criteria used to evaluate animal models of psoriasis. The K5.Stat3C mice constitutively express activated Stat2 in keritinocytes and epidermal hyperplasia upon stimulation with 12-0-tetradecanoylphorbol-13-acetate (TPA) topical treatment.

**[00330]** In an exemplary protocol, mice are treated topically on the ear with TPA (e.g. 3.4 nmol TPA in acetone) or acetone control to induce skin lesions 3 times per week for 4-8 weeks. Real-time PCR in skin samples is used to confirm upregulation of cytokine expression, including IL-23, IL012, TNF-α, IL-β, and/or IL-6. Following induction of skin lesions, formulations comprising the human chemerin C15 peptide or vehicle control are applied topically to the skin lesions daily for 6-12 days. Improvement in the lesions is assessed daily. It is expected that mice treated with the formulations containing the human chemerin C15 peptide will exhibit decreased cytokine expression in the psoriatic lesions and improvement in the psoriatic phenotype of the epidermis as assessed by visual inspection and histological examination of skin samples from the treated versus untreated mice.

**Example 11: Contact hypersensitivity assay**

**[00331]** In this example, the therapeutic activity of a human chemerin C15 peptide is tested in a contact hypersensitivity assay, which is an *in vivo* assay of cell-mediated immune function and a model for human allergic contact dermatitis. In this assay, epidermal cells are exposed to exogenous haptens which results in a delayed-type hypersensitive reaction that can be measured and quantified. The Langerhans cell, which is an $Ia^+$, bone marrow–derived, epidermal cell,

initiates sensitization to haptens by presenting antigens to CD4-bearing T lymphocytes, which, in turn, secrete lymphokines and recruit other cells to the site of the reaction.

**[00332]** Contact hypersensitivity consists of the afferent or initial sensitizing phase, and the efferent or elicitation phase. During the efferent phase, when epidermal cells encounter a particular antigen to which they have previously been exposed, localized swelling occurs (in rodents) and in humans results in eczema of the skin.

**[00333]** In an exemplary protocol, mice are shaved and the skin of their abdomens exposed to a hapten. After 6 days (the afferent phase), the baseline ear thickness is measured prior to initiation of the efferent phase. Finally, the ear is treated epicutaneously with the hapten solution and ear thickness is measured at approximately 24 hr. The model contact allergen used in the study is 2,4,6-trinitrochlorobenzene (TNCB; also known as picryl chloride) dissolved in an acetone/olive oil solution. Other exemplary allergens that can be used include, for examples, FITC, oxazalone, and DNFB. The change in ear thickness after allergen treatment can be
used to calculate the percent suppression of contact hypersensitivity. In exemplary embodiments, the mice are pre-treated with a formulation comprising a human chemerin C15 peptide to examine prevention or suppression of the allergic response. In additional exemplary embodiments, the mice are co-administer the hapten with a formulation comprising a human chemerin C15 peptide to examine prevention or suppression of the allergic response. In additional exemplary embodiments, the mice are treated with the hapten to induce the allergic response and then treated with a formulation comprising a human chemerin C15 peptide to examine treatment of the allergic response. It is expected that treatment with the human chemerin C15 peptide will result in prevention, suppression and/or treatment of the allergic response.

**[00334]** The examples and embodiments described herein are for illustrative purposes and various modifications or changes suggested to persons skilled in the art are to be included within the spirit and purview of this application and scope of the appended claims. The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

WHAT IS CLAIMED IS:

1. A topical formulation comprising:

(a) a chemerin C15 peptide in an amount effective for the treatment of an inflammatory dermatological disorder; and

(b) a pharmaceutically acceptable excipient for topical administration;

wherein the formulation minimizes systemic exposure.

2. The topical formulation of claim 1, wherein the amount of chemerin C15 peptide is effective for inhibiting secretion of one or more inflammatory cytokines by an antigen presenting cell.

3. The topical formulation of claim 1, wherein the amount of chemerin C15 peptide is effective for inhibiting NFκB nuclear translocation or NFκB-mediated gene transcription of an inflammatory cytokine in an antigen presenting cell.

4. The topical formulation of claim 2 or 3, wherein the inflammatory cytokine is IL-23, TNFα, IL-1β, IL-6 or RANTES.

5. The topical formulation of claim 4, wherein the inflammatory cytokine is IL-23.

6. The topical formulation of claim 4, wherein the inflammatory cytokine is TNFα.

7. The topical formulation of claim 4, wherein the inflammatory cytokine is IL-1β.

8. The topical formulation of claim 4, wherein the inflammatory cytokine is RANTES.

9. The topical formulation of claim 2, wherein the antigen presenting cell is an activated macrophage cell, myeloid dendritic cell, or plasmacytoid dendritic cell.

10. The topical formulation of claim 1, wherein the dermatological disorder is an immune disorder, a proliferative disorder, contact with an allergen and/or an irritant, an overproduction of sebum lipids; a fibroblast disorder, or a combination thereof.

11. The topical formulation of claim 1, wherein the dermatological disorder is psoriasis, atopic dermatitis, contact dermatitis, eczematous dermatitis, alopecia areata, scleredoma, a bullous disorder, acne, urticaria, rosacea, scar formation, or melanoma.

12. The topical formulation of any claim 11, wherein the dermatological disorder is psoriasis.

13. The topical formulation of any claim 11, wherein the dermatological disorder is dermatitis.

14. The topical formulation of any claim 11, wherein the dermatological disorder is atopic dermatitis.

15. The topical formulation of any claim 11, wherein the dermatological disorder is contact dermatitis.

16. The topical formulation of claim 1, wherein the chemerin C15 peptide is a human chemerin C15 peptide.

17. The topical formulation of claim 16, wherein the human chemerin C15 peptide comprises the sequence of amino acids AGEDPHSFYFPGQFA.

18. The topical formulation of claim 16, wherein the human chemerin C15 peptide consists essentially of the sequence of amino acids AGEDPHSFYFPGQFA.

19. The topical formulation of claim 1 formulated as an aerosol, liquid, ointment, cream, lotion, solution, spray, suspension, emulsion, paste, gel, powder, salve, plaster, paint, foam, stick, slow release nanoparticle, slow release microparticle, bioadhesive, patch, bandage or wound dressing.

20. The topical formulation of claim 19, formulated as an ointment.

21. The topical formulation of claim 20, wherein the ointment comprises about 1-10 mg of the chemerin C15 peptide per gram of ointment.

22. The topical formulation of claim 20, wherein the ointment comprises petrolatum.

23. The topical formulation of claim 20, wherein the ointment comprises caprylic capric triglyceride.

24. The topical formulation of claim 20, wherein the ointment comprises beeswax.

25. The topical formulation of claim 20, wherein the ointment comprises petrolatum, caprylic triglyceride and beeswax.

26. The topical formulation of claim 25, wherein the ointment comprises about 50% petrolatum, about 45% caprylic triglyceride and about 5% beeswax.

27. The topical formulation of claim 20, wherein the ointment comprises butylated hydroxytoluene, PEG 400, Span 80, white wax, and white petrolatum.

28. The topical formulation of claim 27, wherein the ointment comprises about 0.02% w/w butylated hydroxytoluene, about 15% w/w PEG 400, about 2% w/w Span 80, about 10% w/w white wax, and about 71.98% w/w white petrolatum.

29. The topical formulation of claim 20, wherein the ointment comprises butylated dimethyl isosorbide, butylated hydroxytoluene , Span 80, white wax, and white petrolatum.

30. The topical formulation of claim 29, wherein the ointment comprises about 10% w/w dimethyl isosorbide, about 0.02% w/w butylated hydroxytoluene , about 2% w/w Span 80, about 10% w/w white wax, and about 76.98% w/w white petrolatum.

31. The topical formulation of claim 19, formulated as a solution.

32. The topical formulation of claim 31, formulated as a solution that is applied as a spray.

33. The topical formulation of claim 31, wherein the solution comprises about 1-10 mg of the chemerin C15 peptide per ml of solution.

34. The topical formulation of claim 31, wherein the solution comprises isopropyl myristate, alcohol, undecylenic acid and sodium lauryl sulfate.

35. The topical formulation of claim 34, wherein the solution comprises about 45% isopropyl myristate, about 45% alcohol, about 5% undecylenic acid and about 5% sodium lauryl sulfate.

36. The topical formulation of claim 31, wherein the solution comprises DMSO.

37. The topical formulation of claim 36, wherein the solution comprises about 50% DMSO, and about 50% water

38. The topical formulation of claim 31, wherein the solution comprises dimethyl isosorbide, Transcutol, hexylene glycol, and propylene glycol.

39. The topical formulation of claim 38, wherein the solution comprises about 15% w/w dimethyl isosorbide, about 25% w/w Transcutol, about 12% w/w hexylene glycol, and about 5% w/w propylene glycol.

40. The topical formulation of claim 19, formulated as a cream.

41. The topical formulation of claim 40, wherein the cream comprises about 1-10 mg of the chemerin C15 peptide per ml of cream.

42. The topical formulation of claim 19, formulated as a lotion.

43. The topical formulation of claim 42, wherein the lotion comprises about 1-10 mg of the chemerin C15 peptide per ml of lotion.

44. The topical formulation of claim 42, wherein the lotion comprises Dimethyl isosorbide, Transcutol, Hexylene glycol, Propylene glycol, Methylparaben, Propylparaben, EDTA, Carbopol Ultrez 10, Penmulen TR-1, and Butylated hydroxytoluene.

45. The topical formulation of claim 42, wherein the lotion comprises Dimethyl isosorbide, Transcutol, Hexylene glycol, Propylene glycol, Methylparaben, Propylparaben, EDTA, Carbopol Ultrez 10, Penmulen TR-1, Isopropyl myristate, Oleyl alcohol, Butylated hydroxytoluene, and White petrolatum.

46. The topical formulation of claim 45, wherein the lotion comprises about 13% w/w Dimethyl isosorbide, about 20% w/w Transcutol, about 10% w/w Hexylene glycol, about 4% w/w Propylene glycol, about 0.015% w/w Methylparaben, about 0.05% w/w Propylparaben, about 0.01% w/w EDTA, about 0.5% w/w Carbopol Ultrez 10, about 0.2% w/w Penmulen TR-1, about

3% w/w Isopropyl myristate, about 5% w/w Oleyl alcohol, about 0.2% w/w Butylated hydroxytoluene, and about 5% w/w White petrolatum.

47. The topical formulation of claim 42, wherein the lotion comprises Dimethyl isosorbide, Transcutol, Hexylene glycol, Propylene glycol, Methylparaben, Propylparaben, EDTA, Carbopol Ultrez 10, Penmulen TR-1, Cetyl alcohol, Light mineral oil, Oleic acid, Butylated hydroxytoluene.

48. The topical formulation of claim 47, wherein the lotion comprises about 13% w/w Dimethyl isosorbide, about 20% w/w Transcutol, about 10% w/w Hexylene glycol, about 4% w/w Propylene glycol, about 0.015% w/w Methylparaben, about 0.05% w/w Propylparaben, about 0.01% w/w EDTA, about 0.3% w/w Carbopol Ultrez 10, about 0.2% w/w Penmulen TR-1, about 2% w/w Cetyl alcohol, about 5.5% w/w Light mineral oil, about 5% w/w Oleic acid, and about 0.2% w/w Butylated hydroxytoluene.

49. The topical formulation of claim 1, wherein the topical formulation comprises a skin penetration agent.

50. The topical formulation of claim 49, wherein the skin penetration agent is DMSO.

51. The topical formulation of claim 1, wherein the topical formulation comprises a gelling agent.

52. The topical formulation of claim 1, wherein the topical formulation comprises an emollient.

53. The topical formulation of claim 1, wherein the topical formulation comprises an anti-oxidant.

54. The topical formulation of claim 1, wherein the topical formulation comprises a skin protecting agent.

55. The topical formulation of claim 1, wherein the topical formulation comprises an irritation-mitigating agent.

56. The topical formulation of claim 1, wherein the topical formulation comprises a dry-feel modifier.

57. The topical formulation of claim 1, wherein the topical formulation comprises a surfactant.

58. The topical formulation of claim 1, wherein the topical formulation comprises a preservative.

59. The topical formulation of claim 1, wherein the topical formulation comprises a chelating agent.

60. The topical formulation of claim 1, wherein the topical formulation comprises a lubricant.

61. The topical formulation of claim 1, wherein the topical formulation comprises a thickening agent.

62. The topical formulation of claim 1, wherein the topical formulation comprises at least one additional therapeutic agent.

63. The topical formulation of claim 62, wherein the additional therapeutic agent is an antioxidant, anti-inflammatory agent, antiangiogenic agent, anti-apoptotic agent, vascular endothelial growth factor inhibitor, antimicrobial or antiviral agent.

64. The topical formulation of claim 62, wherein the additional therapeutic agent is a corticosteroid.

65. A method of treating of an inflammatory dermatological disorder in an individual in need thereof, comprising administering to the individual a therapeutically-effective amount of a topical formulation comprising a human chemerin C15 peptide, wherein the topical formulation minimizes systemic exposure to the individual.

66. The method of claim 65, wherein administration inhibits the secretion one or more inflammatory cytokines by an antigen presenting cell.

67. The method of claim 66, wherein administration inhibits NFκB nuclear translocation or NFκB-mediated gene transcription of an inflammatory cytokine in an antigen presenting cell.

68. The method of claim 66 or 67, wherein the inflammatory cytokine is IL-23, TNFα, IL-1β, IL-6 or RANTES.

69. The method of claim 68, wherein the inflammatory cytokine is IL-23.

70. The method of claim 68, wherein the inflammatory cytokine is TNFα.

71. The method of claim 68, wherein the inflammatory cytokine is IL-1β.

72. The method of claim 68, wherein the inflammatory cytokine is RANTES.

73. The method of claim 68, wherein the antigen presenting cell is an activated macrophage cell, myeloid dendritic cell, a plasmacytoid dendritic cell.

74. The method of claim 65, wherein the chemerin C15 peptide comprises the sequence of amino acids AGEDPHSFYFPGQFA.

75. The method of claim 65, wherein the wherein the chemerin C15 peptide consists essentially of the sequence of amino acids AGEDPHSFYFPGQFA.

76. The method of claim 65, wherein the dermatological disorder is an immune disorder, a proliferative disorder, contact with an allergen and/or an irritant, an overproduction of sebum lipids; a fibroblast disorder, or a combination thereof.

77. The method of claim 65, wherein the dermatological disorder is psoriasis, atopic dermatitis, contact dermatitis, eczematous dermatitis, alopecia areata, scleredoma, a bullous disorder, acne, urticaria, rosacea, scar formation, or melanoma.

78. The method of claim 77, wherein the dermatological disorder is psoriasis.

79. The method of claim 77, wherein the dermatological disorder is dermatitis.

80. The method of claim 77, wherein the dermatological disorder is atopic dermatitis.

81. The method of claim 77, wherein the dermatological disorder is contact dermatitis.

82. The method of claim 65, wherein the topical formulation is in the form of an aerosol, liquid, ointment, cream, lotion, solution, suspension, emulsion, paste, gel, powder, salve, plaster, paint, foam, stick, slow release nanoparticle, slow release microparticle, bioadhesive, patch, bandage or wound dressing.

83. The method of claim of claim 82, wherein the topical formulation is an ointment.

84. The method of claim of claim 83, wherein the ointment comprises about 1-10 mg of the chemerin C15 peptide per gram of ointment.

85. The method of claim of claim 83, wherein the ointment comprises petrolatum.

86. The method of claim of claim 83, wherein the ointment comprises caprylic capric triglyceride.

87. The method of claim of claim 83, wherein the ointment comprises beeswax.

88. The method of claim of claim 83, wherein the ointment comprises petrolatum, caprylic triglyceride and beeswax.

89. The method of claim of claim 88, wherein the ointment comprises about 50% petrolatum, about 45% caprylic triglyceride and about 5% beeswax.

90. The method of claim of claim 83, wherein the ointment comprises butylated hydroxytoluene, PEG 400, Span 80, white wax, and white petrolatum.

91. The method of claim of claim 90, wherein the ointment comprises about 0.02% w/w butylated hydroxytoluene, about 15% w/w PEG 400, about 2% w/w Span 80, about 10% w/w white wax, and about 71.98% w/w white petrolatum.

92. The method of claim of claim 83, wherein the ointment comprises butylated dimethyl isosorbide, butylated hydroxytoluene , Span 80, white wax, and white petrolatum.

93. The method of claim of claim 92, wherein the ointment comprises about 10% w/w dimethyl isosorbide, about 0.02% w/w butylated hydroxytoluene , about 2% w/w Span 80, about 10% w/w white wax, and about 76.98% w/w white petrolatum.

94. The method of claim of claim 82, wherein the topical formulation is a solution.

95. The method of claim of claim 94, formulated as a solution that is applied as a spray.

96. The method of claim of claim 94, wherein the solution comprises about 1-10 mg of the chemerin C15 peptide per ml of solution.

97. The method of claim of claim 94, wherein the solution comprises isopropyl myristate, alcohol, undecylenic acid and sodium lauryl sulfate.

98. The method of claim of claim 97, wherein the solution comprises about 45% isopropyl myristate, about 45% alcohol, about 5% undecylenic acid and about 5% sodium lauryl sulfate.

99. The method of claim of claim 94, wherein the solution comprises DMSO.

100. The method of claim of claim 99, wherein the solution comprises about 50% DMSO, and about 50% water

101. The method of claim of claim 94, wherein the solution comprises dimethyl isosorbide, Transcutol, hexylene glycol, and propylene glycol.

102. The method of claim of claim 101, wherein the solution comprises about 15% w/w dimethyl isosorbide, about 25% w/w Transcutol, about 12% w/w hexylene glycol, and about 5% w/w propylene glycol.

103. The method of claim of claim 82, wherein the topical formulation is a cream.

104. The method of claim of claim 103, wherein the cream comprises about 1-10 mg of the chemerin C15 peptide per ml of cream.

105. The method of claim of claim 82, wherein the topical formulation is a lotion.

106. The method of claim of claim 105, wherein the lotion comprises about 1-10 mg of the chemerin C15 peptide per ml of lotion.

107. The method of claim of claim 105, wherein the lotion comprises Dimethyl isosorbide, Transcutol, Hexylene glycol, Propylene glycol, Methylparaben, Propylparaben, EDTA, Carbopol Ultrez 10, Penmulen TR-1, and Butylated hydroxytoluene.

108. The method of claim of claim 105, wherein the lotion comprises Dimethyl isosorbide, Transcutol, Hexylene glycol, Propylene glycol, Methylparaben, Propylparaben, EDTA, Carbopol Ultrez 10, Penmulen TR-1, Isopropyl myristate, Oleyl alcohol, Butylated hydroxytoluene, and White petrolatum.

109. The method of claim of claim 108, wherein the lotion comprises about 13% w/w Dimethyl isosorbide, about 20% w/w Transcutol, about 10% w/w Hexylene glycol, about 4% w/w Propylene glycol, about 0.015% w/w Methylparaben, about 0.05% w/w Propylparaben, about 0.01% w/w EDTA, about 0.5% w/w Carbopol Ultrez 10, about 0.2% w/w Penmulen TR-1, about 3% w/w Isopropyl myristate, about 5% w/w Oleyl alcohol, about 0.2% w/w Butylated hydroxytoluene, and about 5% w/w White petrolatum.

110. The method of claim of claim 105, wherein the lotion comprises Dimethyl isosorbide, Transcutol, Hexylene glycol, Propylene glycol, Methylparaben, Propylparaben, EDTA, Carbopol Ultrez 10, Penmulen TR-1, Cetyl alcohol, Light mineral oil, Oleic acid, Butylated hydroxytoluene.

111. The method of claim of claim 110, wherein the lotion comprises about 13% w/w Dimethyl isosorbide, about 20% w/w Transcutol, about 10% w/w Hexylene glycol, about 4% w/w Propylene glycol, about 0.015% w/w Methylparaben, about 0.05% w/w Propylparaben, about 0.01% w/w EDTA, about 0.3% w/w Carbopol Ultrez 10, about 0.2% w/w Penmulen TR-1, about 2% w/w Cetyl alcohol, about 5.5% w/w Light mineral oil, about 5% w/w Oleic acid, and about 0.2% w/w Butylated hydroxytoluene.

112. The method of claim of claim 65, wherein the topical formulation comprises a skin penetration agent.

113. The method of claim of claim 112, wherein the skin penetration agent is DMSO.

114. The method of claim of claim 65, wherein the topical formulation comprises a gelling agent.

115. The method of claim of claim 65, wherein the topical formulation comprises an emollient.

116. The method of claim of claim 65, wherein the topical formulation comprises an anti-oxidant.

117. The method of claim of claim 65, wherein the topical formulation comprises a skin protecting agent.

118. The method of claim of claim 65, wherein the topical formulation comprises an irritation-mitigating agent.

119. The method of claim of claim 65, wherein the topical formulation comprises a dry-feel modifier.

120. The method of claim of claim 65, wherein the topical formulation comprises a surfactant.

121. The method of claim of claim 65, wherein the topical formulation comprises a preservative.

122. The method of claim of claim 65, wherein the topical formulation comprises a chelating agent.

123. The method of claim of claim 65, wherein the topical formulation comprises a lubricant.

124. The method of claim of claim 65, wherein the topical formulation comprises a thickening agent.

125. The method of claim 65, wherein the topical formulation comprises at least one additional therapeutic agent.

126. The method of claim 125, wherein the additional therapeutic agent is an antioxidant, anti-inflammatory agent, antiangiogenic agent, anti-apoptotic agent, vascular endothelial growth factor inhibitor, antimicrobial or antiviral agent.

127. The method of claim 125, wherein the additional therapeutic agent is a corticosteroid.

128. The method of claim 65, wherein the topical formulation is topically applied to the skin, eye, mouth, nose, vaginal mucosa or anal mucosa.

129. The method of claim 128, wherein administration of the topical formulation results in a local tissue concentration of the chemerin C15 peptide of greater than about 0.1 pM-100 nM, greater than about 1 pM-10 nM, greater than about 1pM-1 nM, greater than about 1-100 pM, or greater than about 1-10 pM at about 1-12 hours following administration to the individual.

130. The method of claim 129, wherein administration of the topical formulation results in a systemic concentration of less than about 100 pM, less than about 10 pM, less than about 1 pM, less than about 0.1 pM , or less than about 0.01 pM.

131. Use of a human chemerin C15 peptide for the manufacture of a topical formulation comprising a therapeutically-effective amount of the peptide for treating an inflammatory dermatological disorder, wherein the formulation is formulated to minimize systemic exposure.

132. The use of claim 131, wherein the amount of the human chemerin C15 peptide is effective for inhibiting the secretion one or more inflammatory cytokines by an antigen presenting cell.

133. The use of claim 131, wherein the amount of the human chemerin C15 peptide is effective for inhibiting the NFκB nuclear translocation or NFκB-mediated gene transcription of an inflammatory cytokine in an antigen presenting cell.

134. The use of claim 132 or 133, wherein the inflammatory cytokine is IL-23, TNFα, IL-1β, IL-6 or RANTES.

135. The use of claim 134, wherein the inflammatory cytokine is IL-23.

136. The use of claim 134, wherein the inflammatory cytokine is TNFα.

137. The use of claim 134, wherein the inflammatory cytokine is IL-1β.

138. The use of claim 134, wherein the inflammatory cytokine is RANTES.

139. The use of claim 134, wherein the antigen presenting cell is an activated macrophage cell, myeloid dendritic cell, a plasmacytoid dendritic cell.

140. The use of claim 131, wherein the chemerin C15 peptide comprises the sequence of amino acids AGEDPHSFYFPGQFA.

141. The use of claim 131, wherein the wherein the chemerin C15 peptide consists essentially of the sequence of amino acids AGEDPHSFYFPGQFA.

142. The use of claim 131, wherein the dermatological disorder is an immune disorder, a proliferative disorder, contact with an allergen and/or an irritant, an overproduction of sebum lipids; a fibroblast disorder, or a combination thereof.

143. The use of claim 131, wherein the dermatological disorder is psoriasis, atopic dermatitis, contact dermatitis, eczematous dermatitis, alopecia areata, scleredoma, a bullous disorder, acne, urticaria, rosacea, scar formation, or melanoma.

144. The use of claim 144, wherein the dermatological disorder is psoriasis.

145. The use of claim 144, wherein the dermatological disorder is dermatitis.

146. The use of claim 144, wherein the dermatological disorder is atopic dermatitis.

147. The use of claim 144, wherein the dermatological disorder is contact dermatitis.

148. The use of claim 131, wherein the topical formulation is in the form of an aerosol, liquid, ointment, cream, lotion, solution, suspension, emulsion, paste, gel, powder, salve, plaster, paint, foam, stick, slow release nanoparticle, slow release microparticle, bioadhesive, patch, bandage or wound dressing.

149. The use of claim of claim 148, wherein the topical formulation is an ointment.

150. The use of claim of claim 149, wherein the ointment comprises about 1-10 mg of the chemerin C15 peptide per gram of ointment.

151. The use of claim of claim 149, wherein the ointment comprises petrolatum.

152. The use of claim of claim 149, wherein the ointment comprises caprylic capric triglyceride.

153. The use of claim of claim 149, wherein the ointment comprises beeswax.

154. The use of claim of claim 149, wherein the ointment comprises petrolatum, caprylic triglyceride and beeswax.

155. The use of claim of claim 154, wherein the ointment comprises about 50% petrolatum, about 45% caprylic triglyceride and about 5% beeswax.

156. The use of claim of claim 149, wherein the ointment comprises butylated hydroxytoluene, PEG 400, Span 80, white wax, and white petrolatum.

157. The use of claim of claim 156, wherein the ointment comprises about 0.02% w/w butylated hydroxytoluene, about 15% w/w PEG 400, about 2% w/w Span 80, about 10% w/w white wax, and about 71.98% w/w white petrolatum.

158. The use of claim of claim 149, wherein the ointment comprises butylated dimethyl isosorbide, butylated hydroxytoluene , Span 80, white wax, and white petrolatum.

159. The use of claim of claim 158, wherein the ointment comprises about 10% w/w dimethyl isosorbide, about 0.02% w/w butylated hydroxytoluene , about 2% w/w Span 80, about 10% w/w white wax, and about 76.98% w/w white petrolatum.

160. The use of claim of claim 148, wherein the topical formulation is a solution.

161. The use of claim of claim 160, formulated as an solution that is applied as a spray.

162. The use of claim of claim 160, wherein the solution comprises about 1-10 mg of the chemerin C15 peptide per ml of solution.

163. The use of claim of claim 160, wherein the solution comprises isopropyl myristate, alcohol, undecylenic acid and sodium lauryl sulfate.

164. The use of claim of claim 163, wherein the solution comprises about 45% isopropyl myristate, about 45% alcohol, about 5% undecylenic acid and about 5% sodium lauryl sulfate.

165. The use of claim of claim 160, wherein the solution comprises DMSO.

166. The use of claim of claim 166, wherein the solution comprises about 50% DMSO, and about 50% water

167. The use of claim of claim 160, wherein the solution comprises dimethyl isosorbide, Transcutol, hexylene glycol, and propylene glycol.

168. The use of claim of claim 168, wherein the solution comprises about 15% w/w dimethyl isosorbide, about 25% w/w Transcutol, about 12% w/w hexylene glycol, and about 5% w/w propylene glycol.

169. The use of claim of claim 148, wherein the topical formulation is a cream.

170. The use of claim of claim 169, wherein the cream comprises about 1-10 mg of the chemerin C15 peptide per ml of cream.

171. The use of claim of claim 148, wherein the topical formulation is a lotion.

172. The use of claim of claim 171, wherein the lotion comprises about 1-10 mg of the chemerin C15 peptide per ml of lotion.

173. The use of claim of claim 171, wherein the lotion comprises Dimethyl isosorbide, Transcutol, Hexylene glycol, Propylene glycol, Methylparaben, Propylparaben, EDTA, Carbopol Ultrez 10, Penmulen TR-1, and Butylated hydroxytoluene.

174. The use of claim of claim 171, wherein the lotion comprises Dimethyl isosorbide, Transcutol, Hexylene glycol, Propylene glycol, Methylparaben, Propylparaben, EDTA, Carbopol Ultrez 10, Penmulen TR-1, Isopropyl myristate, Oleyl alcohol, Butylated hydroxytoluene, and White petrolatum.

175. The use of claim of claim 174, wherein the lotion comprises about 13% w/w Dimethyl isosorbide, about 20% w/w Transcutol, about 10% w/w Hexylene glycol, about 4% w/w Propylene glycol, about 0.015% w/w Methylparaben, about 0.05% w/w Propylparaben, about 0.01% w/w EDTA, about 0.5% w/w Carbopol Ultrez 10, about 0.2% w/w Penmulen TR-1, about 3% w/w Isopropyl myristate, about 5% w/w Oleyl alcohol, about 0.2% w/w Butylated hydroxytoluene, and about 5% w/w White petrolatum.

176. The use of claim of claim 171, wherein the lotion comprises Dimethyl isosorbide, Transcutol, Hexylene glycol, Propylene glycol, Methylparaben, Propylparaben, EDTA, Carbopol Ultrez 10, Penmulen TR-1, Cetyl alcohol, Light mineral oil, Oleic acid, Butylated hydroxytoluene.

177. The use of claim of claim 176, wherein the lotion comprises about 13% w/w Dimethyl isosorbide, about 20% w/w Transcutol, about 10% w/w Hexylene glycol, about 4% w/w Propylene glycol, about 0.015% w/w Methylparaben, about 0.05% w/w Propylparaben, about 0.01% w/w EDTA, about 0.3% w/w Carbopol Ultrez 10, about 0.2% w/w Penmulen TR-1, about 2% w/w Cetyl alcohol, about 5.5% w/w Light mineral oil, about 5% w/w Oleic acid, and about 0.2% w/w Butylated hydroxytoluene.

178. The use of claim of claim 131, wherein the topical formulation comprises a skin penetration agent.

179. The use of claim of claim 178, wherein the skin penetration agent is DMSO.

180. The use of claim of claim 131, wherein the topical formulation comprises a gelling agent.

181. The use of claim of claim 131, wherein the topical formulation comprises an emollient.

182. The use of claim of claim 131, wherein the topical formulation comprises an anti-oxidant.

183. The use of claim of claim 131, wherein the topical formulation comprises a skin protecting agent.

184. The use of claim of claim 131, wherein the topical formulation comprises an irritation-mitigating agent.

185. The use of claim of claim 131, wherein the topical formulation comprises a dry-feel modifier.

186. The use of claim of claim 131, wherein the topical formulation comprises a surfactant.

187. The use of claim of claim 131, wherein the topical formulation comprises a preservative.

188. The use of claim of claim 131, wherein the topical formulation comprises a chelating agent.

189. The use of claim of claim 131, wherein the topical formulation comprises a lubricant.

190. The use of claim of claim 131, wherein the topical formulation comprises a thickening agent.

191. The use of claim 131, wherein the topical formulation comprises at least one additional therapeutic agent.

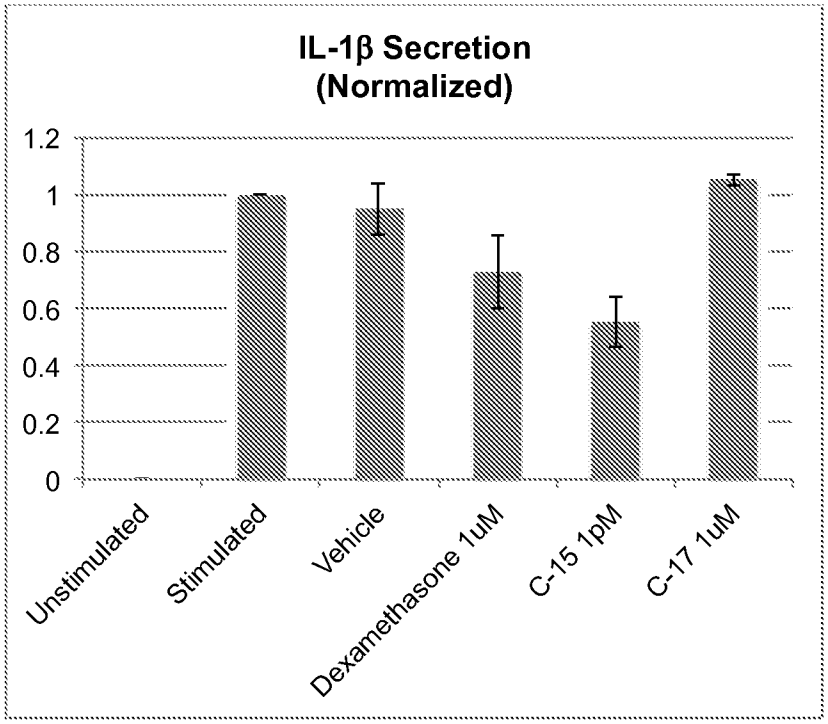
192. The use of claim 191, wherein the additional therapeutic agent is an antioxidant, anti-inflammatory agent, antiangiogenic agent, anti-apoptotic agent, vascular endothelial growth factor inhibitor, antimicrobial or antiviral agent.

193. The use of claim 191, wherein the additional therapeutic agent is a corticosteroid.

194. The use of claim 131, wherein the topical formulation is formulated for application to the skin, eye, mouth, nose, vaginal mucosa or anal mucosa.

FIG. 1

A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Stimulated
Vehicle
Dexamethasone 1uM
C-15 1pM
C-17 1uM

B

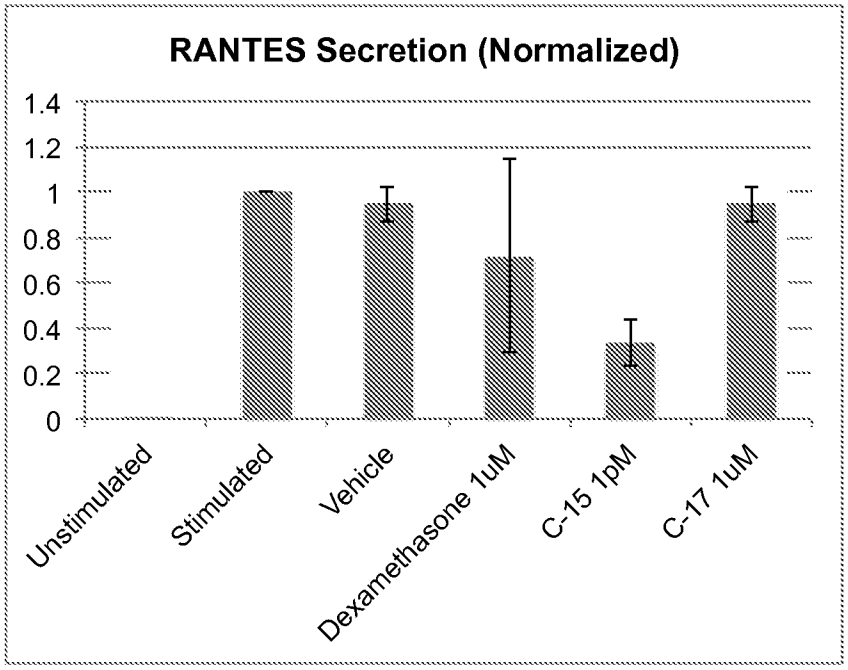
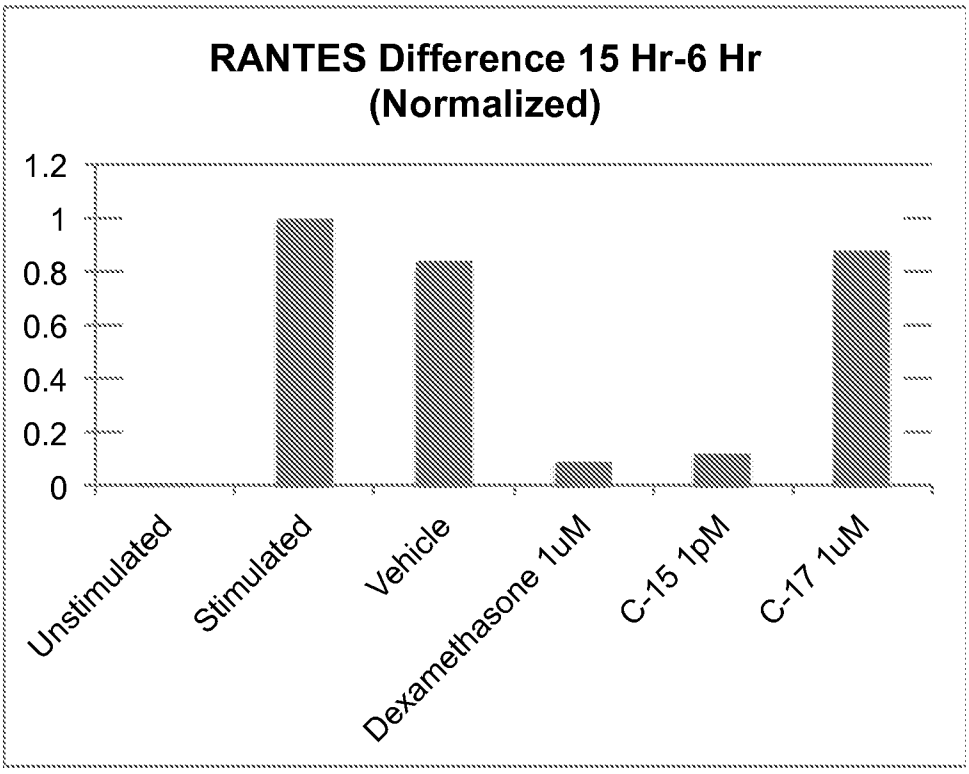

RANTES Secretion (Normalized)
1.4
1.2
1
0.8
0.6
0.4
0.2
0
Unstimulated
Stimulated
Vehicle
Dexamethasone 1uM
C-15 1pM
C-17 1uM

FIG. 1 cont'd

C

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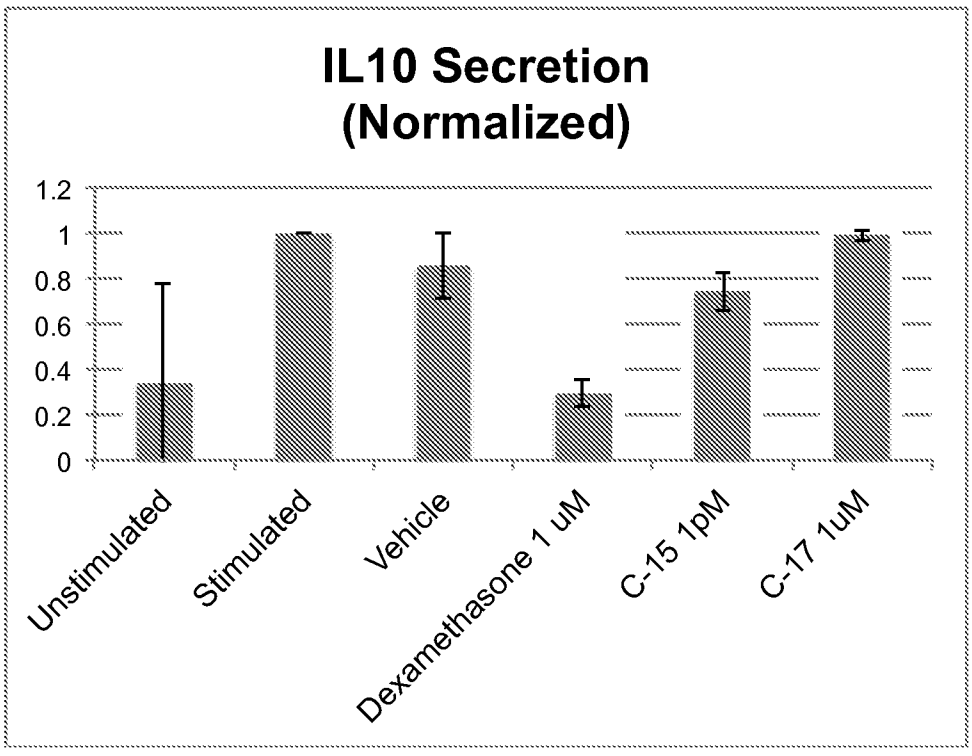

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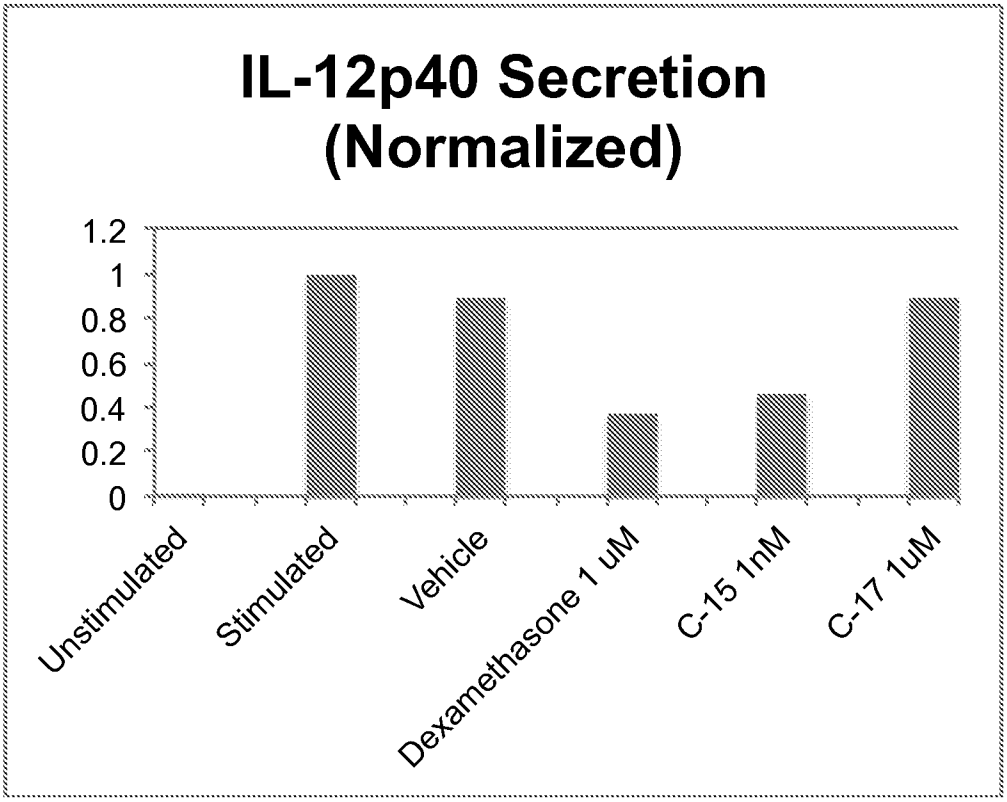
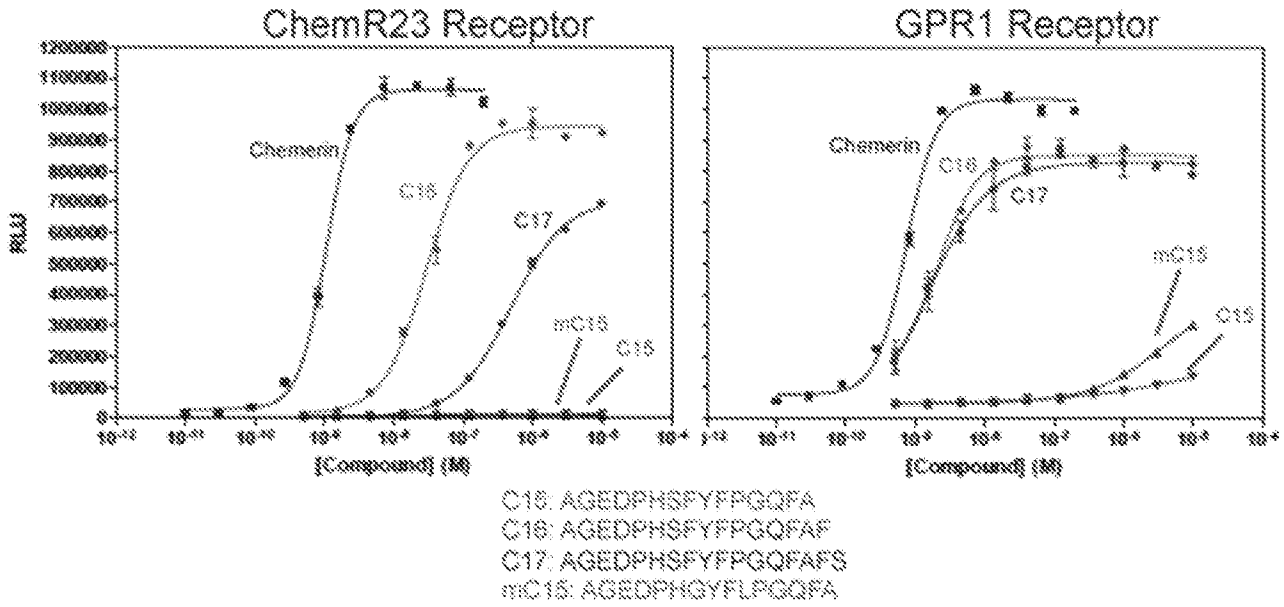

IL-12p40 Secretion (Normalized)
1.2
1
0.8
0.6
0.4
0.2
0
Unstimulated
Stimulated
Vehicle
Dexamethasone 1 uM
C-15 1nM
C-17 1uM

FIG. 2

A


ChemR23 Receptor
GPR1 Receptor
RLU
Chemerin
C16
C17
mC15
C15
[Compound] (M)
C16: AGEDPHSFYFPGQFA
C16: AGEDPHSFYFPGQFAF
C17: AGEDPHSFYFPGQFAFS
mC15: AGEDPHGYFLPGQFA

B

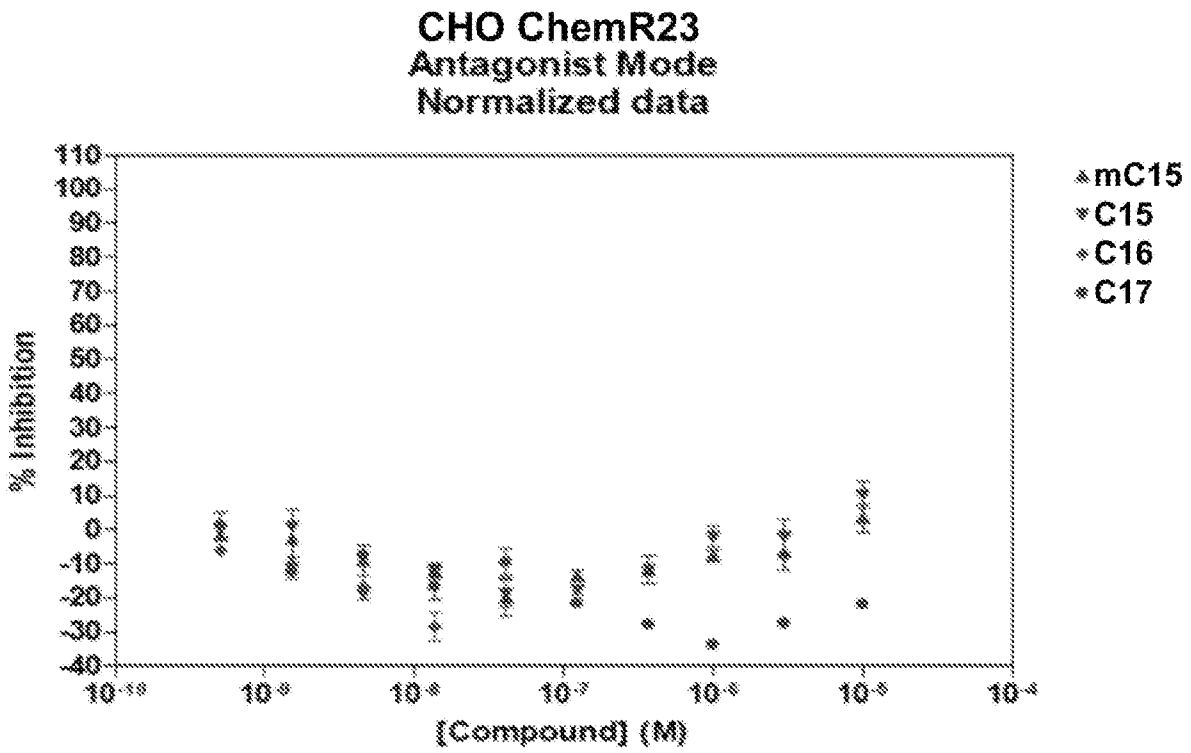

CHO ChemR23
Antagonist Mode
Normalized data
% Inhibition
[Compound] (M)
mC15
C15
C16
C17

FIG. 2 cont'd

C

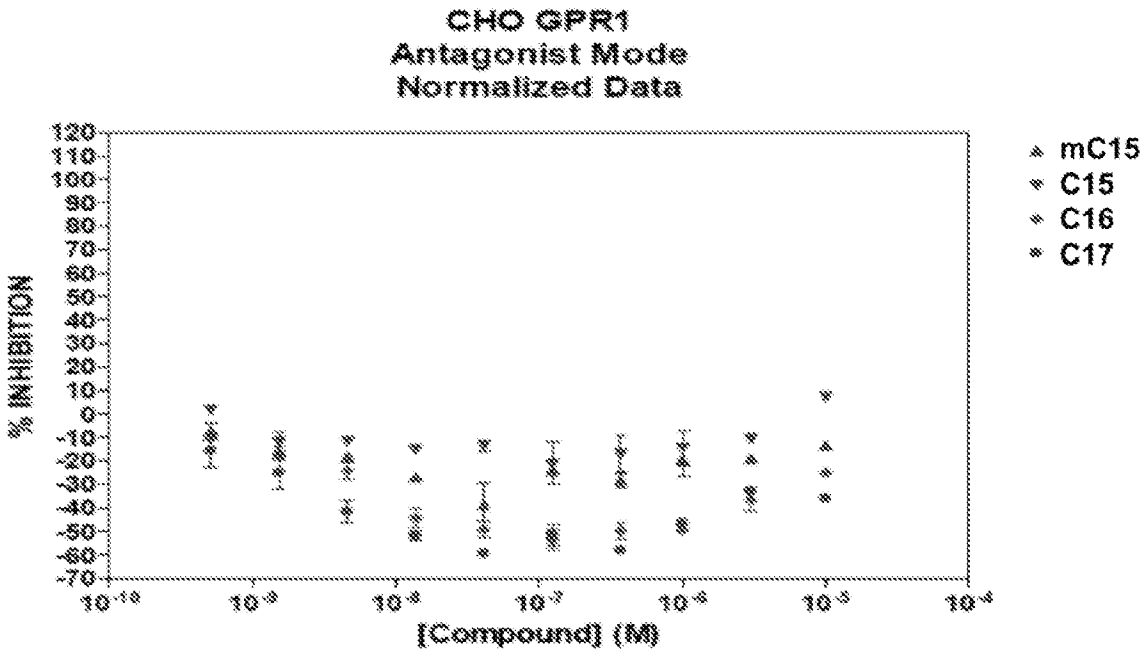
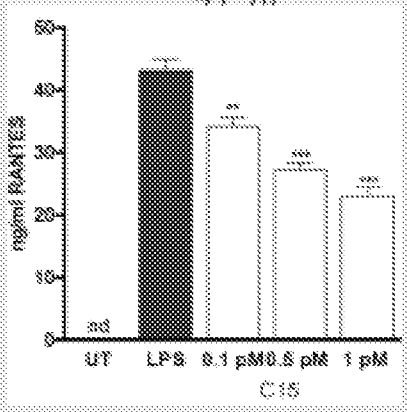
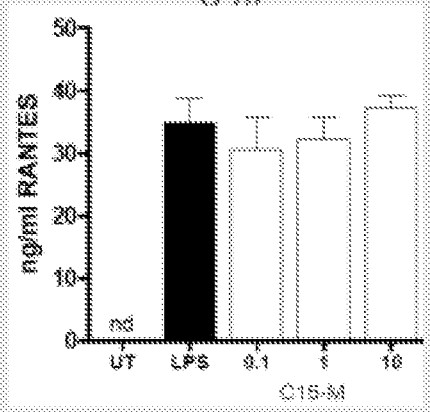

CHO GPR1
Antagonist Mode
Normalized Data
% INHIBITION
[Compound] (M)
mC15
C15
C16
C17

FIG. 3

C15: AGEDPHSFYFPGQFA
mC15: AGEDPHGYFLPGQFA
C15-A: AGEDPHGYFAPGQFA
B-Subunit: P-TFYFP

| Percent Inhibition of LPS/IFNγ-induced Cytokine Expression | | |
|---|---|---|
| Cytokine | C15 | C15-A |
| TNFα | 61% | 0% |
| RANTES | 47% | 0% |



**INTERNATIONAL SEARCH REPORT**

International application No.
**PCT/US2012/060093**

**A. CLASSIFICATION OF SUBJECT MATTER**

***A61K 38/10(2006.01)i, A61K 38/20(2006.01)i, A61K 38/19(2006.01)i, A61P 29/00(2006.01)i, A61P 17/00(2006.01)i***

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

A61K 38/10; C07H 21/04; A61K 38/08; C12P 21/02; A61K 9/70; C07K 14/575; A61K 38/16; A61K 38/22; A61P 3/04

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

Korean utility models and applications for utility models
Japanese utility models and applications for utility models

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

eKOMPASS(KIPO internal) & Keywords:

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | US 2010-0150990 A1 (GREAVES et al.) 17 June 2010<br>See claims 4, 7, 11-13, 19, 23-25 and paragraphs [0030], [0058], and Table 1. | 1-64,131-194 |
| X | US 2006-0100145 A1 (MEDER et al.) 11 May 2006<br>See claim 11, 16, 20. | 1-64,131-194 |
| X | US 2004-0086966 A1 (WITTAMER et al.) 6 May 2004<br>See claims 1, 6, 22, 27, 34. | 1-64,131-194 |
| A | PAROLINI et al., `The role of chemerin in the colocalization of NK and dendritic cell subsets into inflamed tissues`<br>Blood, Vol. 109, No. 9, pp. 3625-3632 (3 January 2007)<br>See whole document. | 1-64,131-194 |
| A | KR 10-2010-025070 A (AMOREPACIFIC CORPORATION) 9 March 2010<br>See paragraph [0003]. | 1-64,131-194 |

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| 27 March 2013 (27.03.2013) | **28 March 2013 (28.03.2013)** |


Name and mailing address of the ISA/KR

Korean Intellectual Property Office
189 Cheongsa-ro, Seo-gu, Daejeon Metropolitan City, 302-701, Republic of Korea

Facsimile No. 82-42-472-7140

Authorized officer

KIM, Seung Beom

Telephone No. 82-42-481-3371

# INTERNATIONAL SEARCH REPORT

International application No.
**PCT/US2012/060093**

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 65-130
because they relate to subject matter not required to be searched by this Authority, namely:
Claims 65-130 pertain to methods for treatment of the human body by therapy, as well as diagnostic methods, and thus relate to a subject matter which this International Searching Authority is not required, under Article 17(2)(a)(i) of the PCT and Rule 39.1(iv) of the Regulations under the PCT, to search.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required addtional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
☐ No protest accompanied the payment of additional search fees.

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International application No.

**PCT/US2012/060093**

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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| | | US 7842453 B2 | 30.11.2010 |

**INTERNATIONAL SEARCH REPORT**

Information on patent family members

International application No.

**PCT/US2012/060093**

| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
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| | | US 8030453 B2 | 04.10.2011 |
| | | WO 03-006996 A2 | 23.01.2003 |
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| KR 10-2010-0025070 A | 09.03.2010 | None | |

(19)中华人民共和国国家知识产权局

(12)发明专利申请

(10)申请公布号 CN 104159594 A
(43)申请公布日 2014.11.19

(21)申请号 201280061652.5
(22)申请日 2012.10.12
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(85)PCT国际申请进入国家阶段日
2014.06.13
(86)PCT国际申请的申请数据
PCT/US2012/060093 2012.10.12
(87)PCT国际申请的公布数据
WO2013/056147 EN 2013.04.18
(71)申请人 托马斯·盖德克
地址 美国加利福尼亚州
(72)发明人 托马斯·盖德克
(74)专利代理机构 北京安信方达知识产权代理有限公司 11262
代理人 王思琪 李平
(51)Int.Cl.
*A61K 38/10*(2006.01)
*A61K 38/20*(2006.01)
*A61K 38/19*(2006.01)
*A61P 29/00*(2006.01)
*A61P 17/00*(2006.01)

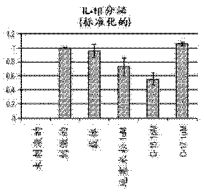
权利要求书8页 说明书67页 附图6页

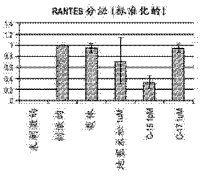
(54)发明名称

用于皮肤病治疗的凯莫瑞C15肽的局部制剂

(57)摘要

本文中描述了用于治疗皮肤疾病、病症或病状的局部制剂。本文中公开的局部制剂包括配制成用于皮肤给药的治疗有效量的人凯莫瑞C15肽。





CN 104159594 A

1. 一种局部制剂，其包含：

(a) 有效治疗炎性皮肤病的量的凯莫瑞 C15 肽；和

(b) 用于局部给药的药学上可接受的赋形剂；

其中该制剂使全身暴露最小化。

2. 权利要求 1 的局部制剂，其中所述凯莫瑞 C15 肽的量对于抑制抗原呈递细胞分泌一种或多种炎性细胞因子是有效的。

3. 权利要求 1 的局部制剂，其中所述凯莫瑞 C15 肽的量对于抑制抗原呈递细胞中炎性细胞因子的 NFκB 核易位或 NFκB 介导的基因转录是有效的。

4. 权利要求 2 或 3 的局部制剂，其中所述炎性细胞因子是 IL-23、TNFα、IL-1β、IL-6 或 RANTES。

5. 权利要求 4 的局部制剂，其中所述炎性细胞因子是 IL-23。

6. 权利要求 4 的局部制剂，其中所述炎性细胞因子是 TNFα。

7. 权利要求 4 的局部制剂，其中所述炎性细胞因子是 IL-1β。

8. 权利要求 4 的局部制剂，其中所述炎性细胞因子是 RANTES。

9. 权利要求 2 的局部制剂，其中所述抗原呈递细胞是活化的巨噬细胞、髓样树突状细胞或浆细胞样树突状细胞。

10. 权利要求 1 的局部制剂，其中所述皮肤病是免疫疾病、增生性疾病、与变应原和 / 或刺激物的接触、皮脂脂质的过度产生、成纤维细胞疾病或其组合。

11. 权利要求 1 的局部制剂，其中所述皮肤病是牛皮癣、特应性皮炎、接触性皮炎、湿疹性皮炎、斑秃、硬皮病、大疱性疾病、痤疮、荨麻疹、红斑痤疮、瘢痕形成或黑素瘤。

12. 权利要求 11 的局部制剂，其中所述皮肤病是牛皮癣。

13. 权利要求 11 的局部制剂，其中所述皮肤病是皮炎。

14. 权利要求 11 的局部制剂，其中所述皮肤病是特应性皮炎。

15. 权利要求 11 的局部制剂，其中所述皮肤病是接触性皮炎。

16. 权利要求 1 的局部制剂，其中所述凯莫瑞 C15 肽是人凯莫瑞 C15 肽。

17. 权利要求 16 的局部制剂，其中所述人凯莫瑞 C15 肽包含氨基酸序列 AGEDPHSFYFPGQFA。

18. 权利要求 16 的局部制剂，其中所述人凯莫瑞 C15 肽基本由氨基酸序列 AGEDPHSFYFPGQFA 组成。

19. 权利要求 1 的局部制剂，其被配制成气雾剂、液体、软膏、乳膏、洗液、溶液、喷雾剂、悬浮液、乳液、糊剂、凝胶、粉末、油膏、硬膏、涂剂、泡沫、药棒、缓释纳米颗粒、缓释微粒、生物粘合剂、贴剂、绷带或创伤敷料。

20. 权利要求 19 的局部制剂，其被配制成软膏。

21. 权利要求 20 的局部制剂，其中所述软膏包含约 1-10mg 凯莫瑞 C15 肽 / 克软膏。

22. 权利要求 20 的局部制剂，其中所述软膏包含凡士林。

23. 权利要求 20 的局部制剂，其中所述软膏包含辛酸癸酸甘油三酯。

24. 权利要求 20 的局部制剂，其中所述软膏包含蜂蜡。

25. 权利要求 20 的局部制剂，其中所述软膏包含凡士林、辛酸甘油三酯和蜂蜡。

26. 权利要求 25 的局部制剂，其中所述软膏包含约 50％的凡士林、约 45％的辛酸甘油

三酯和约 5%的蜂蜡。

27. 权利要求 20 的局部制剂，其中所述软膏包含丁基羟基甲苯、PEG400、Span80、白蜡和白凡士林。

28. 权利要求 27 的局部制剂，其中所述软膏包含约 0.02% w/w 的丁基羟基甲苯、约 15% w/w 的 PEG400、约 2% w/w 的 Span80、约 10% w/w 的白蜡和约 71.98% w/w 的白凡士林。

29. 权利要求 20 的局部制剂，其中所述软膏包含丁基化二甲基异山梨醇酯、丁基羟基甲苯、Span80、白蜡和白凡士林。

30. 权利要求 29 的局部制剂，其中所述软膏包含约 10% w/w 的二甲基异山梨醇酯、约 0.02% w/w 的丁基羟基甲苯、约 2% w/w 的 Span80、约 10% w/w 的白蜡和约 76.98% w/w 的白凡士林。

31. 权利要求 19 的局部制剂，其被配制成溶液。

32. 权利要求 31 的局部制剂，其被配制成作为喷雾剂施加的溶液。

33. 权利要求 31 的局部制剂，其中所述溶液包含约 1-10mg 凯莫瑞 C15 肽 /ml 溶液。

34. 权利要求 31 的局部制剂，其中所述溶液包含肉豆蔻酸异丙酯、醇、十一烯酸和十二烷基硫酸钠。

35. 权利要求 34 的局部制剂，其中所述溶液包含约 45%的肉豆蔻酸异丙酯、约 45%的醇、约 5%的十一烯酸和约 5%的十二烷基硫酸钠。

36. 权利要求 31 的局部制剂，其中所述溶液包含 DMSO。

37. 权利要求 36 的局部制剂，其中所述溶液包含约 50%的 DMSO 和约 50%的水。

38. 权利要求 31 的局部制剂，其中所述溶液包含二甲基异山梨醇酯、Transcutol、己二醇和丙二醇。

39. 权利要求 38 的局部制剂，其中所述溶液包含约 15% w/w 的二甲基异山梨醇酯、约 25% w/w 的 Transcutol、约 12% w/w 的己二醇和约 5% w/w 的丙二醇。

40. 权利要求 19 的局部制剂，其被配制成乳膏。

41. 权利要求 40 的局部制剂，其中所述乳膏包含约 1-10mg 凯莫瑞 C15 肽 /ml 乳膏。

42. 权利要求 19 的局部制剂，其被配制成洗液。

43. 权利要求 42 的局部制剂，其中所述洗液包含约 1-10mg 凯莫瑞 C15 肽 /ml 洗液。

44. 权利要求 42 的局部制剂，其中所述洗液包含二甲基异山梨醇酯、Transcutol、己二醇、丙二醇、对羟基苯甲酸甲酯、对羟基苯甲酸丙酯、EDTA、Carbopol Ultrez10、Penmulen TR-1 和丁基羟基甲苯。

45. 权利要求 42 的局部制剂，其中所述洗液包含二甲基异山梨醇酯、Transcutol、己二醇、丙二醇、对羟基苯甲酸甲酯、对羟基苯甲酸丙酯、EDTA、Carbopol Ultrez10、Penmulen TR-1、肉豆蔻酸异丙酯、油醇、丁基羟基甲苯和白凡士林。

46. 权利要求 45 的局部制剂，其中所述洗液包含约 13% w/w 的二甲基异山梨醇酯、约 20% w/w 的 Transcutol、约 10% w/w 的己二醇、约 4% w/w 的丙二醇、约 0.015% w/w 的对羟基苯甲酸甲酯、约 0.05% w/w 的对羟基苯甲酸丙酯、约 0.01% w/w 的 EDTA、约 0.5% w/w 的 Carbopol Ultrez10、约 0.2% w/w 的 Penmulen TR-1、约 3% w/w 的肉豆蔻酸异丙酯、约 5% w/w 的油醇、约 0.2% w/w 的丁基羟基甲苯和约 5% w/w 的白凡士林。

47. 权利要求 42 的局部制剂，其中所述洗液包含二甲基异山梨醇酯、Transcutol、己二醇、丙二醇、对羟基苯甲酸甲酯、对羟基苯甲酸丙酯、EDTA、Carbopol Ultrez10、Penmulen TR-1、十六醇、轻质矿物油、油酸、丁基羟基甲苯。

48. 权利要求 47 的局部制剂，其中所述洗液包含约 13% w/w 的二甲基异山梨醇酯、约 20% w/w 的 Transcutol、约 10% w/w 的己二醇、约 4% w/w 的丙二醇、约 0.015% w/w 的对羟基苯甲酸甲酯、约 0.05% w/w 的对羟基苯甲酸丙酯、约 0.01% w/w 的 EDTA、约 0.3% w/w 的 Carbopol Ultrez10、约 0.2% w/w 的 Penmulen TR-1、约 2% w/w 的十六醇、约 5.5% w/w 的轻质矿物油、约 5% w/w 的油酸和约 0.2% w/w 的丁基羟基甲苯。

49. 权利要求 1 的局部制剂，其中所述局部制剂包含皮肤渗透剂。

50. 权利要求 49 的局部制剂，其中所述皮肤渗透剂是 DMSO。

51. 权利要求 1 的局部制剂，其中所述局部制剂包含胶凝剂。

52. 权利要求 1 的局部制剂，其中所述局部制剂包含软化剂。

53. 权利要求 1 的局部制剂，其中所述局部制剂包含抗氧化剂。

54. 权利要求 1 的局部制剂，其中所述局部制剂包含皮肤保护剂。

55. 权利要求 1 的局部制剂，其中所述局部制剂包含刺激缓和剂。

56. 权利要求 1 的局部制剂，其中所述局部制剂包含干燥感改性剂。

57. 权利要求 1 的局部制剂，其中所述局部制剂包含表面活性剂。

58. 权利要求 1 的局部制剂，其中所述局部制剂包含防腐剂。

59. 权利要求 1 的局部制剂，其中所述局部制剂包含螯合剂。

60. 权利要求 1 的局部制剂，其中所述局部制剂包含润滑剂。

61. 权利要求 1 的局部制剂，其中所述局部制剂包含增稠剂。

62. 权利要求 1 的局部制剂，其中所述局部制剂包含至少一种另外的治疗剂。

63. 权利要求 62 的局部制剂，其中所述另外的治疗剂是抗氧化剂、抗炎剂、抗血管生成剂、抗凋亡剂、血管内皮生长因子抑制剂、抗微生物或抗病毒剂。

64. 权利要求 62 的局部制剂，其中所述另外的治疗剂是皮质类固醇。

65. 一种在有需要的个体中治疗炎性皮肤病的方法，包括向该个体施用治疗有效量的包含人凯莫瑞 C15 肽的局部制剂，其中该局部制剂使得对该个体的全身暴露最小化。

66. 权利要求 65 的方法，其中所述施用抑制抗原呈递细胞分泌一种或多种炎性细胞因子。

67. 权利要求 66 的方法，其中施用抑制抗原呈递细胞中炎性细胞因子的 NFκB 核易位或 NFκB 介导的基因转录。

68. 权利要求 66 或 67 的方法，其中所述炎性细胞因子是 IL-23、TNFα、IL-1β、IL-6 或 RANTES。

69. 权利要求 68 的方法，其中所述炎性细胞因子是 IL-23。

70. 权利要求 68 的方法，其中所述炎性细胞因子是 TNFα。

71. 权利要求 68 的方法，其中所述炎性细胞因子是 IL-1β。

72. 权利要求 68 的方法，其中所述炎性细胞因子是 RANTES。

73. 权利要求 68 的方法，其中所述抗原呈递细胞是活化的巨噬细胞、髓样树突状细胞、浆细胞样树突状细胞。

74. 权利要求 65 的方法，其中所述凯莫瑞 C15 肽包含氨基酸序列 AGEDPHSFYFPGQFA。

75. 权利要求 65 的方法，其中所述凯莫瑞 C15 肽基本上由氨基酸序列 AGEDPHSFYFPGQFA 组成。

76. 权利要求 65 的方法，其中所述皮肤病是免疫疾病、增生性疾病、与变应原和 / 或刺激物的接触、皮脂脂质的过度产生、成纤维细胞疾病或其组合。

77. 权利要求 65 的方法，其中所述皮肤病是牛皮癣、特应性皮炎、接触性皮炎、湿疹性皮炎、斑秃、硬皮病、大疱性疾病、痤疮、荨麻疹、红斑痤疮、瘢痕形成或黑素瘤。

78. 权利要求 77 的方法，其中所述皮肤病是牛皮癣。

79. 权利要求 77 的方法，其中所述皮肤病是皮炎。

80. 权利要求 77 的方法，其中所述皮肤病是特应性皮炎。

81. 权利要求 77 的方法，其中所述皮肤病是接触性皮炎。

82. 权利要求 65 的方法，其中所述局部制剂是气雾剂、液体、软膏、乳膏、洗液、溶液、喷雾剂、悬浮液、乳液、糊剂、凝胶、粉末、油膏、硬膏、涂剂、泡沫、药棒、缓释纳米颗粒、缓释微粒、生物粘合剂、贴剂、绷带或创伤敷料的形式。

83. 权利要求 82 的方法，其中所述局部制剂是软膏。

84. 权利要求 83 的方法，其中所述软膏包含约 1-10mg 凯莫瑞 C15 肽 / 克软膏。

85. 权利要求 83 的方法，其中所述软膏包含凡士林。

86. 权利要求 83 的方法，其中所述软膏包含辛酸癸酸甘油三酯。

87. 权利要求 83 的方法，其中所述软膏包含蜂蜡。

88. 权利要求 83 的方法，其中所述软膏包含凡士林、辛酸甘油三酯和蜂蜡。

89. 权利要求 88 的方法，其中所述软膏包含约 50％的凡士林、约 45％的辛酸甘油三酯和约 5％的蜂蜡。

90. 权利要求 83 的方法，其中所述软膏包含丁基羟基甲苯、PEG400、Span80、白蜡和白凡士林。

91. 权利要求 90 的方法，其中所述软膏包含约 0.02％ w/w 的丁基羟基甲苯、约 15％ w/w 的 PEG400、约 2％ w/w 的 Span80、约 10％ w/w 的白蜡和约 71.98％ w/w 的白凡士林。

92. 权利要求 83 的方法，其中所述软膏包含丁基化二甲基异山梨醇酯、丁基羟基甲苯、Span80、白蜡和白凡士林。

93. 权利要求 92 的方法，其中所述软膏包含约 10％ w/w 的二甲基异山梨醇酯、约 0.02％ w/w 的丁基羟基甲苯、约 2％ w/w 的 Span80、约 10％ w/w 的白蜡和约 76.98％ w/w 的白凡士林。

94. 权利要求 82 的方法，其中所述局部制剂是溶液。

95. 权利要求 94 的方法，其被配制成作为喷雾剂施加的溶液。

96. 权利要求 94 的方法，其中所述溶液包含约 1-10mg 凯莫瑞 C15 肽 /ml 溶液。

97. 权利要求 94 的方法，其中所述溶液包含肉豆蔻酸异丙酯、醇、十一烯酸和十二烷基硫酸钠。

98. 权利要求 97 的方法，其中所述溶液包含约 45％的肉豆蔻酸异丙酯、约 45％的醇、约 5％的十一烯酸和约 5％的十二烷基硫酸钠。

99. 权利要求 94 的方法，其中所述溶液包含 DMSO。

100. 权利要求 99 的方法，其中所述溶液包含约 50％的 DMSO 和约 50％的水。

101. 权利要求 94 的方法，其中所述溶液包含二甲基异山梨醇酯、Transcutol、己二醇和丙二醇。

102. 权利要求 101 的方法，其中所述溶液包含约 15％ w/w 的二甲基异山梨醇酯、约 25％ w/w 的 Transcutol、约 12％ w/w 的己二醇和约 5％ w/w 的丙二醇。

103. 权利要求 82 的方法，其中所述局部制剂是乳膏。

104. 权利要求 103 的方法，其中所述乳膏包含约 1-10mg 凯莫瑞 C15 肽 /ml 乳膏。

105. 权利要求 82 的方法，其中所述局部制剂是洗液。

106. 权利要求 105 的方法，其中所述洗液包含约 1-10mg 凯莫瑞 C15 肽 /ml 洗液。

107. 权利要求 105 的方法，其中所述洗液包含二甲基异山梨醇酯、Transcutol、己二醇、丙二醇、对羟基苯甲酸甲酯、对羟基苯甲酸丙酯、EDTA、Carbopol Ultrez10、Penmulen TR-1 和丁基羟基甲苯。

108. 权利要求 105 的方法，其中所述洗液包含二甲基异山梨醇酯、Transcutol、己二醇、丙二醇、对羟基苯甲酸甲酯、对羟基苯甲酸丙酯、EDTA、Carbopol Ultrez10、Penmulen TR-1、肉豆蔻酸异丙酯、油醇、丁基羟基甲苯和白凡士林。

109. 权利要求 108 的方法，其中所述洗液包含约 13％ w/w 的二甲基异山梨醇酯、约 20％ w/w 的 Transcutol、约 10％ w/w 的己二醇、约 4％ w/w 的丙二醇、约 0.015％ w/w 的对羟基苯甲酸甲酯、约 0.05％ w/w 的对羟基苯甲酸丙酯、约 0.01％ w/w 的 EDTA、约 0.5％ w/w 的 Carbopol Ultrez10、约 0.2％ w/w 的 Penmulen TR-1、约 3％ w/w 的肉豆蔻酸异丙酯、约 5％ w/w 的油醇、约 0.2％ w/w 的丁基羟基甲苯和约 5％ w/w 的白凡士林。

110. 权利要求 105 的方法，其中所述洗液包含二甲基异山梨醇酯、Transcutol、己二醇、丙二醇、对羟基苯甲酸甲酯、对羟基苯甲酸丙酯、EDTA、Carbopol Ultrez10、Penmulen TR-1、十六醇、轻质矿物油、油酸、丁基羟基甲苯。

111. 权利要求 110 的方法，其中所述洗液包含约 13％ w/w 的二甲基异山梨醇酯、约 20％ w/w 的 Transcutol、约 10％ w/w 的己二醇、约 4％ w/w 的丙二醇、约 0.015％ w/w 的对羟基苯甲酸甲酯、约 0.05％ w/w 的对羟基苯甲酸丙酯、约 0.01％ w/w 的 EDTA、约 0.3％ w/w 的 Carbopol Ultrez10、约 0.2％ w/w 的 Penmulen TR-1、约 2％ w/w 的十六醇、约 5.5％ w/w 的轻质矿物油、约 5％ w/w 的油酸和约 0.2％ w/w 的丁基羟基甲苯。

112. 权利要求 65 的方法，其中所述局部制剂包含皮肤渗透剂。

113. 权利要求 112 的方法，其中所述皮肤渗透剂是 DMSO。

114. 权利要求 65 的方法，其中所述局部制剂包含胶凝剂。

115. 权利要求 65 的方法，其中所述局部制剂包含软化剂。

116. 权利要求 65 的方法，其中所述局部制剂包含抗氧化剂。

117. 权利要求 65 的方法，其中所述局部制剂包含皮肤保护剂。

118. 权利要求 65 的方法，其中所述局部制剂包含刺激缓和剂。

119. 权利要求 65 的方法，其中所述局部制剂包含干燥感改性剂。

120. 权利要求 65 的方法，其中所述局部制剂包含表面活性剂。

121. 权利要求 65 的方法，其中所述局部制剂包含防腐剂。

122. 权利要求 65 的方法，其中所述局部制剂包含螯合剂。

123. 权利要求 65 的方法，其中所述局部制剂包含润滑剂。

124. 权利要求 65 的方法，其中所述局部制剂包含增稠剂。

125. 权利要求 65 的方法，其中所述局部制剂包含至少一种另外的治疗剂。

126. 权利要求 125 的方法，其中所述另外的治疗剂是抗氧化剂、抗炎剂、抗血管生成剂、抗凋亡剂、血管内皮生长因子抑制剂、抗微生物或抗病毒剂。

127. 权利要求 125 的方法，其中所述另外的治疗剂是皮质类固醇。

128. 权利要求 65 的方法，其中将所述局部制剂局部施加到皮肤、眼、口、鼻、阴道粘膜或肛门粘膜。

129. 权利要求 128 的方法，其中在向所述个体给药后 1-12 小时，所述局部制剂的给药导致大于约 0.1pM-100nM、大于约 1pM-10nM、大于约 1pM-1nM、大于约 1-100pM 或者大于约 1-10pM 的凯莫瑞 C15 肽的局部组织浓度。

130. 权利要求 129 的方法，其中所述局部制剂的给药导致小于约 100pM、小于约 10pM、小于约 1pM、小于约 0.1pM 或小于约 0.01pM 的全身浓度。

131. 人凯莫瑞 C15 肽用于制备局部制剂的用途，所述局部制剂包含用于治疗炎性皮肤病的治疗有效量的该肽，其中配制所述制剂以使全身暴露最小化。

132. 权利要求 131 的用途，其中所述人凯莫瑞 C15 肽的量对于抑制抗原呈递细胞分泌一种或多种炎性细胞因子是有效的。

133. 权利要求 131 的用途，其中所述人凯莫瑞 C15 肽的量对于抑制抗原呈递细胞中炎性细胞因子的 NFκB 核易位或 NFκB 介导的基因转录是有效的。

134. 权利要求 132 或 133 的用途，其中所述炎性细胞因子是 IL-23、TNFα、IL-1β、IL-6 或 RANTES。

135. 权利要求 134 的用途，其中所述炎性细胞因子是 IL-23。

136. 权利要求 134 的用途，其中所述炎性细胞因子是 TNFα。

137. 权利要求 134 的用途，其中所述炎性细胞因子是 IL-1β。

138. 权利要求 134 的用途，其中所述炎性细胞因子是 RANTES。

139. 权利要求 134 的用途，其中所述抗原呈递细胞是活化的巨噬细胞、髓样树突状细胞、浆细胞样树突状细胞。

140. 权利要求 131 的用途，其中所述凯莫瑞 C15 肽包含氨基酸序列 AGEDPHSFYFPGQFA。

141. 权利要求 131 的用途，其中所述凯莫瑞 C15 肽基本上由氨基酸序列 AGEDPHSFYFPGQFA 组成。

142. 权利要求 131 的用途，其中所述皮肤病是免疫疾病、增生性疾病、与变应原和 / 或刺激物的接触、皮脂脂质的过度产生、成纤维细胞疾病或其组合。

143. 权利要求 131 的用途，其中所述皮肤病是牛皮癣、特应性皮炎、接触性皮炎、湿疹性皮炎、斑秃、硬皮病、大疱性疾病、痤疮、荨麻疹、红斑痤疮、瘢痕形成或黑素瘤。

144. 权利要求 144 的用途，其中所述皮肤病是牛皮癣。

145. 权利要求 144 的用途，其中所述皮肤病是皮炎。

146. 权利要求 144 的用途，其中所述皮肤病是特应性皮炎。

147. 权利要求 144 的用途，其中所述皮肤病是接触性皮炎。

148. 权利要求 131 的用途，其中所述局部制剂是气雾剂、液体、软膏、乳膏、洗液、溶液、

喷雾剂、悬浮液、乳液、糊剂、凝胶、粉末、油膏、硬膏、涂剂、泡沫、药棒、缓释纳米颗粒、缓释微粒、生物粘合剂、贴剂、绷带或创伤敷料的形式。

149. 权利要求 148 的用途，其中所述局部制剂是软膏。

150. 权利要求 149 的用途，其中所述软膏包含约 1-10mg 凯莫瑞 C15 肽 / 克软膏。

151. 权利要求 149 的用途，其中所述软膏包含凡士林。

152. 权利要求 149 的用途，其中所述软膏包含辛酸癸酸甘油三酯。

153. 权利要求 149 的用途，其中所述软膏包含蜂蜡。

154. 权利要求 149 的用途，其中所述软膏包含凡士林、辛酸甘油三酯和蜂蜡。

155. 权利要求 154 的局部制剂，其中所述软膏包含约 50％的凡士林、约 45％的辛酸甘油三酯和约 5％的蜂蜡。

156. 权利要求 149 的用途，其中所述软膏包含丁基羟基甲苯、PEG400、Span80、白蜡和白凡士林。

157. 权利要求 156 的用途，其中所述软膏包含约 0.02％ w/w 的丁基羟基甲苯、约 15％ w/w 的 PEG400、约 2％ w/w 的 Span80、约 10％ w/w 的白蜡和约 71.98％ w/w 的白凡士林。

158. 权利要求 149 的用途，其中所述软膏包含丁基化二甲基异山梨醇酯、丁基羟基甲苯、Span80、白蜡和白凡士林。

159. 权利要求 158 的用途，其中所述软膏包含约 10％ w/w 的二甲基异山梨醇酯、约 0.02％ w/w 的丁基羟基甲苯、约 2％ w/w 的 Span80、约 10％ w/w 的白蜡和约 76.98％ w/w 的白凡士林。

160. 权利要求 148 的用途，其中所述局部制剂是溶液。

161. 权利要求 160 的用途，其被配制成作为喷雾剂施加的溶液。

162. 权利要求 160 的用途，其中所述溶液包含约 1-10mg 凯莫瑞 C15 肽 /ml 溶液。

163. 权利要求 160 的用途，其中所述溶液包含肉豆蔻酸异丙酯、醇、十一烯酸和十二烷基硫酸钠。

164. 权利要求 163 的用途，其中所述溶液包含约 45％的肉豆蔻酸异丙酯、约 45％的醇、约 5％的十一烯酸和约 5％的十二烷基硫酸钠。

165. 权利要求 160 的用途，其中所述溶液包含 DMSO。

166. 权利要求 165 的用途，其中所述溶液包含约 50％的 DMSO 和约 50％的水。

167. 权利要求 160 的用途，其中所述溶液包含二甲基异山梨醇酯、Transcutol、己二醇和丙二醇。

168. 权利要求 168 的用途，其中所述溶液包含约 15％ w/w 的二甲基异山梨醇酯、约 25％ w/w 的 Transcutol、约 12％ w/w 的己二醇和约 5％ w/w 的丙二醇。

169. 权利要求 148 的用途，其中所述局部制剂是乳膏。

170. 权利要求 169 的用途，其中所述乳膏包含约 1-10mg 凯莫瑞 C15 肽 /ml 乳膏。

171. 权利要求 148 的用途，其中所述局部制剂是洗液。

172. 权利要求 171 的用途，其中所述洗液包含约 1-10mg 凯莫瑞 C15 肽 /ml 洗液。

173. 权利要求 171 的用途，其中所述洗液包含二甲基异山梨醇酯、Transcutol、己二醇、丙二醇、对羟基苯甲酸甲酯、对羟基苯甲酸丙酯、EDTA、Carbopol Ultrez10、Penmulen TR-1 和丁基羟基甲苯。

174. 权利要求 171 的用途，其中所述洗液包含二甲基异山梨醇酯、Transcutol、己二醇、丙二醇、对羟基苯甲酸甲酯、对羟基苯甲酸丙酯、EDTA、Carbopol Ultrez10、Penmulen TR-1、肉豆蔻酸异丙酯、油醇、丁基羟基甲苯和白凡士林。

175. 权利要求 174 的用途，其中所述洗液包含约 13％ w/w 的二甲基异山梨醇酯、约 20％ w/w 的 Transcutol、约 10％ w/w 的己二醇、约 4％ w/w 的丙二醇、约 0.015％ w/w 的对羟基苯甲酸甲酯、约 0.05％ w/w 的对羟基苯甲酸丙酯、约 0.01％ w/w 的 EDTA、约 0.5％ w/w 的 Carbopol Ultrez10、约 0.2％ w/w 的 Penmulen TR-1、约 3％ w/w 的肉豆蔻酸异丙酯、约 5％ w/w 的油醇、约 0.2％ w/w 的丁基羟基甲苯和约 5％ w/w 的白凡士林。

176. 权利要求 171 的用途，其中所述洗液包含二甲基异山梨醇酯、Transcutol、己二醇、丙二醇、对羟基苯甲酸甲酯、对羟基苯甲酸丙酯、EDTA、Carbopol Ultrez10、Penmulen TR-1、十六醇、轻质矿物油、油酸、丁基羟基甲苯。

177. 权利要求 176 的用途，其中所述洗液包含约 13％ w/w 的二甲基异山梨醇酯、约 20％ w/w 的 Transcutol、约 10％ w/w 的己二醇、约 4％ w/w 的丙二醇、约 0.015％ w/w 的对羟基苯甲酸甲酯、约 0.05％ w/w 的对羟基苯甲酸丙酯、约 0.01％ w/w 的 EDTA、约 0.3％ w/w 的 Carbopol Ultrez10、约 0.2％ w/w 的 Penmulen TR-1、约 2％ w/w 的十六醇、约 5.5％ w/w 的轻质矿物油、约 5％ w/w 的油酸和约 0.2％ w/w 的丁基羟基甲苯。

178. 权利要求 131 的用途，其中所述局部制剂包含皮肤渗透剂。

179. 权利要求 178 的用途，其中所述皮肤渗透剂是 DMSO。

180. 权利要求 131 的用途，其中所述局部制剂包含胶凝剂。

181. 权利要求 131 的用途，其中所述局部制剂包含软化剂。

182. 权利要求 131 的用途，其中所述局部制剂包含抗氧化剂。

183. 权利要求 131 的用途，其中所述局部制剂包含皮肤保护剂。

184. 权利要求 131 的用途，其中所述局部制剂包含刺激缓和剂。

185. 权利要求 131 的用途，其中所述局部制剂包含干燥感改性剂。

186. 权利要求 131 的用途，其中所述局部制剂包含表面活性剂。

187. 权利要求 131 的用途，其中所述局部制剂包含防腐剂。

188. 权利要求 131 的用途，其中所述局部制剂包含螯合剂。

189. 权利要求 131 的用途，其中所述局部制剂包含润滑剂。

190. 权利要求 131 的用途，其中所述局部制剂包含增稠剂。

191. 权利要求 131 的用途，其中所述局部制剂包含至少一种另外的治疗剂。

192. 权利要求 191 的用途，其中所述另外的治疗剂是抗氧化剂、抗炎剂、抗血管生成剂、抗凋亡剂、血管内皮生长因子抑制剂、抗微生物或抗病毒剂。

193. 权利要求 191 的用途，其中所述另外的治疗剂是皮质类固醇。

194. 权利要求 131 的用途，其中将所述局部制剂配制成用于施加到皮肤、眼、口、鼻、阴道粘膜或肛门粘膜。

# 用于皮肤病治疗的凯莫瑞 C15 肽的局部制剂

交叉引用

[0001] 本申请要求 2011 年 10 月 13 日提交的、名称为“在皮肤病治疗中高度有效的免疫细胞拮抗剂 (Highly potent antagonists of immune cells in the treatment of skin disorders)”的美国临时专利申请号 61/546,833 的优先权，通过引用将其整体并入至此。

## 发明内容

[0002] 在某些实施方案中，本文中公开了凯莫瑞 (chemerin)C15 肽。本文中进一步公开了包含凯莫瑞 C15 肽和任选的药学上可接受的赋形剂的局部制剂。本文中另外公开了在有需要的个体中治疗炎性皮肤病的方法，包括施用本文中公开的凯莫瑞 C15 肽或者包含本文中公开的凯莫瑞 C15 肽的局部制剂。本文中进一步公开了在有需要的个体中抑制炎性细胞因子或趋化因子的活性的方法，包括施用本文中公开的凯莫瑞 C15 肽或者包含本文中公开的凯莫瑞 C15 肽的局部制剂。在某些实施方案中，本文中还公开了在有需要的个体中抑制炎性细胞因子的核易位或 NFκB 介导的基因转录的方法，包括施用本文中公开的凯莫瑞 C15 肽或者包含本文中公开的凯莫瑞 C15 肽的局部制剂。在一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。在一些实施方案中，该凯莫瑞 C15 肽是凯莫瑞 C15 肽的盐。在一些实施方案中，该凯莫瑞 C15 肽是羧化的。在一些实施方案中，该凯莫瑞 C15 肽是酰胺化的。在一些实施方案中，该凯莫瑞 C15 肽是环状的。在一些实施方案中，该凯莫瑞 C15 肽与天然存在的凯莫瑞 C15 肽至少 80％、85％、90％、91％、92％、93％、94％、95％、96％、97％、98％、99％、99.5％、99.6％、99.7％、99.8％或 99.9％同源。

[0003] 在某些实施方案中，本文中公开了用于治疗皮肤病（即：表皮、真皮和 / 或皮下组织的异常状态）的局部制剂。在某些实施方案中，本文中公开了用于治疗以下疾病的局部制剂：免疫疾病（例如自身免疫疾病（例如湿疹、牛皮癣））；增生性疾病（例如，黑素瘤）；与变应原（例如，漆酚）和 / 或刺激物（例如，醇、二甲苯、松节油、酯、丙酮、酮）的接触；皮脂脂质的过度产生（例如，痤疮）；成纤维细胞疾病（例如，伤痕形成）；或其组合。在某些实施方案中，本文中公开了用于治疗牛皮癣、特应性皮炎、接触性皮炎、湿疹性皮炎、斑秃、硬皮病 (scleredoma)、大疱性疾病、痤疮、荨麻疹、红斑痤疮、瘢痕形成和 / 或黑素瘤的局部制剂。在一些实施方案中，本文中公开的局部制剂包含治疗有效量的凯莫瑞 C15 肽。在一些实施方案中，在与变应原和 / 或刺激物接触之前或之后施用本文中公开的局部制剂。在一些实施方案中，在物理创伤（例如，外科手术）之前或之后施用本文中公开的局部制剂。

[0004] 在某些实施方案中，本文中描述了一种局部制剂，其包含：(a) 有效治疗炎性皮肤病的量的凯莫瑞 C15 肽；和 (b) 用于局部给药的药学上可接受的赋形剂，其中该制剂使全身暴露最小化。在本文中提供的局部制剂的一些实施方案中，凯莫瑞 C15 肽的量对于抑制抗原呈递细胞分泌一种或多种炎性细胞因子是有效的。在本文中提供的局部制剂的一些实施方案中，凯莫瑞 C15 肽的量对于抑制抗原呈递细胞中炎性细胞因子的 NFκB 核易位或 NFκB 介导的基因转录是有效的。在本文中提供的局部制剂的一些实施方案中，该炎性细胞因子是 IL-23、TNFα、IL-1β、IL-6 或 RANTES。在本文中提供的局部制剂的一些实施方

案中，该炎性细胞因子是 IL-23。在本文中提供的局部制剂的一些实施方案中，该炎性细胞因子是 TNFα。在本文中提供的局部制剂的一些实施方案中，该炎性细胞因子是 IL-1β。在本文中提供的局部制剂的一些实施方案中，该炎性细胞因子是 RANTES。在本文中提供的局部制剂的一些实施方案中，该抗原呈递细胞是活化的巨噬细胞、髓样树突状细胞或浆细胞样树突状细胞。在本文中提供的局部制剂的一些实施方案中，该皮肤病是免疫疾病、增生性疾病、与变应原和 / 或刺激物的接触、皮脂脂质的过度产生、成纤维细胞疾病或其组合。在本文中提供的局部制剂的一些实施方案中，该皮肤病是牛皮癣、特应性皮炎、接触性皮炎、湿疹性皮炎、斑秃、硬皮病、大疱性疾病、痤疮、荨麻疹、红斑痤疮、瘢痕形成或黑素瘤。在本文中提供的局部制剂的一些实施方案中，其中皮肤病是牛皮癣。在本文中提供的局部制剂的一些实施方案中，其中皮肤病是皮炎。在本文中提供的局部制剂的一些实施方案中，其中皮肤病是特应性皮炎。在本文中提供的局部制剂的一些实施方案中，其中皮肤病是接触性皮炎。在本文中提供的局部制剂的一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。在本文中提供的局部制剂的一些实施方案中，人凯莫瑞 C15 肽包含氨基酸序列 AGEDPHSFYFPGQFA。在本文中提供的局部制剂的一些实施方案中，人凯莫瑞 C15 肽基本上由氨基酸序列 AGEDPHSFYFPGQFA 组成。在本文中提供的局部制剂的一些实施方案中，该局部制剂被配制为软膏。在本文中提供的局部制剂的一些实施方案中，该软膏包含约 1-10mg 凯莫瑞 C15 肽 / 克软膏。在本文中提供的局部制剂的一些实施方案中，该软膏包含石蜡油。在本文中提供的局部制剂的一些实施方案中，该软膏包含辛酸癸酸甘油三酯。在本文中提供的局部制剂的一些实施方案中，该软膏包含蜂蜡。在本文中提供的局部制剂的一些实施方案中，该软膏包含石蜡油、辛酸甘油三酯和蜂蜡。在本文中提供的局部制剂的一些实施方案中，该软膏包含约 50％的石蜡油、约 45％的辛酸甘油三酯和约 5％的蜂蜡。在本文中提供的局部制剂的一些实施方案中，该软膏包含丁基羟基甲苯、PEG400、Span80、白蜡和白凡士林。在本文中提供的局部制剂的一些实施方案中，该软膏包含约 0.02％ w/w 的丁基羟基甲苯、约 15％ w/w 的 PEG400、约 2％ w/w 的 Span80、约 10％ w/w 的白蜡和约 71.98％ w/w 的白凡士林。在本文中提供的局部制剂的一些实施方案中，该软膏包含丁基化二甲基异山梨醇酯、丁基羟基甲苯、Span80、白蜡和白凡士林。在本文中提供的局部制剂的一些实施方案中，该软膏包含约 10％ w/w 的二甲基异山梨醇酯、约 0.02％ w/w 的丁基羟基甲苯、约 2％ w/w 的 Span80、约 10％ w/w 的白蜡和约 76.98％ w/w 的白凡士林。在本文中提供的局部制剂的一些实施方案中，该局部制剂被配制为溶液。在本文中提供的局部制剂的一些实施方案中，该局部制剂被配制成作为喷雾剂施加的溶液。在本文中提供的局部制剂的一些实施方案中，该溶液包含约 1-10mg 凯莫瑞 C15 肽 /ml 溶液。在本文中提供的局部制剂的一些实施方案中，该溶液包含肉豆蔻酸异丙酯、醇、十一烯酸和十二烷基硫酸钠。在本文中提供的局部制剂的一些实施方案中，该溶液包含约 45％的肉豆蔻酸异丙酯、约 45％的醇、约 5％的十一烯酸和约 5％的十二烷基硫酸钠。在本文中提供的局部制剂的一些实施方案中，该溶液包含 DMSO。在本文中提供的局部制剂的一些实施方案中，该溶液包含约 50％的 DMSO 和约 50％的水。在本文中提供的局部制剂的一些实施方案中，该溶液包含二甲基异山梨醇酯、Transcutol、己二醇和丙二醇。在本文中提供的局部制剂的一些实施方案中，该溶液包含约 15％ w/w 的二甲基异山梨醇酯、约 25％ w/w 的 Transcutol、约 12％ w/w 的己二醇和约 5％ w/w 的丙二醇。在本文中提供的局部制剂的一些实施方案中，该局部制剂被配制成乳膏。在

本文中提供的局部制剂的一些实施方案中，该乳膏包含约 1-10mg 凯莫瑞 C15 肽 /ml 乳膏。在本文中提供的局部制剂的一些实施方案中，该局部制剂被配制为洗液。在本文中提供的局部制剂的一些实施方案中，该洗液包含约 1-10mg 凯莫瑞 C15 肽 /ml 洗液。在本文中提供的局部制剂的一些实施方案中，该洗液包含二甲基异山梨醇酯、Transcutol、己二醇、丙二醇、对羟基苯甲酸甲酯、对羟基苯甲酸丙酯、EDTA、Carbopol Ultrez10、Penmulen TR-1 和丁基羟基甲苯。在本文中提供的局部制剂的一些实施方案中，该洗液包含二甲基异山梨醇酯、Transcutol、己二醇、丙二醇、对羟基苯甲酸甲酯、对羟基苯甲酸丙酯、EDTA、Carbopol Ultrez10、Penmulen TR-1、肉豆蔻酸异丙酯、油醇、丁基羟基甲苯和白凡士林。在本文中提供的局部制剂的一些实施方案中，该洗液包含约 13％ w/w 的二甲基异山梨醇酯、约 20％ w/w 的 Transcutol、约 10％ w/w 的己二醇、约 4％ w/w 的丙二醇、约 0.015％ w/w 的对羟基苯甲酸甲酯、约 0.05％ w/w 的对羟基苯甲酸丙酯、约 0.01％ w/w 的 EDTA、约 0.5％ w/w 的 Carbopol Ultrez10、约 0.2％ w/w 的 Penmulen TR-1、约 3％ w/w 的肉豆蔻酸异丙酯、约 5％ w/w 的油醇、约 0.2％ w/w 的丁基羟基甲苯和约 5％ w/w 的白凡士林。在本文中提供的局部制剂的一些实施方案中，该洗液包含二甲基异山梨醇酯、Transcutol、己二醇、丙二醇、对羟基苯甲酸甲酯、对羟基苯甲酸丙酯、EDTA、Carbopol Ultrez10、Penmulen TR-1、十六醇、轻质矿物油、油酸和丁基羟基甲苯。在本文中提供的局部制剂的一些实施方案中，该洗液包含约 13％ w/w 的二甲基异山梨醇酯、约 20％ w/w 的 Transcutol、约 10％ w/w 的己二醇、约 4％ w/w 的丙二醇、约 0.015％ w/w 的对羟基苯甲酸甲酯、约 0.05％ w/w 的对羟基苯甲酸丙酯、约 0.01％ w/w 的 EDTA、约 0.3％ w/w 的 Carbopol Ultrez10、约 0.2％ w/w 的 Penmulen TR-1、约 2％ w/w 的十六醇、约 5.5％ w/w 的轻质矿物油、约 5％ w/w 的油酸和约 0.2％ w/w 的丁基羟基甲苯。在本文中提供的局部制剂的一些实施方案中，该局部制剂包含皮肤渗透剂。在本文中提供的局部制剂的一些实施方案中，该皮肤渗透剂是 DMSO。在本文中提供的局部制剂的一些实施方案中，该局部制剂包含胶凝剂。在本文中提供的局部制剂的一些实施方案中，该局部制剂包含软化剂。在本文中提供的局部制剂的一些实施方案中，该局部制剂包含抗氧化剂。在本文中提供的局部制剂的一些实施方案中，该局部制剂包含皮肤保护剂。在本文中提供的局部制剂的一些实施方案中，该局部制剂包含刺激缓和剂。在本文中提供的局部制剂的一些实施方案中，该局部制剂包含干燥感改性剂。在本文中提供的局部制剂的一些实施方案中，该局部制剂包含表面活性剂。在本文中提供的局部制剂的一些实施方案中，该局部制剂包含防腐剂。在本文中提供的局部制剂的一些实施方案中，该局部制剂包含螯合剂。在本文中提供的局部制剂的一些实施方案中，其中该局部制剂包含润滑剂。在本文中提供的局部制剂的一些实施方案中，该局部制剂包含增稠剂。在本文中提供的局部制剂的一些实施方案中，该局部制剂包含至少一种另外的治疗剂。在本文中提供的局部制剂的一些实施方案中，该另外的治疗剂是抗氧化剂、抗炎剂、抗血管生成剂、抗凋亡剂、血管内皮生长因子抑制剂、抗微生物或抗病毒剂。在本文中提供的局部制剂的一些实施方案中，该另外的治疗剂是皮质类固醇。

[0005] 在某些实施方案中，本文中公开了被配制成气雾剂、液体、软膏、乳膏、洗液、溶液、喷雾剂、悬浮液、乳液、糊剂、凝胶、粉末、油膏、硬膏、涂剂、泡沫、药棒、缓释纳米颗粒、缓释微粒、生物粘合剂、贴剂、绷带或创伤敷料的凯莫瑞 C15 肽的局部制剂。在本文中提供的局部制剂的一些实施方案中，凯莫瑞 C15 肽是人凯莫瑞 C15 肽。在本文中提供的局部制剂的

一些实施方案中，人凯莫瑞C15肽包含氨基酸序列AGEDPHSFYFPGQFA。在本文中提供的局部制剂的一些实施方案中，人凯莫瑞C15肽基本上由氨基酸序列AGEDPHSFYFPGQFA组成。在本文中提供的局部制剂的一些实施方案中，该局部制剂被配制为软膏。在本文中提供的局部制剂的一些实施方案中，该软膏包含约1-10mg凯莫瑞C15肽/克软膏。在本文中提供的局部制剂的一些实施方案中，该软膏包含石蜡油。在本文中提供的局部制剂的一些实施方案中，该软膏包含辛酸癸酸甘油三酯。在本文中提供的局部制剂的一些实施方案中，该软膏包含蜂蜡。在本文中提供的局部制剂的一些实施方案中，该软膏包含石蜡油、辛酸甘油三酯和蜂蜡。在本文中提供的局部制剂的一些实施方案中，该软膏包含约50％的石蜡油、约45％的辛酸甘油三酯和约5％的蜂蜡。在本文中提供的局部制剂的一些实施方案中，该软膏包含丁基羟基甲苯、PEG400、Span80、白蜡和白凡士林。在本文中提供的局部制剂的一些实施方案中，该软膏包含约0.02％ w/w的丁基羟基甲苯、约15％ w/w的PEG400、约2％ w/w的Span80、约10％ w/w的白蜡和约71.98％ w/w的白凡士林。在本文中提供的局部制剂的一些实施方案中，该软膏包含丁基化二甲基异山梨醇酯、丁基羟基甲苯、Span80、白蜡和白凡士林。在本文中提供的局部制剂的一些实施方案中，该软膏包含约10％ w/w的二甲基异山梨醇酯、约0.02％ w/w的丁基羟基甲苯、约2％ w/w的Span80、约10％ w/w的白蜡和约76.98％ w/w的白凡士林。在本文中提供的局部制剂的一些实施方案中，该局部制剂被配制为溶液。在本文中提供的局部制剂的一些实施方案中，该局部制剂被配制成作为喷雾剂施加的溶液。在本文中提供的局部制剂的一些实施方案中，该溶液包含约1-10mg凯莫瑞C15肽/ml溶液。在本文中提供的局部制剂的一些实施方案中，该溶液包含肉豆蔻酸异丙酯、醇、十一烯酸和十二烷基硫酸钠。在本文中提供的局部制剂的一些实施方案中，该溶液包含约45％的肉豆蔻酸异丙酯、约45％的醇、约5％的十一烯酸和约5％的十二烷基硫酸钠。在本文中提供的局部制剂的一些实施方案中，该溶液包含DMSO。在本文中提供的局部制剂的一些实施方案中，该溶液包含约50％的DMSO和约50％的水。在本文中提供的局部制剂的一些实施方案中，该溶液包含二甲基异山梨醇酯、Transcutol、己二醇和丙二醇。在本文中提供的局部制剂的一些实施方案中，该溶液包含约15％ w/w的二甲基异山梨醇酯、约25％ w/w的Transcutol、约12％ w/w的己二醇和约5％ w/w的丙二醇。在本文中提供的局部制剂的一些实施方案中，该局部制剂被配制为乳膏。在本文中提供的局部制剂的一些实施方案中，该乳膏包含约1-10mg凯莫瑞C15肽/ml乳膏。在本文中提供的局部制剂的一些实施方案中，该局部制剂被配制为洗液。在本文中提供的局部制剂的一些实施方案中，该洗液包含约1-10mg凯莫瑞C15肽/ml洗液。在本文中提供的局部制剂的一些实施方案中，该洗液包含二甲基异山梨醇酯、Transcutol、己二醇、丙二醇、对羟基苯甲酸甲酯、对羟基苯甲酸丙酯、EDTA、Carbopol Ultrez10、Penmulen TR-1和丁基羟基甲苯。在本文中提供的局部制剂的一些实施方案中，该洗液包含二甲基异山梨醇酯、Transcutol、己二醇、丙二醇、对羟基苯甲酸甲酯、对羟基苯甲酸丙酯、EDTA、Carbopol Ultrez10、Penmulen TR-1、肉豆蔻酸异丙酯、油醇、丁基羟基甲苯和白凡士林。在本文中提供的局部制剂的一些实施方案中，该洗液包含约13％ w/w的二甲基异山梨醇酯、约20％ w/w的Transcutol、约10％ w/w的己二醇、约4％ w/w的丙二醇、约0.015％ w/w的对羟基苯甲酸甲酯、约0.05％ w/w的对羟基苯甲酸丙酯、约0.01％ w/w的EDTA、约0.5％ w/w的Carbopol Ultrez10、约0.2％ w/w的Penmulen TR-1、约3％ w/w的肉豆蔻酸异丙酯、约5％ w/w的油醇、约0.2％ w/w的丁基羟基

甲苯和约 5% w/w 的白凡士林。在本文中提供的局部制剂的一些实施方案中，该洗液包含二甲基异山梨醇酯、Transcutol、己二醇、丙二醇、对羟基苯甲酸甲酯、对羟基苯甲酸丙酯、EDTA、Carbopol Ultrez10、Penmulen TR-1、十六醇、轻质矿物油、油酸和丁基羟基甲苯。在本文中提供的局部制剂的一些实施方案中，该洗液包含约 13% w/w 的二甲基异山梨醇酯、约 20% w/w 的 Transcutol、约 10% w/w 的己二醇、约 4% w/w 的丙二醇、约 0.015% w/w 的对羟基苯甲酸甲酯、约 0.05% w/w 的对羟基苯甲酸丙酯、约 0.01% w/w 的 EDTA、约 0.3% w/w 的 Carbopol Ultrez10、约 0.2% w/w 的 Penmulen TR-1、约 2% w/w 的十六醇、约 5.5% w/w 的轻质矿物油、约 5% w/w 的油酸和约 0.2% w/w 的丁基羟基甲苯。在本文中提供的局部制剂的一些实施方案中，该局部制剂包含皮肤渗透剂。在本文中提供的局部制剂的一些实施方案中，该皮肤渗透剂是 DMSO。在本文中提供的局部制剂的一些实施方案中，该局部制剂包含胶凝剂。在本文中提供的局部制剂的一些实施方案中，该局部制剂包含软化剂。在本文中提供的局部制剂的一些实施方案中，该局部制剂包含抗氧化剂。在本文中提供的局部制剂的一些实施方案中，该局部制剂包含皮肤保护剂。在本文中提供的局部制剂的一些实施方案中，该局部制剂包含刺激缓和剂。在本文中提供的局部制剂的一些实施方案中，该局部制剂包含干燥感改性剂。在本文中提供的局部制剂的一些实施方案中，该局部制剂包含表面活性剂。在本文中提供的局部制剂的一些实施方案中，该局部制剂包含防腐剂。在本文中提供的局部制剂的一些实施方案中，该局部制剂包含螯合剂。在本文中提供的局部制剂的一些实施方案中，其中该局部制剂包含润滑剂。在本文中提供的局部制剂的一些实施方案中，该局部制剂包含增稠剂。在本文中提供的局部制剂的一些实施方案中，该局部制剂包含至少一种另外的治疗剂。在本文中提供的局部制剂的一些实施方案中，该另外的治疗剂是抗氧化剂、抗炎剂、抗血管生成剂、抗凋亡剂、血管内皮生长因子抑制剂、抗微生物或抗病毒剂。在本文中提供的局部制剂的一些实施方案中，该另外的治疗剂是皮质类固醇。

[0006] 在某些实施方案中，本文中公开了在有需要的个体中治疗炎性皮肤病的方法，包括向该个体施用治疗有效量的包含人凯莫瑞 C15 肽的局部制剂，其中该制剂被配制成使得对个体的全身暴露最小化。在本文中提供的方法的一些实施方案中，施用抑制抗原呈递细胞分泌一种或多种炎性细胞因子。在本文中提供的方法的一些实施方案中，施用抑制抗原呈递细胞中炎性细胞因子的 NFκB 核易位或 NFκB 介导的基因转录。在本文中提供的方法的一些实施方案中，该炎性细胞因子是 IL-23、TNFα、IL-1β、IL-6 或 RANTES。在本文中提供的方法的一些实施方案中，该炎性细胞因子是 IL-23。在本文中提供的方法的一些实施方案中，该炎性细胞因子是 TNFα。在本文中提供的方法的一些实施方案中，该炎性细胞因子是 IL-1β。在本文中提供的方法的一些实施方案中，该炎性细胞因子是 RANTES。在本文中提供的方法的一些实施方案中，该抗原呈递细胞是活化的巨噬细胞、髓样树突状细胞、浆细胞样树突状细胞。在本文中提供的方法的一些实施方案中，人凯莫瑞 C15 肽包含氨基酸序列 AGEDPHSFYFPGQFA。在本文中提供的方法的一些实施方案中，人凯莫瑞 C15 肽基本上由氨基酸序列 AGEDPHSFYFPGQFA 组成。在本文中提供的方法的一些实施方案中，该皮肤病是免疫疾病、增生性疾病、与变应原和 / 或刺激物的接触、皮脂脂质的过度产生、成纤维细胞疾病或其组合。在本文中提供的方法的一些实施方案中，该皮肤病是牛皮癣、特应性皮炎、接触性皮炎、湿疹性皮炎、斑秃、硬皮病、大疱性疾病、痤疮、荨麻疹、红斑痤疮、瘢痕形成或黑素瘤。在本文中提供的方法的一些实施方案中，该皮肤病是牛皮癣。在本文中提供的

方法的一些实施方案中，该皮肤病是皮炎。在本文中提供的方法的一些实施方案中，该皮肤病是特应性皮炎。在本文中提供的方法的一些实施方案中，该皮肤病是接触性皮炎。在本文中提供的方法的一些实施方案中，该局部制剂是气雾剂、液体、软膏、乳膏、洗液、溶液、悬浮液、乳液、糊剂、凝胶、粉末、油膏、硬膏、涂剂、泡沫、药棒、缓释纳米颗粒、缓释微粒、生物粘合剂、贴剂、绷带或创伤敷料的形式。在本文中提供的方法的一些实施方案中，该制剂被配制为软膏。在本文中提供的方法的一些实施方案中，该软膏包含约 1-10mg 凯莫瑞 C15 肽 / 克软膏。在本文中提供的方法的一些实施方案中，该软膏包含石蜡油。在本文中提供的方法的一些实施方案中，该软膏包含辛酸癸酸甘油三酯。在本文中提供的方法的一些实施方案中，该软膏包含蜂蜡。在本文中提供的方法的一些实施方案中，该软膏包含石蜡油、辛酸甘油三酯和蜂蜡。在本文中提供的方法的一些实施方案中，该软膏包含约 50％的石蜡油、约 45％的辛酸甘油三酯和约 5％的蜂蜡。在本文中提供的方法的一些实施方案中，该软膏包含丁基羟基甲苯、PEG400、Span80、白蜡和白凡士林。在本文中提供的方法的一些实施方案中，该软膏包含约 0.02％ w/w 的丁基羟基甲苯、约 15％ w/w 的 PEG400、约 2％ w/w 的 Span80、约 10％ w/w 的白蜡和约 71.98％ w/w 的白凡士林。在本文中提供的方法的一些实施方案中，该软膏包含丁基化二甲基异山梨醇酯、丁基羟基甲苯、Span80、白蜡和白凡士林。在本文中提供的方法的一些实施方案中，该软膏包含约 10％ w/w 的二甲基异山梨醇酯、约 0.02％ w/w 的丁基羟基甲苯、约 2％ w/w 的 Span80、约 10％ w/w 的白蜡和约 76.98％ w/w 的白凡士林。在本文中提供的方法的一些实施方案中，该制剂被配制为溶液。在本文中提供的方法的一些实施方案中，该制剂被配制成作为喷雾剂施加的溶液。在本文中提供的方法的一些实施方案中，该溶液包含约 1-10mg 凯莫瑞 C15 肽 /ml 溶液。在本文中提供的方法的一些实施方案中，该溶液包含肉豆蔻酸异丙酯、醇、十一烯酸和十二烷基硫酸钠。在本文中提供的方法的一些实施方案中，该溶液包含约 45％的肉豆蔻酸异丙酯、约 45％的醇、约 5％的十一烯酸和约 5％的十二烷基硫酸钠。在本文中提供的方法的一些实施方案中，该溶液包含 DMSO。在本文中提供的方法的一些实施方案中，该溶液包含约 50％的 DMSO 和约 50％的水。在本文中提供的方法的一些实施方案中，该溶液包含二甲基异山梨醇酯、Transcutol、己二醇和丙二醇。在本文中提供的方法的一些实施方案中，该溶液包含约 15％ w/w 的二甲基异山梨醇酯、约 25％ w/w 的 Transcutol、约 12％ w/w 的己二醇和约 5％ w/w 的丙二醇。在本文中提供的方法的一些实施方案中，该制剂被配制为乳膏。在本文中提供的方法的一些实施方案中，该乳膏包含约 1-10mg 凯莫瑞 C15 肽 /ml 乳膏。在本文中提供的方法的一些实施方案中，该制剂被配制为洗液。在本文中提供的方法的一些实施方案中，该洗液包含约 1-10mg 凯莫瑞 C15 肽 /ml 洗液。在本文中提供的方法的一些实施方案中，该洗液包含二甲基异山梨醇酯、Transcutol、己二醇、丙二醇、对羟基苯甲酸甲酯、对羟基苯甲酸丙酯、EDTA、Carbopol Ultrez10、Penmulen TR-1 和丁基羟基甲苯。在本文中提供的方法的一些实施方案中，该洗液包含二甲基异山梨醇酯、Transcutol、己二醇、丙二醇、对羟基苯甲酸甲酯、对羟基苯甲酸丙酯、EDTA、Carbopol Ultrez10、Penmulen TR-1、肉豆蔻酸异丙酯、油醇、丁基羟基甲苯和白凡士林。在本文中提供的方法的一些实施方案中，该洗液包含约 13％ w/w 的二甲基异山梨醇酯、约 20％ w/w 的 Transcutol、约 10％ w/w 的己二醇、约 4％ w/w 的丙二醇、约 0.015％ w/w 的对羟基苯甲酸甲酯、约 0.05％ w/w 的对羟基苯甲酸丙酯、约 0.01％ w/w 的 EDTA、约 0.5％ w/w 的 Carbopol Ultrez10、约 0.2％ w/w 的 Penmulen TR-1、约 3％ w/w 的肉

豆蔻酸异丙酯、约 5% w/w 的油醇、约 0.2% w/w 的丁基羟基甲苯和约 5% w/w 的白凡士林。在本文中提供的方法的一些实施方案中，该洗液包含二甲基异山梨醇酯、Transcutol、己二醇、丙二醇、对羟基苯甲酸甲酯、对羟基苯甲酸丙酯、EDTA、Carbopol Ultrez10、Penmulen TR-1、十六醇、轻质矿物油、油酸和丁基羟基甲苯。在本文中提供的方法的一些实施方案中，该洗液包含约 13% w/w 的二甲基异山梨醇酯、约 20% w/w 的 Transcutol、约 10% w/w 的己二醇、约 4% w/w 的丙二醇、约 0.015% w/w 的对羟基苯甲酸甲酯、约 0.05% w/w 的对羟基苯甲酸丙酯、约 0.01% w/w 的 EDTA、约 0.3% w/w 的 Carbopol Ultrez10、约 0.2% w/w 的 Penmulen TR-1、约 2% w/w 的十六醇、约 5.5% w/w 的轻质矿物油、约 5% w/w 的油酸和约 0.2% w/w 的丁基羟基甲苯。在本文中提供的方法的一些实施方案中，该局部制剂包含皮肤渗透剂。在本文中提供的方法的一些实施方案中，该皮肤渗透剂是 DMSO。在本文中提供的方法的一些实施方案中，该局部制剂包含胶凝剂。在本文中提供的方法的一些实施方案中，该局部制剂包含软化剂。在本文中提供的方法的一些实施方案中，该局部制剂包含抗氧化剂。在本文中提供的方法的一些实施方案中，该局部制剂包含皮肤保护剂。在本文中提供的方法的一些实施方案中，该局部制剂包含刺激缓和剂。在本文中提供的方法的一些实施方案中，该局部制剂包含干燥感改性剂。在本文中提供的方法的一些实施方案中，该局部制剂包含表面活性剂。在本文中提供的方法的一些实施方案中，该局部制剂包含防腐剂。在本文中提供的方法的一些实施方案中，该局部制剂包含螯合剂。在本文中提供的方法的一些实施方案中，该局部制剂包含润滑剂。在本文中提供的方法的一些实施方案中，该局部制剂包含增稠剂。在本文中提供的方法的一些实施方案中，该局部制剂包含至少一种另外的治疗剂。在本文中提供的方法的一些实施方案中，该另外的治疗剂是抗氧化剂、抗炎剂、抗血管生成剂、抗凋亡剂、血管内皮生长因子抑制剂、抗微生物或抗病毒剂。在本文中提供的方法的一些实施方案中，该另外的治疗剂是皮质类固醇。在本文中提供的方法的一些实施方案中，该局部制剂被局部施加到皮肤、眼、口、鼻、阴道粘膜或肛门粘膜。在本文中提供的方法的一些实施方案中，在向该个体施用后约 1-12 小时，该局部制剂的施用导致大于约 0.1pM-100nM、大于约 1pM-10nM、大于约 1pM-1nM、大于约 1-100pM 或者大于约 1-10pM 的凯莫瑞 C15 肽的局部组织浓度。在本文中提供的方法的一些实施方案中，该局部制剂的施用导致小于约 100pM、小于约 10pM、小于约 1pM、小于约 0.1pM 或小于约 0.01pM 的凯莫瑞 C15 肽的全身浓度。

[0007] 在某些实施方案中，本文中公开了人凯莫瑞 C15 肽用于制备局部制剂的用途，该局部制剂包含用于治疗炎性皮肤病的治疗有效量的肽，其中该制剂被配制成使全身暴露最小化。在本文中提供的用途的一些实施方案中，该人凯莫瑞 C15 肽的量对于抑制抗原呈递细胞分泌一种或多种炎性细胞因子是有效的。在本文中提供的用途的一些实施方案中，该人凯莫瑞 C15 肽的量对于抑制抗原呈递细胞中炎性细胞因子的 NFκB 核易位或 NFκB 介导的基因转录是有效的。在本文中提供的用途的一些实施方案中，该炎性细胞因子是 IL-23、TNFα、IL-1β、IL-6 或 RANTES。在本文中提供的用途的一些实施方案中，该炎性细胞因子是 IL-23。在本文中提供的用途的一些实施方案中，该炎性细胞因子是 TNFα。在本文中提供的用途的一些实施方案中，该炎性细胞因子是 IL-1β。在本文中提供的用途的一些实施方案中，该炎性细胞因子是 RANTES。在本文中提供的用途的一些实施方案中，该抗原呈递细胞是活化的巨噬细胞、髓样树突状细胞、浆细胞样树突状细胞。在本文中提供的用途的一些

实施方案中，该凯莫瑞 C15 肽包含氨基酸序列 AGEDPHSFYFPGQFA。在本文中提供的用途的一些实施方案中，其中凯莫瑞 C15 肽基本上由氨基酸序列 AGEDPHSFYFPGQFA 组成。在本文中提供的用途的一些实施方案中，该皮肤病是免疫疾病、增生性疾病、与变应原和 / 或刺激物的接触、皮脂脂质的过度产生、成纤维细胞疾病或其组合。在本文中提供的用途的一些实施方案中，该皮肤病是牛皮癣、特应性皮炎、接触性皮炎、湿疹性皮炎、斑秃、硬皮病、大疱性疾病、痤疮、荨麻疹、红斑痤疮、瘢痕形成或黑素瘤。在本文中提供的用途的一些实施方案中，该皮肤病是牛皮癣。在本文中提供的用途的一些实施方案中，该皮肤病是皮炎。在本文中提供的用途的一些实施方案中，该皮肤病是特应性皮炎。在本文中提供的用途的一些实施方案中，该皮肤病是接触性皮炎。在本文中提供的用途的一些实施方案中，该局部制剂是气雾剂、液体、软膏、乳膏、洗液、溶液、悬浮液、乳液、糊剂、凝胶、粉末、油膏、硬膏、涂剂、泡沫、药棒、缓释纳米颗粒、缓释微粒、生物粘合剂、贴剂、绷带或创伤敷料的形式。在本文中提供的用途的一些实施方案中，该局部制剂被配制为软膏。在本文中提供的用途的一些实施方案中，该软膏包含约 1-10mg 凯莫瑞 C15 肽 / 克软膏。在本文中提供的用途的一些实施方案中，该软膏包含石蜡油。在本文中提供的用途的一些实施方案中，该软膏包含辛酸癸酸甘油三酯。在本文中提供的用途的一些实施方案中，该软膏包含蜂蜡。在本文中提供的用途的一些实施方案中，该软膏包含石蜡油、辛酸甘油三酯和蜂蜡。在本文中提供的用途的一些实施方案中，该软膏包含约 50％的石蜡油、约 45％的辛酸甘油三酯和约 5％的蜂蜡。在本文中提供的用途的一些实施方案中，该软膏包含丁基羟基甲苯、PEG400、Span80、白蜡和白凡士林。在本文中提供的用途的一些实施方案中，该软膏包含约 0.02％ w/w 的丁基羟基甲苯、约 15％ w/w 的 PEG400、约 2％ w/w 的 Span80、约 10％ w/w 的白蜡和约 71.98％ w/w 的白凡士林。在本文中提供的用途的一些实施方案中，该软膏包含丁基化二甲基异山梨醇酯、丁基羟基甲苯、Span80、白蜡和白凡士林。在本文中提供的用途的一些实施方案中，该软膏包含约 10％ w/w 的二甲基异山梨醇酯、约 0.02％ w/w 的丁基羟基甲苯、约 2％ w/w 的 Span80、约 10％ w/w 的白蜡和约 76.98％ w/w 的白凡士林。在本文中提供的用途的一些实施方案中，该局部制剂被配制为溶液。在本文中提供的用途的一些实施方案中，该局部制剂被配制成作为喷雾剂施加的溶液。在本文中提供的用途的一些实施方案中，该溶液包含约 1-10mg 凯莫瑞 C15 肽 /ml 溶液。在本文中提供的用途的一些实施方案中，该溶液包含肉豆蔻酸异丙酯、醇、十一烯酸和十二烷基硫酸钠。在本文中提供的用途的一些实施方案中，该溶液包含约 45％的肉豆蔻酸异丙酯、约 45％的醇、约 5％的十一烯酸和约 5％的十二烷基硫酸钠。在本文中提供的用途的一些实施方案中，该溶液包含 DMSO。在本文中提供的用途的一些实施方案中，该溶液包含约 50％的 DMSO 和约 50％的水。在本文中提供的用途的一些实施方案中，该溶液包含二甲基异山梨醇酯、Transcutol、己二醇和丙二醇。在本文中提供的用途的一些实施方案中，该溶液包含约 15％ w/w 的二甲基异山梨醇酯、约 25％ w/w 的 Transcutol、约 12％ w/w 的己二醇和约 5％ w/w 的丙二醇。在本文中提供的用途的一些实施方案中，该局部制剂被配制为乳膏。在本文中提供的用途的一些实施方案中，该乳膏包含约 1-10mg 凯莫瑞 C15 肽 /ml 乳膏。在本文中提供的用途的一些实施方案中，该局部制剂被配制为洗液。在本文中提供的用途的一些实施方案中，该洗液包含约 1-10mg 凯莫瑞 C15 肽 /ml 洗液。在本文中提供的用途的一些实施方案中，该洗液包含二甲基异山梨醇酯、Transcutol、己二醇、丙二醇、对羟基苯甲酸甲酯、对羟基苯甲酸丙酯、EDTA、Carbopol Ultrez10、Penmulen

TR-1 和丁基羟基甲苯。在本文中提供的用途的一些实施方案中，该洗液包含二甲基异山梨醇酯、Transcutol、己二醇、丙二醇、对羟基苯甲酸甲酯、对羟基苯甲酸丙酯、EDTA、Carbopol Ultrez10、Penmulen TR-1、肉豆蔻酸异丙酯、油醇、丁基羟基甲苯和白凡士林。在本文中提供的用途的一些实施方案中，该洗液包含约 13％ w/w 的二甲基异山梨醇酯、约 20％ w/w 的 Transcutol、约 10％ w/w 的己二醇、约 4％ w/w 的丙二醇、约 0.015％ w/w 的对羟基苯甲酸甲酯、约 0.05％ w/w 的对羟基苯甲酸丙酯、约 0.01％ w/w 的 EDTA、约 0.5％ w/w 的 Carbopol Ultrez10、约 0.2％ w/w 的 Penmulen TR-1、约 3％ w/w 的肉豆蔻酸异丙酯、约 5％ w/w 的油醇、约 0.2％ w/w 的丁基羟基甲苯和约 5％ w/w 的白凡士林。在本文中提供的用途的一些实施方案中，该洗液包含二甲基异山梨醇酯、Transcutol、己二醇、丙二醇、对羟基苯甲酸甲酯、对羟基苯甲酸丙酯、EDTA、Carbopol Ultrez10、Penmulen TR-1、十六醇、轻质矿物油、油酸、丁基羟基甲苯。在本文中提供的用途的一些实施方案中，该洗液包含约 13％ w/w 的二甲基异山梨醇酯、约 20％ w/w 的 Transcutol、约 10％ w/w 的己二醇、约 4％ w/w 的丙二醇、约 0.015％ w/w 的对羟基苯甲酸甲酯、约 0.05％ w/w 的对羟基苯甲酸丙酯、约 0.01％ w/w 的 EDTA、约 0.3％ w/w 的 Carbopol Ultrez10、约 0.2％ w/w 的 Penmulen TR-1、约 2％ w/w 的十六醇、约 5.5％ w/w 的轻质矿物油、约 5％ w/w 的油酸和约 0.2％ w/w 的丁基羟基甲苯。在本文中提供的用途的一些实施方案中，该局部制剂包含皮肤渗透剂。在本文中提供的用途的一些实施方案中，该皮肤渗透剂是 DMSO。在本文中提供的用途的一些实施方案中，该局部制剂包含胶凝剂。在本文中提供的用途的一些实施方案中，该局部制剂包含软化剂。在本文中提供的用途的一些实施方案中，该局部制剂包含抗氧化剂。在本文中提供的用途的一些实施方案中，该局部制剂包含皮肤保护剂。在本文中提供的用途的一些实施方案中，该局部制剂包含刺激缓和剂。在本文中提供的用途的一些实施方案中，该局部制剂包含干燥感改性剂。在本文中提供的用途的一些实施方案中，该局部制剂包含表面活性剂。在本文中提供的用途的一些实施方案中，该局部制剂包含防腐剂。在本文中提供的用途的一些实施方案中，该局部制剂包含螯合剂。在本文中提供的用途的一些实施方案中，该局部制剂包含润滑剂。在本文中提供的用途的一些实施方案中，该局部制剂包含增稠剂。在本文中提供的用途的一些实施方案中，该局部制剂包含至少一种另外的治疗剂。在本文中提供的用途的一些实施方案中，该另外的治疗剂是抗氧化剂、抗炎剂、抗血管生成剂、抗凋亡剂、血管内皮生长因子抑制剂、抗微生物或抗病毒剂。在本文中提供的用途的一些实施方案中，该另外的治疗剂是皮质类固醇。在本文中提供的用途的一些实施方案中，该局部制剂被配制为用于施加到皮肤、眼、口、鼻、阴道粘膜或肛门粘膜。

## 附图说明

[0008] 在所附权利要求书中详细阐明了本发明的新颖特征。通过参考以下阐明了说明性实施方案的详细说明（其中利用了本发明的原理）和附图，将获得对本发明特征和优点的更好的理解，附图中：

[0009] 图 1 举例说明了人凯莫瑞 C15 和 C17 肽对 IFNγ/LPS 刺激的人巨噬细胞中的细胞因子产生的效果。A)15 小时的 IL-1β；B)15 小时的 RANTES；C)RANTES（从 6 到 15 小时的差异）；D)15 小时的 IL-12p40；和 E)15 小时的 IL-10。

[0010] 图 2 举例说明了在凯莫瑞、人凯莫瑞 C15、16 或 C17 肽、或者小鼠凯莫瑞 C15 肽的

存在下，ChemR23 和 GPR1 受体的激动剂和拮抗剂剂量响应曲线。

[0011] 图 3 举例说明了由 FYFP 基序的修饰引起的人凯莫瑞 C15 肽抗炎活性的损失。

## 具体实施方式

[0012] 在某些实施方案中，本文中公开了凯莫瑞 C15 肽。本文中进一步公开了包含凯莫瑞 C15 肽和任选的药学上可接受的赋形剂的局部制剂。本文中另外公开了在有需要的个体中治疗炎性皮肤病的方法，包括施用本文中公开的凯莫瑞 C15 肽或者包含本文中公开的凯莫瑞 C15 肽的局部制剂。本文中进一步公开了在有需要的个体中抑制炎性细胞因子或趋化因子的活性的方法，包括施用本文中公开的凯莫瑞 C15 肽或者包含本文中公开的凯莫瑞 C15 肽的局部制剂。在某些实施方案中，本文中还公开了在有需要的个体中抑制炎性细胞因子的核易位或 NF κ B 介导的基因转录的方法，包括施用本文中公开的凯莫瑞 C15 肽或者包含本文中公开的凯莫瑞 C15 肽的局部制剂。在一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。在一些实施方案中，该凯莫瑞 C15 肽是凯莫瑞 C15 肽的盐。在一些实施方案中，该凯莫瑞 C15 肽是羧化的。在一些实施方案中，该凯莫瑞 C15 肽是酰胺化的。在一些实施方案中，该凯莫瑞 C15 肽是环状的。在一些实施方案中，该凯莫瑞 C15 肽与天然存在的凯莫瑞 C15 肽至少 80％、85％、90％、91％、92％、93％、94％、95％、96％、97％、98％、99％、99.5％、99.6％、99.7％、99.8％或 99.9％同源。

某些术语

[0013] 如本文中使用的，“凯莫瑞 C15 肽”是指包含氨基酸序列 AGEDPHSFYFPGQFA 的肽，该氨基酸序列是人凯莫瑞多肽、人凯莫瑞 C15 肽的物种变体（例如小鼠或大鼠凯莫瑞 C15 肽）或者如本文中所述的人凯莫瑞 C15 肽的其它变体的序列。

[0014] 如本文中使用的，“肽”旨在具有本领域公认的含义，即：通过酰胺键连接的两个或更多个氨基酸，例如，式 --C( ＝ O)CH( 侧链 )NH-- 的重复单元，其最简单的形式终止于胺或羧酸。如本领域普通技术人员将认识到的，对肽主链进行多种修饰而不改变分子的整体性质是可能的，包括末端基团的修饰，例如本文中描述的那些修饰。

[0015] 如本文中使用的，“氨基酸”旨在具有本领域公认的含义，即：通式 HOC( ＝ O)CH( 侧链 )(NH2) 的羧酸。氨基酸的侧链是本领域公知的，并且包括天然存在的和非天然存在的部分。非天然存在的（即，非天然的）氨基酸侧链是例如氨基酸类似物中用来代替天然存在的氨基酸侧链的部分。

[0016] 术语“个体”、“患者”或“受试者”可互换使用。如本文中使用的，它们意指任何哺乳动物。在一方面，该哺乳动物是人。这些术语均不要求该个体 / 患者 / 受试者处于医疗专业人员（例如，医生、护士、医师助理、注册护士、执业护士、临终关怀工作人员、护理员等等）的护理下。

[0017] 术语“治疗”(treat、treating 或 treatment) 及本文中使用的其它语法等同物，包括减轻、缓和、抑制、减少或改善疾病或疾病的症状，延迟其发作，阻止其进展，和 / 或诱导其消退。该术语还包括疾病的预防性治疗。该术语进一步包括获得任何治疗益处。治疗益处意指所治疗的基础疾病的根除或改善，和 / 或与基础疾病有关的一种或多种生理学症状的根除或改善，使得在个体中观察到或察觉到改善。

[0018] 术语“预防 (prevent、preventing 或 prevention)”及本文中使用的其它语法等同

物，包括抑制（阻止或停止）疾病的发展和/或抑制（阻止或停止）疾病的进一步进展。这些术语旨在包括预防。为了获得预防益处，将该组合物施用于处于特定疾病发展风险中的个体，或者报告了疾病的一种或多种生理学症状的个体，或者处于疾病复发风险中的个体。

[0019] 如本文中使用的术语“有效量”或“治疗有效量”，是指实现所需结果（例如，将所治疗的疾病、病症或病状的一个或多个症状减轻到某种程度）的药剂（例如，凯莫瑞C15肽）的施用量。在某些情况下，该结果是疾病的至少一种指征、症状或病因的减少和/或减轻，或者是生物系统的任何其它期望的变化。在某些情况下，治疗用途的“有效量”是提供疾病、病症或病状的至少一种症状在临床上显著减轻所需的、包含本文所述药剂的组合物的量。采用任何合适的技术（例如，剂量递增研究）来确定在任何个体情况中的合适的“有效量”。例如，如本文中使用的，局部施加到组织的局部药剂（例如，凯莫瑞C15肽）的合适的有效量是足以达到局部治疗浓度的量，该浓度已经在体外证明可抑制与炎症有关的细胞过程，例如NFκB的抑制和/或对一种或多种炎性细胞因子的产生和/或分泌的抑制。

[0020] 如本文中使用的，术语“给药”、“施用”等是指用来使凯莫瑞C15肽能够递送到生物作用所需部位（例如，皮肤病的部位）的方法。这些方法包括用于皮肤（即，局部）给药的任何合适的方法。

[0021] 如本文中使用的，术语“制剂”或“组合物”可互换使用。它们意指包含本文中公开的凯莫瑞C15肽和药学上可接受的赋形剂的产品。

[0022] 如本文中使用的，“局部”给药是指施用到受试者的皮肤、眼或粘膜表面，如口、鼻、阴道或肛门的表面）。

[0023] 如本文中使用的“局部治疗”是指对免疫或炎性疾病的治疗，其中将药物局部递送，而不是通过全身递送来递送。在一些实施方案中，这包括许多不同的局部区域或几个不同的局部区域，例如在皮肤的治疗中，其中药物被施加到皮肤上的多个不同的位置或几个不同的位置，并且其中通过透过皮肤的吸收来将药物递送到皮肤内和接近皮肤的组织。在一些实施方案中，药物被递送到粘膜表面，例如口、鼻、肛门或阴道，并透过在粘膜内或接近粘附的组织的上皮表面而吸收。

[0024] 如本文中使用的，“局部组织浓度”是指在已经递送并吸收了凯莫瑞C15肽的组织区域内凯莫瑞C15肽的浓度。

[0025] 如本文中使用的，术语“药学上可接受的”是指不会消除本文所述的药剂的生物活性或性质并且相对无毒（即，该材料的毒性不会明显超过该材料的益处）的材料。

凯莫瑞C-端肽和炎性皮肤病的概述

[0026] 在某些实施方案中，本文中公开了凯莫瑞C15肽。本文中进一步公开了包含凯莫瑞C15肽和任选的药学上可接受的赋形剂的局部制剂。本文中另外公开了在有需要的个体中治疗炎性皮肤病的方法，包括施用本文中公开的凯莫瑞C15肽或者包含本文中公开的凯莫瑞C15肽的局部制剂。本文中进一步公开了在有需要的个体中抑制炎性细胞因子或趋化因子的活性的方法，包括施用本文中公开的凯莫瑞C15肽或者包含本文中公开的凯莫瑞C15肽的局部制剂。在某些实施方案中，本文中还公开了在有需要的个体中抑制炎性细胞因子的核易位或NFκB介导的基因转录的方法，包括施用本文中公开的凯莫瑞C15肽或者包含本文中公开的凯莫瑞C15肽的局部制剂。在一些实施方案中，该凯莫瑞C15肽是人凯莫瑞C15肽。在一些实施方案中，该凯莫瑞C15肽是凯莫瑞C15肽的盐。在一些实施方案中，该

凯莫瑞 C15 肽是羧化的。在一些实施方案中，该凯莫瑞 C15 肽是酰胺化的。在一些实施方案中，该凯莫瑞 C15 肽是环状的。在一些实施方案中，该凯莫瑞 C15 肽与天然存在的凯莫瑞 C15 肽至少 80％、85％、90％、91％、92％、93％、94％、95％、96％、97％、98％、99％、99.5％、99.6％、99.7％、99.8％或 99.9％同源。

[0027] 在某些情况下，皮肤病的特征是皮肤中增加的炎症。在某些情况下，皮肤病是由包括巨噬细胞、树突细胞、单核细胞、嗜中性粒细胞和 NK 细胞在内的炎症细胞向皮肤组织中的浸润引起的。来自这些细胞的抗原呈递激活了皮肤病中的自反应性 T- 细胞。目前已经批准的针对皮肤病的疗法包括抗体和生物制剂靶向细胞因子，包括，例如 TNFα、IL-12、IL-13、IL-1β 和 / 或 IL-6。这些制剂的效力与在患病皮肤组织中 TNFα、IL-12、IL-13、IL-1β 和 / 或 IL-6 水平的减少有关。与炎性皮肤病症和疾病有关的另外的细胞因子包括但不限于 IL-1、IL-2、IL-3、IL-4、IL-5、IL-6、IL-7、IL-8、IL-9、IL-11、IL-12、IL-13、IL-14、IL-15、IL-16、IL-17、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 以及 TNF 家族成员、IFN 家族成员、RANTES、MCP-1 和 MIP-1。这些抗细胞因子抗体和生物制剂通常是全身给药，因而导致全身的免疫抑制，这使患者处于增大的无意副作用（包括增加的感染和死亡）的风险中。在一个例子中，在几例 PML 和死亡病例与其应用相关联后，将单克隆抗体 Raptiva（一种已批准的牛皮癣治疗）从市场上撤除。

[0028] 凯莫瑞，也称作视黄酸受体应答蛋白 2(RARRES2)、他扎罗汀诱导的基因 2 蛋白 (TIG2) 或 RAR 响应性蛋白 TIG2，是一种 157 个氨基酸的血浆蛋白质，它是由其 163 个氨基酸的前体—原凯莫瑞 (prochemerin)—的酶切而产生的。

[0029] 人凯莫瑞源具有氨基酸序列：MRRLLIPLALWLGAVGVGVAELTEAQRRGLQVALEEFHKHPPVQWAFQETSVESAVDTPFPAGIFVRLEFKLQQTSCRKRDWKKPECKVRPNGRKRKCLACIKLGSEDKVLGRLVHCPIETQVLREAEEHQETQCLRVQRAGEDPHSFYFPGQFAFSKALPRS。

[0030] 成熟人凯莫瑞具有氨基酸序列：VGVAELTEAQRRGLQVALEEFHKHPPVQWAFQETSVESAVDTPFPAGIFVRLEFKLQQTSCRKRDWKKPECKVRPNGRKRKCLACIKLGSEDKVLGRLVHCPIETQVLREAEEHQETQCLRVQRAGEDPHSFYFPGQFAFSKALPRS。

[0031] 小鼠凯莫瑞源具有氨基酸序列：

[0032] MKCLLISLALWLGTVGTRGTEPELSETQRRSLQVALEEFHKHPPVQLAFQEIGVDRAEEVLFSAGTFVRLEFKLQQTNCPKKDWKKPECTIKPNGRRRKCLACIKMDPKGKILGRIVHCPILKQGPQDPQELQCIKIAQAGEDPHGYFLPGQFAFSRALRTK。

[0033] 成熟小鼠凯莫瑞具有氨基酸序列：

[0034] TEPELSETQRRSLQVALEEFHKHPPVQLAFQEIGVDRAEEVLFSAGTFVRLEFKLQQTNCPKKDWKKPECTIKPNGRRRKCLACIKMDPKGKILGRIVHCPILKQGPQDPQELQCIKIAQAGEDPHGYFLPGQFAFSRALRTK。

[0035] 大鼠凯莫瑞源具有氨基酸序列：

[0036] TELELSETQRRGLQVALEEFHRHPPVQWAFQEIGVDSADDLFFSAGTFVRLEFKLQQTSCLKKDWKKPECTIKPNGRKRKCLACIKLDPKGKVLGRMVHCPILKQGPQQEPQESQCSKIAQAGEDSRIYFFPGQFAFSRALQSK。

[0037] 成熟小鼠凯莫瑞具有氨基酸序列：

[0038] MKCLLISLALWLGTADIHGTELELSETQRRGLQVALEEFHRHPPVQWAFQEIGVDSADDLFFSAGTFVRLEFKLQQTSCLKKDWKKPECTIKPNGRKRKCLACIKLDPKGKVLGRMVHCPILKQGPQQEPQESQCSKIAQAGED

SRIYFFPGQFAFSRALQSK。

[0039] 凯莫瑞是通过G蛋白偶联受体ChemR23起作用的强力巨噬细胞化学引诱物。小鼠凯莫瑞的蛋白水解组合物在Chem23受体的存在下抑制巨噬细胞活化和对炎症的抑制。小鼠凯莫瑞的15个氨基酸的C端肽(mC15)(AGEDPHGYFLPGQFA)在ChemR23的存在下抑制巨噬细胞的活化。如本文中提供的数据所示,人凯莫瑞C15肽(例如,AGEDPHSFYFPGQFA)也是强力的炎性抑制剂。

[0040] 因此,在某些实施方案中,本文中公开了调节表达凯莫瑞GPCR受体ChemR23的细胞的活性的方法。在一些实施方案中,这些细胞是抗原呈递细胞。在一些实施方案中,这些细胞尤其包括巨噬细胞、树突细胞、单核细胞、嗜中性粒细胞和NK细胞,它们是与炎性皮肤病有关的细胞因子的来源。在一些实施方案中,凯莫瑞C15肽起到减少表达ChemR23的细胞分泌细胞因子的作用。在一些实施方案中,凯莫瑞C15肽减少炎性细胞因子如IL-23、TNFα、IL-1β、IL-6和RANTES的释放。在一些实施方案中,凯莫瑞C15肽减少IL-23的释放。在一些实施方案中,凯莫瑞C15肽减少TNFα的释放。在一些实施方案中,凯莫瑞C15肽减少IL-1β的释放。在一些实施方案中,凯莫瑞C15肽减少IL-6的释放。在一些实施方案中,凯莫瑞C15肽减少RANTES的释放。在一些实施方案中,凯莫瑞C15肽防止炎性免疫细胞的募集。在一些实施方案中,凯莫瑞C15肽抑制炎性细胞因子如IL-23、TNFα、IL-1β、IL-6和RANTES的转录。在一些实施方案中,凯莫瑞C15肽抑制IL-23的转录。在一些实施方案中,凯莫瑞C15肽抑制TNFα的转录。在一些实施方案中,凯莫瑞C15肽抑制IL-1β的转录。在一些实施方案中,凯莫瑞C15肽抑制IL-6的转录。在一些实施方案中,凯莫瑞C15肽抑制RANTES的转录。在一些实施方案中,凯莫瑞C15肽防止炎性免疫细胞的募集。在一些实施方案中,凯莫瑞C15肽防止炎性免疫细胞的活化。在一些实施方案中,凯莫瑞C15肽抑制T细胞的活化。

[0041] 如本文中提供的数据所示,凯莫瑞C15肽不是与ChemR23结合的凯莫瑞的直接竞争性抑制剂。因此,凯莫瑞C15肽表现出显性阴性抑制剂、偏倚配体或变构拮抗剂的性质。因而,它们能够经由凯莫瑞/ChemR23信号传导和/或与ChemR23的辅助蛋白质有关的信号传导,有利地阻断炎性信号(例如,细胞因子释放),而不会由于抑制“正常”的凯莫瑞/ChemR23和/或与ChemR23的辅助蛋白质有关的信号传导而导致“副作用”。此外,C15肽抑制由TNFα、IFNγ、LPS、酵母聚糖和其它不直接通过ChemR23发信号的刺激物刺激的炎性过程。以这种方式,C15肽表现出NFκB途径抑制剂的性质。因而,它们能够通过防止NFκB活化、核易位、细胞因子基因转录和/或细胞因子释放而有利地阻断炎性信号(例如,细胞因子释放),而不表现出肾上腺抑制(adrenosuppression)或与皮质类固醇有关的其它副作用。

[0042] 此外,如本文中提供的数据所示,凯莫瑞C15肽含有FYFP基序,并且如果该肽在FYFP基序中被修饰为FYAP或YFAP则丧失在刺激的巨噬细胞中抑制炎性细胞因子产生的能力。在人C15中,FYFP基序体现在它的精确FYFP序列中,而在鼠C15中,FYFP基序体现在YFLP氨基酸序列中。FYFP基序类似于PP2A调节性B-亚单位的保守FYFP基序。B-亚单位与PP2A核心酶A和C亚单位的结合取决于FYFP基序(Davis AJ等人,J Biol Chem.2008;283:16104-14)。在静止状态下,蛋白磷酸酶2A(PP2A)核心酶与IKK(IκB激酶)缔合,该激酶使IκB磷酸化并将它维持在无活性的非磷酸化的状态。此外,PP2A核心与NFκB/IκB

复合物的NFκB缔合，将其维持在静止的非磷酸化状态。在NFκB途径的活化期间，NFκB和IκB被磷酸化，并且与PP2A调节性B-亚单位的缔合削弱了PP2A与NFκB/IκB的缔合。IκB也得到释放，从而使得NFκB可易位到核，在核中它参与细胞因子转录，包括IL-23转录的诱导。在一些实施方案中，凯莫瑞C15肽与PP2A的结合干扰了调节性B-亚单位与复合物的结合，从而将NFκB/IκB稳定在静止状态。在一些实施方案中，凯莫瑞C15肽通过抑制从NFκB释放IκB来抑制细胞因子产生，这阻止了核易位和基因活化。

[0043] 在某些实施方案中，本文中描述了用于治疗炎性皮肤病的包含凯莫瑞C15肽的局部制剂。在一些实施方案中，该炎性皮肤病是慢性发疱性疾病、痤疮、牛皮癣、皮炎（例如，接触性或特应性皮炎）、湿疹、扁平苔癣、斑秃、荨麻疹、红斑痤疮、瘢痕形成（即，瘢痕（例如，瘢痕疙瘩伤疤或肥厚性瘢痕）的形成）和/或黑素瘤。在一些实施方案中，该炎性皮肤病是牛皮癣。在一些实施方案中，该炎性皮肤病是皮炎。在一些实施方案中，该炎性皮肤病是特应性皮炎。在一些实施方案中，该炎性皮肤病是接触性皮炎。在一些实施方案中，本文中公开的局部制剂包含治疗有效量的凯莫瑞C15肽。本文中公开的局部制剂将治疗水平的凯莫瑞C15肽在角质层下递送到表皮和真皮，并提供对皮肤病，特别是对炎性皮肤病的增强的治疗。

[0044] 本文中还公开了施用包含凯莫瑞C15肽的局部制剂的方法。在一个方面，凯莫瑞C15肽的局部制剂提供了对皮肤病状的局部治疗。在一个方面，用凯莫瑞C15肽对皮肤病状的局部治疗减少了与凯莫瑞C15肽全身给药有关的可能的副作用。在一个方面，凯莫瑞C15肽向哺乳动物的局部给药使凯莫瑞C15肽的全身吸收最小化。在一些实施方案中，在与变应原和/或刺激物接触之前或之后施用本文中公开的局部制剂。

[0045] 在某些实施方案中，与目前批准的用于治疗皮肤病的局部药剂相比，针对皮肤病局部施加的凯莫瑞C15肽将具有更少的或严重性更低的副作用。这些批准的局部药剂包括类固醇（例如，皮质类固醇）和钙依赖磷酸酶拮抗剂（例如，Elidel），其在皮肤病的治疗中局部使用时，具有使皮肤变薄、白内障、青光眼和/或肿瘤的已知风险。在某些实施方案中，针对皮肤病局部施加的凯莫瑞C15肽是天然存在的生物制剂，比目前批准的用于治疗皮肤病的全身生物制剂具有更少的或严重性更低的副作用。这些批准的全身生物制剂包括单克隆抗体（例如，Stelara）和融合蛋白（例如，Enbrel），其具有已知的抗原反应、感染和恶性肿瘤的风险。

[0046] 在某些实施方案中，凯莫瑞C15肽被配制用于局部给药，以使凯莫瑞C15肽的全身暴露最小化。在某些实施方案中，设计凯莫瑞C15肽的局部制剂，以使凯莫瑞C15肽的全身暴露最小化（例如，排除特定的赋形剂，这些赋形剂可能导致凯莫瑞C15肽穿透皮肤并且变得可到达全身）。在一些实施方案中，全身暴露的最小化减少了施用凯莫瑞C15肽的不希望的副作用（例如，对身体的非靶向部分的作用）。

[0047] 本文中公开了凯莫瑞C15肽在药物制备中的用途，该药物适合于向哺乳动物局部给药，以治疗或预防皮肤疾病、病症或病状。

[0048] 本文中描述了使用凯莫瑞C15肽的、适合于局部给药的药物组合物、治疗方法、配制局部制剂的方法、生产方法、制备方法、治疗策略。

凯莫瑞C15肽

[0049] 在某些实施方案中，本文中公开了凯莫瑞C15肽。本文中进一步公开了包含凯莫

瑞 C15 肽和任选的药学上可接受的赋形剂的局部制剂。本文中另外公开了在有需要的个体中治疗炎性皮肤病的方法，包括施用本文中公开的凯莫瑞 C15 肽或者包含本文中公开的凯莫瑞 C15 肽的局部制剂。本文中进一步公开了在有需要的个体中抑制炎性细胞因子或趋化因子的活性的方法，包括施用本文中公开的凯莫瑞 C15 肽或者包含本文中公开的凯莫瑞 C15 肽的局部制剂。在某些实施方案中，本文中还公开了在有需要的个体中抑制炎性细胞因子的核易位或 NF κ B 介导的基因转录的方法，包括施用本文中公开的凯莫瑞 C15 肽或者包含本文中公开的凯莫瑞 C15 肽的局部制剂。在一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。在一些实施方案中，该凯莫瑞 C15 肽是凯莫瑞 C15 肽的盐。在一些实施方案中，该凯莫瑞 C15 肽是羧化的。在一些实施方案中，该凯莫瑞 C15 肽是酰胺化的。在一些实施方案中，该凯莫瑞 C15 肽是环状的。在一些实施方案中，该凯莫瑞 C15 肽与天然存在的凯莫瑞 C15 肽至少 80％、85％、90％、91％、92％、93％、94％、95％、96％、97％、98％、99％、99.5％、99.6％、99.7％、99.8％或 99.9％同源。

[0050] 本文中提供的用于给药的凯莫瑞 C15 肽表现出一种或多种作为炎性疾病或病症的局部治疗有用的性质或活性。在一些实施方案中，本文中公开的凯莫瑞 C15 肽抑制炎症。在一些实施方案中，本文中公开的凯莫瑞 C15 肽抑制与皮肤疾病或病症有关的炎症。在一些实施方案中，本文中公开的凯莫瑞 C15 肽抑制与炎症有关的一种或多种细胞过程。在一些实施方案中，本文中公开的凯莫瑞 C15 肽抑制一种或多种炎性细胞因子的释放。示例性的炎性细胞因子包括但不限于 IL-23、IL-12、TNF α 、IL-1 β 、IL-6 或 RANTES。在一些实施方案中，本文中公开的凯莫瑞 C15 肽抑制 IL-23、IL-12、TNF α 、IL-1 β 、IL-6 或 RANTES 的释放。在一些实施方案中，本文中公开的凯莫瑞 C15 肽抑制一种或多种炎性细胞因子的转录。在一些实施方案中，本文中公开的凯莫瑞 C15 肽抑制 IL-23、IL-12、TNF α 、IL-1 β 、IL-6 或 RANTES 的转录。在一些实施方案中，本文中公开的凯莫瑞 C15 肽抑制一种或多种炎性细胞因子的产生。在一些实施方案中，本文中公开的凯莫瑞 C15 肽抑制 IL-23、IL-12、TNF α 、IL-1 β 、IL-6 或 RANTES 的产生和 / 或释放。在一些实施方案中，本文中公开的凯莫瑞 C15 肽抑制免疫细胞产生和 / 或释放一种或多种炎性细胞因子。在一些实施方案中，本文中公开的凯莫瑞 C15 肽抑制免疫细胞产生和 / 或释放 IL-23、IL-12、TNF α 、IL-1 β 、IL-6 或 RANTES。在一些实施方案中，本文中公开的凯莫瑞 C15 肽抑制抗原呈递细胞产生和 / 或释放一种或多种炎性细胞因子。在一些实施方案中，本文中公开的凯莫瑞 C15 肽抑制抗原呈递细胞产生和 / 或释放 IL-23、IL-12、TNF α 、IL-1 β 、IL-6 或 RANTES。在一些实施方案中，本文中公开的凯莫瑞 C15 肽抑制在髓样树突状细胞 (mDC)、浆细胞样树突状细胞 (pDC) 或巨噬细胞中一种或多种炎性细胞因子的产生和 / 或释放。在一些实施方案中，本文中公开的凯莫瑞 C15 肽抑制髓样树突状细胞 (mDC)、浆细胞样树突状细胞 (pDC) 或巨噬细胞中 IL-23、IL-12、TNF α 、IL-1 β 、IL-6 或 RANTES 的产生和 / 或释放。在一些实施方案中，本文中公开的凯莫瑞 C15 肽抑制表达 ChemR23 受体的免疫细胞产生和 / 或释放一种或多种炎性细胞因子。在一些实施方案中，本文中公开的凯莫瑞 C15 肽抑制表达 ChemR23 受体的免疫细胞产生和 / 或释放 IL-23、IL-12、TNF α 、IL-1 β 、IL-6 或 RANTES。

[0051] 在一些实施方案中，本文中公开的凯莫瑞 C15 肽抑制 NF- κ B 的活化。在一些实施方案中，本文中公开的凯莫瑞 C15 肽抑制与炎症有关的 NF- κ B 的活化。在一些实施方案中，本文中公开的凯莫瑞 C15 肽抑制在表达 ChemR23 受体的细胞中 NF- κ B 的活化。在一些实

施方案中，本文中公开的凯莫瑞 C15 肽与蛋白磷酸酶 2A 核心酶结合。在一些实施方案中，本文中公开的凯莫瑞 C15 肽防止 IκB 从 NF-κB 的释放。在一些实施方案中，本文中公开的凯莫瑞 C15 肽防止 NF-κB 的核易位。在一些实施方案中，本文中公开的凯莫瑞 C15 肽抑制 Th1 和 / 或 Th17T- 细胞活化。在一些实施方案中，本文中公开的凯莫瑞 C15 肽抑制与炎症有关的 Th1 和 / 或 Th17T- 细胞活化。

[0052] 在一些实施方案中，该凯莫瑞 C15 肽是任何适合于局部给药的凯莫瑞 C15 肽。在一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。在一些实施方案中，该凯莫瑞 C15 肽包括氨基酸序列 AGEDPHSFYFPGQFA。在一些实施方案中，该凯莫瑞 C15 肽具有基本由氨基酸序列 AGEDPHSFYFPGQFA 组成的氨基酸序列。

[0053] 在一些实施方案中，该凯莫瑞 C15 肽是小鼠凯莫瑞 C15 肽。在一些实施方案中，该凯莫瑞 C15 肽包含氨基酸序列 AGEDPHGYFLPGQFA。在一些实施方案中，该凯莫瑞 C15 肽具有基本由氨基酸序列 AGEDPHGYFLPGQFA 组成的氨基酸序列。

[0054] 在一些实施方案中，该凯莫瑞 C15 肽是包含来源于人凯莫瑞 C15 肽和非人凯莫瑞 C15 肽的氨基酸序列的嵌合凯莫瑞 C15 肽。在一些实施方案中，该凯莫瑞 C15 肽是包含来源于人凯莫瑞 C15 肽和小鼠凯莫瑞 C15 肽的氨基酸序列的嵌合凯莫瑞 C15 肽。在一些实施方案中，该凯莫瑞 C15 肽包含氨基酸序列 AGEDPHGYYFPGQFA。在一些实施方案中，该凯莫瑞 C15 肽具有基本由氨基酸序列 AGEDPHGYYFPGQFA 组成的氨基酸序列。

[0055] 在一些实施方案中，该凯莫瑞 C15 肽是包含氨基酸序列 $AGEDPHSX_1X_2X_3PGQFA$ 的肽，其中 $X_1$、$X_2$ 和 $X_3$ 是疏水性氨基酸。在一些实施方案中，该凯莫瑞 C15 肽是包含氨基酸序列 $AGEDPHSX_1X_2X_3PGQFA$ 的肽，其中 $X_1$、$X_2$ 和 $X_3$ 是芳香族氨基酸。在一些实施方案中，$X_1$ 是酪氨酸或苯丙氨酸。在一些实施方案中，$X_2$ 是酪氨酸或苯丙氨酸。在一些实施方案中，$X_2$ 是酪氨酸或苯丙氨酸。

[0056] 在一些实施方案中，该凯莫瑞 C15 肽包含来源于凯莫瑞 C15 肽和 PP2A 的调节性 B- 亚单位的氨基酸序列。在一些实施方案中，该凯莫瑞 C15 肽包含来源于人凯莫瑞 C15 肽和 PP2A 的人调节性 B- 亚单位的氨基酸序列。在一些实施方案中，该凯莫瑞 C15 肽包含氨基酸序列 PTFYFP。在一些实施方案中，该凯莫瑞 C15 肽包含氨基酸序列 AGEDPTFYFPGQFA。在一些实施方案中，该凯莫瑞 C15 肽基本上由氨基酸序列 AGEDPTFYFPGQFA 组成。

[0057] 在一些实施方案中，该凯莫瑞 C15 肽包含氨基酸序列 AGEDPHSFYFPGQFA，其中该序列 AGEDPHSFYFPGQFA 的一个或多个氨基酸被置换。在一些实施方案中，1、2、3、4、5、6、7、8、9、10、11、12、13、14 或 15 个氨基酸被置换。

[0058] 在一些实施方案中，该凯莫瑞 C15 肽包含氨基酸序列 AGEDPHSFYFPGQFA，其中序列 PHSFYFP 中的一个或多个氨基酸被置换。在一些实施方案中，1、2、3、4、5、6 或 7 个氨基酸被置换。

[0059] 在一些实施方案中，该凯莫瑞 C15 肽包含 L- 氨基酸。在一些实施方案中，该凯莫瑞 C15 肽包含氨基酸序列 AGEDPHSFYFPGQFA，其中该肽包含 L- 氨基酸。在一些实施方案中，该凯莫瑞 C15 肽具有基本上由氨基酸序列 AGEDPHSFYFPGQFA 组成的氨基酸序列，其中该肽包含 L- 氨基酸。

[0060] 在一些实施方案中，该凯莫瑞 C15 肽包含 D- 和 / 或 L- 氨基酸。在一些实施方案中，该凯莫瑞 C15 肽包含氨基酸序列 AGEDPHSFYFPGQFA，其中该肽包含 D- 和 / 或 L- 氨基酸。

在一些实施方案中，该凯莫瑞 C15 肽具有基本上由氨基酸序列 AGEDPHSFYFPGQFA 组成的氨基酸序列，其中该肽包含 D- 和 / 或 L- 氨基酸。

[0061] 在一些实施方案中，该凯莫瑞 C15 肽包含氨基酸序列 AGEDPHSFYFPGQFA，其中该序列 AGEDPHSFYFPGQFA 的一个或多个氨基酸处于 D- 构型。在一些实施方案中，该凯莫瑞 C15 肽包含氨基酸序列 AGEDPHSFYFPGQFA，其中该序列 AGEDPHSFYFPGQFA 的每个氨基酸处于 D- 构型。在这样的例子中，其中该序列的每个氨基酸处于 D- 构型的序列被称作反倒位 (retroinverso) 肽序列。在这样的例子中，该凯莫瑞 C15 肽包含氨基酸序列 AFQGPFYFSHPDEGA。

[0062] 在一些实施方案中，该凯莫瑞 C15 肽包含如下氨基酸序列，该氨基酸序列包含代表人凯莫瑞序列的凯莫瑞 C- 端片段（例如，AGEDPHSFYFPGQFA）的反倒位序列。在一些实施方案中，该凯莫瑞 C15 肽包含如下氨基酸序列，该氨基酸序列包含代表非人凯莫瑞序列如小鼠凯莫瑞 C15 肽的凯莫瑞 C- 端片段（例如 AGEDPHGYYFPGQFA）的反倒位序列。

[0063] 在一些实施方案中，该凯莫瑞 C15 肽包含衍生物或类似物，其中置换的氨基酸残基不是由遗传密码编码的氨基酸残基（即，非天然氨基酸）。在一些实施方案中，该凯莫瑞 C15 肽包含一个或多个非天然氨基酸。在一些实施方案中，该凯莫瑞 C15 肽包含氨基酸序列 AGEDPHSFYFPGQFA，其中一个或多个氨基酸是非天然氨基酸。在一些实施方案中，该凯莫瑞 C15 肽具有基本上由氨基酸序列 AGEDPHSFYFPGQFA 组成的氨基酸序列，其中一个或多个氨基酸是非天然氨基酸。

[0064] 可并入提供的凯莫瑞 C15 肽的非天然氨基酸的例子包括但不限于：高丝氨酸 (hSer)、高丝氨酸内酯 (hSerlac)、高半胱氨酸 (Hcy)、高精氨酸 (hArg)、高瓜氨酸 (Hci)、青霉胺 (Pen)、Na- 甲基精氨酸 (N-MeArg)、正亮氨酸 (Nle)、正缬氨酸 (Nval)、正异亮氨酸 (NIle)、N- 甲基异亮氨酸 (N-MeIle)、苯基甘氨酸 (PhG)、叔丁基甘氨酸 (Tle)、羟脯氨酸 (Hyp)、3,4- 脱氢脯氨酸 (Δ-Pro)、焦谷氨酰胺 (Pyr、Glp)、鸟氨酸 (Orn)、1- 氨基异丁酸 (1-Aib)、2- 氨基异丁酸 (2-Aib)、2- 氨基丁酸 (2-Abu)、4- 氨基丁酸 (4-Abu)、2,4- 二氨基丁酸 (A2bu)、α - 氨基辛二酸 (Asu)、合欢氨酸 (Abz)、β - 环己基丙氨酸 (Cha)、3-(1- 萘基）丙氨酸 (1-Nal)、3-(2- 萘基）丙氨酸 (2-Nal)、瓜氨酸 (Cit)、哌可林酸 (Pip)、4- 氯苯丙氨酸 (4-ClPhe)、4- 氟苯丙氨酸 (4-FPhe)、肌氨酸 (Sar) 和 1- 氨基丙烷羧酸 (1-NCPC)。另外的非天然氨基酸包括但不限于在美国专利申请公开号 2004/0121438 和美国专利号 US5656727 中公开的那些非天然氨基酸。天然和非天然氨基酸两者都可从例如 NovaBiochem(San Diego,CA,USA) 和 Bachem(Torrance,CA,USA) 的供应商商购获得。

[0065] 在一些实施方案中，该凯莫瑞 C15 肽包含氨基酸序列 AGEDPHSFYFPGQFA，其中 1、2、3、4、5、6、7、8、9、10、11、12、13、14 或 15 个氨基酸是非天然氨基酸。在一些实施方案中，该凯莫瑞 C15 肽具有基本上由氨基酸序列 AGEDPHSFYFPGQFA 组成的氨基酸序列，其中 1、2、3、4、5、6、7、8、9、10、11、12、13、14 或 15 个氨基酸是非天然氨基酸。

[0066] 在一些实施方案中，该凯莫瑞 C15 肽包含氨基酸序列 $AGEDPHX_1FYFPGQFA$，其中 $X_1$ 是非天然氨基酸。在一些实施方案中，该凯莫瑞 C15 肽具有基本上由氨基酸序列 $AGEDPHX_1FYFPGQFA$ 组成的氨基酸序列，其中 $X_1$ 是非天然氨基酸。在一些实施方案中，$X_1$ 是氨基酸丝氨酸的衍生物。在一些实施方案中，$X_1$ 是高丝氨酸。

[0067] 在一些实施方案中，该凯莫瑞 C15 肽包含氨基酸序列 $AGEDPHSX_1YFPGQFA$，其

中 $X_1$ 是非天然氨基酸。在一些实施方案中，该凯莫瑞 C15 肽具有基本上由氨基酸序列 AGEDPHS$X_1$YFPGQFA 组成的氨基酸序列，其中 $X_1$ 是非天然氨基酸。在一些实施方案中，$X_1$ 是氨基酸苯丙氨酸或酪氨酸的衍生物。在一些实施方案中，$X_1$ 是对氯苯丙氨酸。在一些实施方案中，$X_1$ 是萘基丙氨酸。

[0068] 在一些实施方案中，该凯莫瑞 C15 肽包含氨基酸序列 AGEDPHS$X_1$Y$X_2$PGQFA，其中 $X_1$ 和 $X_2$ 是非天然氨基酸。在一些实施方案中，$X_1$ 和 $X_2$ 是相同的非天然氨基酸。在一些实施方案中，$X_1$ 和 $X_2$ 是不同的非天然氨基酸。在一些实施方案中，该凯莫瑞 C15 肽具有基本上由氨基酸序列 AGEDPHS$X_1$Y$X_2$PGQFA 组成的氨基酸序列，其中 $X_1$ 和 $X_2$ 是非天然氨基酸。在一些实施方案中，$X_1$ 和 $X_2$ 是相同的非天然氨基酸。在一些实施方案中，$X_1$ 和 $X_2$ 是不同的非天然氨基酸。在一些实施方案中，$X_1$ 是芳香族非天然氨基酸。在一些实施方案中，$X_1$ 是氨基酸苯丙氨酸或酪氨酸的衍生物。在一些实施方案中，$X_1$ 是对氯苯丙氨酸。在一些实施方案中，$X_1$ 是萘基丙氨酸。在一些实施方案中，$X_2$ 是芳香族非天然氨基酸。在一些实施方案中，$X_2$ 是对氯苯丙氨酸。在一些实施方案中，$X_2$ 是萘基丙氨酸。

[0069] 在一些实施方案中，该凯莫瑞 C15 肽包含氨基酸序列 AGEDPHS$X_1X_2X_3$PGQFA，其中 $X_1$、$X_2$ 和 $X_3$ 是非天然氨基酸。在一些实施方案中，$X_1$ 和 $X_2$ 是相同的非天然氨基酸。在一些实施方案中，$X_1$ 和 $X_2$ 是不同的非天然氨基酸。在一些实施方案中，$X_1$ 和 $X_3$ 是相同的非天然氨基酸。在一些实施方案中，$X_1$ 和 $X_3$ 是不同的非天然氨基酸。在一些实施方案中，$X_2$ 和 $X_3$ 是相同的非天然氨基酸。在一些实施方案中，$X_2$ 和 $X_3$ 是不同的非天然氨基酸。在一些实施方案中，$X_1$、$X_2$ 和 $X_3$ 是相同的非天然氨基酸。在一些实施方案中，$X_1$、$X_2$ 和 $X_3$ 是不同的非天然氨基酸。在一些实施方案中，$X_1$ 是芳香族非天然氨基酸。在一些实施方案中，$X_1$ 是氨基酸苯丙氨酸或酪氨酸的衍生物。在一些实施方案中，$X_1$ 是对氯苯丙氨酸。在一些实施方案中，$X_1$ 是萘基丙氨酸。在一些实施方案中，$X_2$ 是芳香族非天然氨基酸。在一些实施方案中，$X_2$ 是氨基酸苯丙氨酸或酪氨酸的衍生物。在一些实施方案中，$X_2$ 是对氯苯丙氨酸。在一些实施方案中，$X_2$ 是萘基丙氨酸。在一些实施方案中，$X_3$ 是芳香族非天然氨基酸。在一些实施方案中，$X_3$ 是氨基酸苯丙氨酸或酪氨酸的衍生物。在一些实施方案中，$X_3$ 是对氯苯丙氨酸。在一些实施方案中，$X_3$ 是萘基丙氨酸。

[0070] 在一些实施方案中，非天然氨基酸选自可商购获得的氨基酸。在一些实施方案中，非天然氨基酸选自在自然界中不存在的 D- 构型、L- 构型或非手性氨基酸（例如，在 Accelrys Available Chemicals Directory(ACD) 中所列的，http://accelrys.com）。在一些实施方案中，选择非天然氨基酸，用于改善该肽的可溶性、稳定性、效力、作用机理和 / 或药学性质。

[0071] 在一些实施方案中，该凯莫瑞 C15 肽包含如下氨基酸序列，该氨基酸序列包含含有一种或多种非天然氨基酸的嵌合序列和反倒位序列，该非天然氨基酸选自可商购获得的非天然氨基酸（例如，在 Accelrys Available Chemicals Directory(ACD) 中所列的，http://accelrys.com）以及是为了改善该肽的可溶性、稳定性、效力、作用机理和 / 或药学性质而选择的。

[0072] 在一些实施方案中，与具有氨基酸序列 AGEDPHSFYFPGQFAF 的人凯莫瑞 C16 肽相比，该凯莫瑞 C15 肽表现出增加的对刺激的巨噬细胞中细胞因子产生的抑制。在一些实施方案中，与具有氨基酸序列 AGEDPHSFYFPGQFAF 的人凯莫瑞 C16 肽相比，该凯莫瑞 C15 肽表

现出增加的对刺激的巨噬细胞中 IL-23 产生的抑制。

[0073] 在一些实施方案中，与具有氨基酸序列 AGEDPHSFYFPGQFAFS 的人凯莫瑞 C17 肽相比，该凯莫瑞 C15 肽表现出增加的对刺激的巨噬细胞中细胞因子产生的抑制。在一些实施方案中，与具有氨基酸序列 AGEDPHSFYFPGQFAFS 的人凯莫瑞 C17 肽相比，该凯莫瑞 C15 肽表现出增加的对刺激的巨噬细胞中 IL-23 产生的抑制。

[0074] 在一些实施方案中，与具有氨基酸序列 AGEDPHGYFLPGQFA 的小鼠凯莫瑞 C15 肽相比，该凯莫瑞 C15 肽表现出增加的对刺激的巨噬细胞中细胞因子产生的抑制。在一些实施方案中，与具有氨基酸序列 AGEDPHGYFLPGQFA 的小鼠凯莫瑞 C15 肽相比，该凯莫瑞 C15 肽表现出增加的对刺激的巨噬细胞中 IL-23 产生的抑制。

[0075] 在一些实施方案中，该凯莫瑞 C15 肽不表现出对 Chem23 受体的激动剂活性。

[0076] 在一些实施方案中，该凯莫瑞 C15 肽是肽盐，例如药学上可接受的酸加成盐或碱加成盐。通过已知的方法制备肽或功能等同物的盐，这些方法一般包括肽与药学上可接受的酸混合以形成酸加成盐，或者肽与药学上可接受的碱混合以形成碱加成盐。酸或碱是否是药学上可接受的，可以由本领域技术人员在考虑了该化合物的特定的预期用途之后轻易地确定。取决于预期的用途，药学上可接受的酸包括有机和无机酸，例如甲酸、乙酸、丙酸、乳酸、羟基乙酸、草酸、丙酮酸、琥珀酸、马来酸、丙二酸、肉桂酸、硫酸、盐酸、氢溴酸、硝酸、高氯酸、磷酸和硫氰酸，它们与肽和功能等同物的游离氨基形成铵盐。与肽和功能等同物的游离羧基形成羧酸盐的药学上可接受的碱包括乙胺、甲胺、二甲胺、三乙胺、异丙胺、二异丙胺和其它的单、二或三烷基胺以及芳基胺。另外，还包括药学上可接受的溶剂化物、复合物或加合物，例如水合物或醚合物 (ethurates)；碱金属盐，例如锂、钠或钾盐；或其它的盐，例如但不限于钙镁铝、锌或铁盐。

[0077] 在一些实施方案中，该凯莫瑞 C15 肽是包含一种或多种凯莫瑞 C15 肽的多聚体。

肽的修饰

[0078] 在一些实施方案中，进一步修饰该凯莫瑞 C15 肽，以改善该凯莫瑞 C15 肽的一种或多种性质。示例性的性质包括但不限于该凯莫瑞 C15 肽的可溶性、稳定性、效力、作用机理、被检测到的能力和 / 或药学性质。通常，该修饰不会显著降低凯莫瑞 C15 肽的治疗性质，例如凯莫瑞 C15 肽的抗炎性，例如包括抑制 NF κ B 和一种或多种炎性细胞因子 ( 例如，IL-23、IL-12、TNF α 、IL-1 β 、IL-6 或 RANTES) 的分泌和 / 或产生。

[0079] 在一些实施方案中，该凯莫瑞 C15 肽通过自然过程进一步修饰，例如加工和其它已知的翻译后修饰，或者通过本领域公知的化学或酶技术进一步修饰。已知的修饰包括但不限于：乙酰化、酰化、ADP- 核糖基化、酰胺化、黄素的共价连接、血红素部分的共价连接、核苷酸或核苷酸衍生物的共价连接、脂质或脂质衍生物的共价连接、磷脂酰肌醇的共价连接、交联、环化、二硫键形成、脱甲基化、共价交联的形成、半胱氨酸的形成、焦谷氨酸的形成、甲酰化、γ - 羧基化、糖基化、GPI 锚形成、羟基化、碘化、甲基化、豆蔻酰化、氧化、蛋白水解加工、磷酸化、异戊烯化、外消旋化、硒化、硫酸化、转移 -RNA 介导的氨基酸向蛋白质的添加，例如精氨酰化和泛素化。

[0080] 在一些实施方案中，该修饰增加了凯莫瑞 C15 肽的溶解度。在一个例子中，酰胺化增加了凯莫瑞 C15 肽的溶解度。在一些实施方案中，该修饰使得凯莫瑞 C15 肽对蛋白酶降解更较不敏感。在一些实施方案中，该修饰增加了凯莫瑞 C15 肽穿透皮肤的能力。在一个

实施方案中，脂化增加了凯莫瑞 C15 肽穿透皮肤的能力。在一些实施方案中，该肽的 N- 端氨基的氢被替换。在一些实施方案中，该肽的整个 N- 端氨基被替换。在一些实施方案中，C- 端羧基的羟基 (OH) 被替换。在一些实施方案中，整个 C- 端羧基被替换。

[0081] 在一些实施方案中，被修饰的凯莫瑞 C15 肽的官能团包括羟基、氨基、胍基、羧基、酰胺、苯酚、咪唑 (imidizole) 环或巯基。这些基团的示例性的非限制性反应包括羟基被烷基卤的乙酰化；羧基的酯化、酰胺化或氢化（即，还原成醇）；氨基（例如，肽的伯氨基或赖氨酸残基的氨基）的脱酰胺化、酰化、烷基化、芳基化；酪氨酸酚基的卤化或硝化。

[0082] 肽的修饰是本领域技术人员公知的，并且已经在科学文献中非常详细地描述。几种特别常见的修饰，例如糖基化、脂质连接、硫酸化、谷氨酸残基的 γ- 羧基化、羟基化和 ADP- 核糖基化，描述在大多数基础教科书中，例如 Proteins-Structure&Molecular Properties（第二版，T.E.Creighton,W.H.Freeman&Co.,NY,1993）。关于该主题的许多详细的评述是可获得的，例如 Wold,Posttranslational Covalent Modification of Proteins,1-12(Johnson,ed.,Acad.Press,NY,1983)；Seifter 等人，182Meth.Enzymol.626-46(1990)；和 Rattan 等人，663Ann.N.Y.Acad.Sci.48-62(1992)。

[0083] 在一些实施方案中，该凯莫瑞 C15 肽与可溶或不可溶的载体分子偶联，以根据需要改变其溶解性质，并且提高该肽在目标组织中的局部浓度。可溶性载体分子的例子包括但不限于：聚乙二醇 (PEG) 和聚乙烯吡咯烷酮的聚合物；不溶性聚合物的例子包括硅酸盐、聚苯乙烯和纤维素。

[0084] 在一些实施方案中，该凯莫瑞 C15 肽是微囊包封的，以提高它们在治疗应用期间和之后的稳定性。在一些实施方案中，用聚酯或 PEG 微球包封并稳定化该凯莫瑞 C15 肽。各种制备用于肽包封的微球的方法是本领域已知的。选择的方法取决于将要包封的肽组合物的亲水或疏水性。用于此类方法的方案的例子可见于 Wang HT 等人 (1991,J.Control.Release17:23-25) 和美国专利号 4,324,683，这两者都整体并入本文。在一些实施方案中，进行体外肽释放研究，来确定该肽在并入微球之后的相对可用性。在示例性的方法中，将微球（大约 200mg）悬浮在 pH7.2 的磷酸盐缓冲盐水 (PBS)(2.5ml) 中，并且在环境培养箱震荡器 (G-24,New Brunswick Scientific Co.,Edison,N.J.) 中在 37℃和 100rpm 下搅拌。在特定的采样时间（对于前 4 天时每天，之后每隔一天），将缓冲溶液完全移除，并用新鲜 PBS 替换。采用 Bradford 法或其它一般用于蛋白质分析的适当定量分析来测量 PBS 的肽含量。

[0085] 在一些实施方案中，通过可检测部分如荧光染料或放射性标记的部分的连接来进一步修饰该凯莫瑞 C15 肽。示例性的可检测部分是本领域已知的，包括但不限于：罗丹明、荧光素、Cy3、Alexa Fluor405、Alexa Fluor488、Alexa Fluor546、Alexa Fluor555、Alexa Fluor633、Alexa Fluor647、别藻蓝素 (APC)、APC-Cy7、异硫氰酸荧光素 (FITC)、太平洋蓝、R- 藻红蛋白 (R-PE)、PE-Cy5、PE-Cy7、得克萨斯红、PE- 得克萨斯红、多甲藻黄素叶绿素蛋白 (PerCP)、PerCP-Cy5.5。

[0086] 在一些实施方案中，该肽与免疫原性载体肽偶联。在一些实施方案中，与免疫原性载体肽的偶联允许产生 C15 肽特异性抗体。在一些实施方案中，该免疫原性肽是匙孔蝾血蓝蛋白 (KLH)。

凯莫瑞 C15 肽的产生

[0087] 在某些实施方案中，本文中公开了凯莫瑞 C15 肽。本文中进一步公开了包含凯莫

瑞 C15 肽和任选的药学上可接受的赋形剂的局部制剂。本文中另外公开了在有需要的个体中治疗炎性皮肤病的方法，包括施用本文中公开的凯莫瑞 C15 肽或者包含本文中公开的凯莫瑞 C15 肽的局部制剂。本文中进一步公开了在有需要的个体中抑制炎性细胞因子或趋化因子的活性的方法，包括施用本文中公开的凯莫瑞 C15 肽或者包含本文中公开的凯莫瑞 C15 肽的局部制剂。在某些实施方案中，本文中还公开了在有需要的个体中抑制炎性细胞因子的核易位或 NF κ B 介导的基因转录的方法，包括施用本文中公开的凯莫瑞 C15 肽或者包含本文中公开的凯莫瑞 C15 肽的局部制剂。在一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。在一些实施方案中，该凯莫瑞 C15 肽是凯莫瑞 C15 肽的盐。在一些实施方案中，该凯莫瑞 C15 肽是羧化的。在一些实施方案中，该凯莫瑞 C15 肽是酰胺化的。在一些实施方案中，该凯莫瑞 C15 肽是环状的。在一些实施方案中，该凯莫瑞 C15 肽与天然存在的凯莫瑞 C15 肽至少 80％、85％、90％、91％、92％、93％、94％、95％、96％、97％、98％、99％、99.5％、99.6％、99.7％、99.8％或 99.9％同源。

[0088] 可以采用本领域技术人员已知的任何方法来产生本文中提供的凯莫瑞 C15 肽。在一些实施方案中，通过在细胞中或在动物中表达肽的重组方法来产生该肽。在一些实施方案中，该肽采用化学合成在体外产生。

[0089] 在一些例子中，通过凯莫瑞多肽的蛋白酶切割来产生该凯莫瑞 C15 肽。在一些实施方案中，通过体外蛋白酶反应来产生该凯莫瑞 C15 肽，其中凯莫瑞多肽与半胱氨酸蛋白酶一起孵育，该半胱氨酸蛋白酶切割该多肽的 C 末端，以产生 15 个氨基酸长度的凯莫瑞 C15 肽。在一些实施方案中，用于该反应中的凯莫瑞多肽是天然蛋白质。在一些实施方案中，用于该反应中的凯莫瑞多肽是重组蛋白质。在一些实施方案中，通过合适的纯化方法例如 HPLC 或透析将凯莫瑞 C15 肽从反应中纯化。在一些实施方案中，将纯化的凯莫瑞 C15 肽按本文中其它部分描述的进一步修饰。

[0090] 在一些实施方案中，采用本领域技术人员已知的化学合成方法产生该肽，例如在 Merrifield,R.B.,Solid Phase Peptide Synthesis I.,J.Am.Chem.Soc.85:2149-2154(1963)；Carpino,L.A. 等人，[(9-Fluorenylmethyl)Oxy]Carbonyl(Fmoc)Amino Acid Chlorides:Synthesis,Characterization,And Application To The Rapid Synthesis Of Short Peptides,J.Org.Chem.37:51:3732-3734；Merrifield,R.B. 等人，Instrument For Automated Synthesis Of Peptides,Anal.Chem.38:1905-1914(1966)；或 Kent,S.B.H. 等人，High Yield Chemical Synthesis Of Biologically Active Peptides On An Automated Peptide Synthesizer Of Novel Design,IN:Peptides1984(Ragnarsson U.,ed.)Almqvist and Wiksell Int.,Stockholm(Sweden),185-188 页中公开的方法，通过引用将所有这些文献整体并入本文。在一些实施方案中，采用能够向生长的肽链连续添加氨基酸的机器来产生该肽。在一些实施方案中，采用标准溶液相方法来制备该肽，该方法能够适合于大规模生产尝试。在示例性的方法中，采用固相合成，通过添加 FMOC- 保护的氨基酸，之后采用三氟乙酸 (TFA) 对肽进行最终裂解来产生该肽。在一些实施方案中，随后对该肽进行纯化。在一些实施方案中，通过 HPLC 纯化对该肽进行纯化。在一些实施方案中，通过在 C18 柱上使用水 / 乙腈梯度的 HPLC 纯化对该肽进行纯化。

皮肤疾病（皮肤病）

[0091] 在某些实施方案中，本文中公开了凯莫瑞 C15 肽。本文中进一步公开了包含凯莫瑞 C15 肽和任选的药学上可接受的赋形剂的局部制剂。本文中另外公开了在有需要的个体中治疗炎性皮肤病的方法，包括施用本文中公开的凯莫瑞 C15 肽或者包含本文中公开的凯莫瑞 C15 肽的局部制剂。本文中进一步公开了在有需要的个体中抑制炎性细胞因子或趋化因子的活性的方法，包括施用本文中公开的凯莫瑞 C15 肽或者包含本文中公开的凯莫瑞 C15 肽的局部制剂。在某些实施方案中，本文中还公开了在有需要的个体中抑制炎性细胞因子的核易位或 NF κ B 介导的基因转录的方法，包括施用本文中公开的凯莫瑞 C15 肽或者包含本文中公开的凯莫瑞 C15 肽的局部制剂。在一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。在一些实施方案中，该凯莫瑞 C15 肽是凯莫瑞 C15 肽的盐。在一些实施方案中，该凯莫瑞 C15 肽是羧化的。在一些实施方案中，该凯莫瑞 C15 肽是酰胺化的。在一些实施方案中，该凯莫瑞 C15 肽是环状的。在一些实施方案中，该凯莫瑞 C15 肽与天然存在的凯莫瑞 C15 肽至少 80％、85％、90％、91％、92％、93％、94％、95％、96％、97％、98％、99％、99.5％、99.6％、99.7％、99.8％或 99.9％同源。

[0092] 如本文中使用的，炎性皮肤病包括（部分或完全地）由免疫疾病（例如，自身免疫疾病（例如，湿疹、牛皮癣））、增生性疾病（例如，黑素瘤）、接触变应原和 / 或刺激物、皮脂脂质的过度产生（例如，痤疮）、成纤维细胞疾病（例如，创伤（例如外科手术）后的瘢痕形成）或其组合引起的皮肤病。皮肤病包括但不限于 :牛皮癣、特应性皮炎、刺激性接触性皮炎、湿疹性皮炎、慢性发疱性（大疱性）疾病、痤疮、免疫介导的疾病的脂溢性皮肤表现、脱发、斑秃、成人呼吸窘迫综合征、肺纤维化、硬皮病、瘢痕形成（例如，瘢痕疙瘩或肥厚性瘢痕）、荨麻疹、红斑痤疮、黑素瘤、慢性阻塞性肺病 (COPD)、肾移植引起的炎症、哮喘、化脓性汗腺炎 (hidradentis supporativa)、类风湿性关节炎、牛皮癣关节炎、舍格伦综合征、葡萄膜炎、移植物抗宿主病 (GVHD)、口腔扁平苔癣、关节痛或胰岛细胞移植炎症。在一些实施方案中，该皮肤病是牛皮癣。在一些实施方案中，该皮肤病是皮炎。在一些实施方案中，该皮肤病是特应性皮炎。在一些实施方案中，该皮肤病是接触性皮炎。

牛皮癣

[0093] 本文中公开了在有需要的个体中治疗牛皮癣的方法，包括施用本文中公开的凯莫瑞 C15 肽或者包含本文中公开的凯莫瑞 C15 肽的局部制剂。在一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。在一些实施方案中，该凯莫瑞 C15 肽是凯莫瑞 C15 肽的盐。在一些实施方案中，该凯莫瑞 C15 肽是羧化的。在一些实施方案中，该凯莫瑞 C15 肽是酰胺化的。在一些实施方案中，该凯莫瑞 C15 肽是环状的。在一些实施方案中，该凯莫瑞 C15 肽与天然存在的凯莫瑞 C15 肽至少 80％、85％、90％、91％、92％、93％、94％、95％、96％、97％、98％、99％、99.5％、99.6％、99.7％、99.8％或 99.9％同源。

[0094] 在某些情况下，牛皮癣的症状（部分或完全地）由血浆从血管和毛细血管到表皮、真皮和 / 或皮下组织中的渗出引起。T 辅助 (Th)17 细胞与牛皮癣和其它自身免疫炎性疾病的发病机理有关。白细胞介素 (IL)-23 刺激 Th17 细胞的存活和增殖，从而作为这些疾病的主要的细胞因子调节剂。在牛皮癣中，IL-23 由树突细胞和角质形成细胞过度产生。IL-23 刺激真皮中的 Th17 细胞，以生成 IL-17A 和 IL-22。特别是，IL-22 在牛皮癣中驱动角质形成细胞的过度增殖 (Fitch 等人，(2007)Curr Rheumatol Rep.9(6):461-7)。白细胞介素 -12/23p40 和 TNF-α 单克隆抗体和抑制剂已被证明在人类患者的牛皮癣的治疗中是有

效的(Krueger等人(2007)N Engl J Med356:580-592;Koutrube等人(2010)Therapeutics and Clinical Risk Management6:123-141;Mercuri 和 Naldi(2010)Biologics:Targets and Therapy4:119-129)。

[0095] 多项全基因组关联研究也已经表明,NFκB活化在牛皮癣中起着重要的作用(Stuart等人(2010)Nat Gen42,1000-1004;Nair等人(2009)Nat.Genet.41(2):199-204)。在某些情况下,削弱的NFκB的负调节是由于抑制性IKK的功能的丧失引起的(Perera等人(2012)Annu Rev Pathol Mech Dis)。许多研究已经表明,NFκB信号途径涉及与牛皮癣有关的免疫和炎性应答(Chen等人(2000)J.Invest.Dermatol.115,1124-1133;Danning 等 人 (2000)Arthritis Rheum.,43,1244-1256;3)Aronica 等 人 (1999)J.Immunol.,163,5116-5124;4)Hawiger 等 人 (2001)Immunol.Res.,23,99-109)。 此 外,已经表明,几种抗牛皮癣药物如阿维A和富马酸二甲酯(dimethylfumart)(DMF)通过抑制NFκB信号途径而发挥其作用(Zhang等人(2008)Arch Dermatol Res.300(10):575-81;Mrowietz等人(2005)Trend Mol Med11(1):43-48)。例如,阿维A和DMF抑制NFκB易位,并降低人角质形成细胞(keritinocytes)的核中NFκB的浓度。Rotterin,另一种强NFκB抑制剂,也具有抗牛皮癣性质(Maioli等人(2010)Curr.Drug Metab.11(5):425-30)。

[0096] 在一些实施方案中,施用凯莫瑞C15肽局部制剂,以通过抑制与牛皮癣发病机理有关的一种或多种细胞因子的产生或分泌来治疗牛皮癣。在一些实施方案中,施用凯莫瑞C15肽局部制剂,以通过抑制与牛皮癣发病机理有关的一种或多种细胞因子的NFκB-介导的基因转录来治疗牛皮癣。在一些实施方案中,施用凯莫瑞C15肽局部制剂来治疗与牛皮癣有关的炎症。

皮炎

[0097] 本文中公开了在有需要的个体中治疗皮炎的方法,包括施用本文中公开的凯莫瑞C15肽或者包含本文中公开的凯莫瑞C15肽的局部制剂。在一些实施方案中,该凯莫瑞C15肽是人凯莫瑞C15肽。在一些实施方案中,该凯莫瑞C15肽是凯莫瑞C15肽的盐。在一些实施方案中,该凯莫瑞C15肽是羧化的。在一些实施方案中,该凯莫瑞C15肽是酰胺化的。在一些实施方案中,该凯莫瑞C15肽是环状的。在一些实施方案中,该凯莫瑞C15肽与天然存在的凯莫瑞C15肽至少80%、85%、90%、91%、92%、93%、94%、95%、96%、97%、98%、99%、99.5%、99.6%、99.7%、99.8%或99.9%同源。

[0098] 如本文中使用的,皮炎意指皮肤的炎性病状。在某些实施方案中,皮炎是急性的,并且(部分或完全地)由接触触犯剂(offending agent)引起。在某些实施方案中,皮炎是慢性的,并且(部分或完全地)由超敏反应引起。在一些实施方案中,该皮炎是特应性皮炎。在一些实施方案中,该皮炎是接触性皮炎。在一个实施方案中,该皮炎是慢性的。在一个实施方案中,该皮炎是急性的。

[0099] 在某些情况下,皮炎(例如,慢性或急性皮炎)的症状(部分或完全地)由免疫系统的病症引起。已经证明NFκB途径在变应性疾病的疾病严重度中发挥重要作用(Tanaka等人(2007)J Invest Dermatol127(4):855-63)。用NFκB抑制剂对特应性皮炎的动物模型的局部治疗在病变部位减少了角质形成细胞的增生和炎症细胞的浸润。此外,NFκB抑制压制了免疫活性细胞的增殖、脾B细胞的IgE产生和肥大细胞在体外的IgE活化。此外,已经表明抑制剂如甘草查耳酮E对NFκB途径的下调能够降低IL-12p40表达,从而导致对

慢性变应性接触性皮炎的抑制。

[0100] 在一些实施方案中，施用凯莫瑞 C15 肽局部制剂，以通过抑制抗原呈递细胞如树突细胞或巨噬细胞来治疗皮炎。在一些实施方案中，施用凯莫瑞 C15 肽局部制剂，以通过抑制一种或多种炎性细胞因子的产生来治疗皮炎。在一些实施方案中，施用凯莫瑞 C15 肽局部制剂，以通过抑制与皮炎发病机理有关的一种或多种细胞因子的 NFκB- 介导的基因转录来治疗皮炎。在一些实施方案中，施用凯莫瑞 C15 肽局部制剂来治疗与皮炎有关的炎症。

大疱性疾病

[0101] 本文中公开了在有需要的个体中治疗大疱性疾病的方法，包括施用本文中公开的凯莫瑞 C15 肽或者包含本文中公开的凯莫瑞 C15 肽的局部制剂。在一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。在一些实施方案中，该凯莫瑞 C15 肽是凯莫瑞 C15 肽的盐。在一些实施方案中，该凯莫瑞 C15 肽是羧化的。在一些实施方案中，该凯莫瑞 C15 肽是酰胺化的。在一些实施方案中，该凯莫瑞 C15 肽是环状的。在一些实施方案中，该凯莫瑞 C15 肽与天然存在的凯莫瑞 C15 肽至少 80％、85％、90％、91％、92％、93％、94％、95％、96％、97％、98％、99％、99.5％、99.6％、99.7％、99.8％或 99.9％同源。

[0102] 在某些情况下，大疱性疾病的特征在于水疱的形成（即，流体在皮肤上层中的细胞之间的积累）。在某些情况下，大疱性疾病是免疫疾病，其中免疫系统攻击皮肤，并引起起疱。在某些情况下，大疱性疾病与炎症应答的诱导有关。在大疱性类天疱疮患者的水疱中已经发现了高水平的细胞因子，例如 IL-6 和 TNF-α (Rhodes 等人 (1999)Acta Dermato-Venereologica79(4):288)。

[0103] 大疱性疾病包括但不限于：大疱性类天疱疮、寻常天疱疮、增殖型天疱疮、叶状天疱疮、副肿瘤性天疱疮、粘膜类天疱疮、线性 IgA 大疱性疾病、疱疹样皮炎和获得性大疱性表皮松解。

[0104] 在一些实施方案中，施用凯莫瑞 C15 肽局部制剂来治疗与大疱性疾病有关的炎症。在一些实施方案中，施用凯莫瑞 C15 肽局部制剂，以通过抑制抗原呈递细胞如树突细胞或巨噬细胞来治疗大疱性疾病。在一些实施方案中，施用凯莫瑞 C15 肽局部制剂，以通过抑制一种或多种炎性细胞因子的产生来治疗大疱性疾病。在一些实施方案中，施用凯莫瑞 C15 肽局部制剂，以通过抑制与大疱性疾病发病机理有关的一种或多种细胞因子的 NFκB- 介导的基因转录来治疗皮炎。

湿疹

[0105] 本文中公开了在有需要的个体中治疗湿疹的方法，包括施用本文中公开的凯莫瑞 C15 肽或者包含本文中公开的凯莫瑞 C15 肽的局部制剂。在一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。在一些实施方案中，该凯莫瑞 C15 肽是凯莫瑞 C15 肽的盐。在一些实施方案中，该凯莫瑞 C15 肽是羧化的。在一些实施方案中，该凯莫瑞 C15 肽是酰胺化的。在一些实施方案中，该凯莫瑞 C15 肽是环状的。在一些实施方案中，该凯莫瑞 C15 肽与天然存在的凯莫瑞 C15 肽至少 80％、85％、90％、91％、92％、93％、94％、95％、96％、97％、98％、99％、99.5％、99.6％、99.7％、99.8％或 99.9％同源。

[0106] 如本文中使用的，湿疹是皮肤的慢性炎性状态。在一些实施方案中，施用凯莫瑞 C15 肽局部制剂来治疗与湿疹有关的炎症。在一些实施方案中，施用凯莫瑞 C15 肽局部制剂，以通过抑制抗原呈递细胞如树突细胞或巨噬细胞来治疗湿疹。在一些实施方案中，施用

凯莫瑞 C15 肽局部制剂，以通过抑制一种或多种炎性细胞因子的产生来治疗湿疹。在一些实施方案中，施用凯莫瑞 C15 肽局部制剂，以通过抑制与湿疹发病机理有关的一种或多种细胞因子的 NF κ B- 介导的基因转录来治疗湿疹。

荨麻疹

[0107] 本文中公开了在有需要的个体中治疗荨麻疹的方法，包括施用本文中公开的凯莫瑞 C15 肽或者包含本文中公开的凯莫瑞 C15 肽的局部制剂。在一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。在一些实施方案中，该凯莫瑞 C15 肽是凯莫瑞 C15 肽的盐。在一些实施方案中，该凯莫瑞 C15 肽是羧化的。在一些实施方案中，该凯莫瑞 C15 肽是酰胺化的。在一些实施方案中，该凯莫瑞 C15 肽是环状的。在一些实施方案中，该凯莫瑞 C15 肽与天然存在的凯莫瑞 C15 肽至少 80％、85％、90％、91％、92％、93％、94％、95％、96％、97％、98％、99％、99.5％、99.6％、99.7％、99.8％或 99.9％同源。

[0108] 在某些情况下，荨麻疹（部分或完全地）由超敏反应或另一种免疫疾病引起。皮肤划痕性荨麻疹是荨麻疹最常见的类型之一，其中当抓伤或擦破时，皮肤变得凸起并发炎。

[0109] 在一些实施方案中，施用凯莫瑞 C15 肽局部制剂来治疗与荨麻疹有关的炎症。在一些实施方案中，施用凯莫瑞 C15 肽局部制剂，以通过抑制抗原呈递细胞如树突细胞或巨噬细胞来治疗荨麻疹。在一些实施方案中，施用凯莫瑞 C15 肽局部制剂，以通过抑制一种或多种炎性细胞因子的产生来治疗荨麻疹。在一些实施方案中，施用凯莫瑞 C15 肽局部制剂，以通过抑制涉及与荨麻疹有关的炎症的发病机理的一种或多种细胞因子的 NF κ B- 介导的基因转录来治疗荨麻疹。

红斑痤疮

[0110] 本文中公开了在有需要的个体中治疗红斑痤疮的方法，包括施用本文中公开的凯莫瑞 C15 肽或者包含本文中公开的凯莫瑞 C15 肽的局部制剂。在一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。在一些实施方案中，该凯莫瑞 C15 肽是凯莫瑞 C15 肽的盐。在一些实施方案中，该凯莫瑞 C15 肽是羧化的。在一些实施方案中，该凯莫瑞 C15 肽是酰胺化的。在一些实施方案中，该凯莫瑞 C15 肽是环状的。在一些实施方案中，该凯莫瑞 C15 肽与天然存在的凯莫瑞 C15 肽至少 80％、85％、90％、91％、92％、93％、94％、95％、96％、97％、98％、99％、99.5％、99.6％、99.7％、99.8％或 99.9％同源。

[0111] 如本文中使用的，红斑痤疮是指任何的红斑痤疮 (erythematotelangiectatic rosacea)(ETR)、丘疹脓疱性红斑痤疮和 / 或红斑痤疮 (Phymatous rosacea)。在一些情况下，红斑痤疮的特征在于抗菌肽 (cathelicidin) 抗微生物肽的释放，导致诱导促炎细胞因子释放和恶化的先天免疫应答 (Yamasaki 等人，Nature Medicine13,975-980(2007))。

[0112] 在一些实施方案中，施用凯莫瑞 C15 肽局部制剂来治疗与红斑痤疮有关的炎症。在一些实施方案中，施用凯莫瑞 C15 肽局部制剂，以通过抑制抗原呈递细胞如树突细胞或巨噬细胞来治疗红斑痤疮。在一些实施方案中，施用凯莫瑞 C15 肽局部制剂，以通过抑制一种或多种炎性细胞因子的产生来治疗红斑痤疮。在一些实施方案中，施用凯莫瑞 C15 肽局部制剂，以通过抑制与红斑痤疮发病机理有关的一种或多种细胞因子的 NF κ B- 介导的基因转录来治疗红斑痤疮。

皮肤溃疡

[0113] 本文中公开了在有需要的个体中治疗皮肤溃疡的方法，包括施用本文中公开的凯

莫瑞 C15 肽或者包含本文中公开的凯莫瑞 C15 肽的局部制剂。在一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。在一些实施方案中，该凯莫瑞 C15 肽是凯莫瑞 C15 肽的盐。在一些实施方案中，该凯莫瑞 C15 肽是羧化的。在一些实施方案中，该凯莫瑞 C15 肽是酰胺化的。在一些实施方案中，该凯莫瑞 C15 肽是环状的。在一些实施方案中，该凯莫瑞 C15 肽与天然存在的凯莫瑞 C15 肽至少 80％、85％、90％、91％、92％、93％、94％、95％、96％、97％、98％、99％、99.5％、99.6％、99.7％、99.8％或 99.9％同源。

[0114] 如本文中使用的，溃疡是以表皮且经常是真皮的部分甚至是皮下脂肪的降解为特征的皮肤病。在某些情况下，溃疡是坏死组织的区域。在某些情况下，溃疡是由免疫系统机能障碍（例如，嗜中性粒细胞的异常功能）引起的，并且与炎症有关。

[0115] 在一些实施方案中，施用凯莫瑞 C15 肽局部制剂来治疗与皮肤溃疡有关的炎症。在一些实施方案中，施用凯莫瑞 C15 肽局部制剂，以通过抑制抗原呈递细胞如树突细胞或巨噬细胞来治疗皮肤溃疡。在一些实施方案中，施用凯莫瑞 C15 肽局部制剂，以通过抑制一种或多种炎性细胞因子的产生来治疗皮肤溃疡。在一些实施方案中，施用凯莫瑞 C15 肽局部制剂，以通过抑制与皮肤溃疡发病机理有关的一种或多种细胞因子的 NFκB- 介导的基因转录来治疗皮肤溃疡。

瘢痕形成

[0116] 本文中公开了在有需要的个体中治疗瘢痕形成的方法，包括施用本文中公开的凯莫瑞 C15 肽或者包含本文中公开的凯莫瑞 C15 肽的局部制剂。在一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。在一些实施方案中，该凯莫瑞 C15 肽是凯莫瑞 C15 肽的盐。在一些实施方案中，该凯莫瑞 C15 肽是羧化的。在一些实施方案中，该凯莫瑞 C15 肽是酰胺化的。在一些实施方案中，该凯莫瑞 C15 肽是环状的。在一些实施方案中，该凯莫瑞 C15 肽与天然存在的凯莫瑞 C15 肽至少 80％、85％、90％、91％、92％、93％、94％、95％、96％、97％、98％、99％、99.5％、99.6％、99.7％、99.8％或 99.9％同源。

[0117] 如本文中使用的，瘢痕形成是指瘢痕的形成。在一方面，瘢痕是肥厚性瘢痕，或瘢痕疙瘩，或由痤疮引起的瘢痕。在某些情况下，瘢痕是由胶原过度产生引起的纤维组织的区域。在某些情况下，创伤愈合包括成纤维细胞向损伤部位的迁移。在某些情况下，成纤维细胞沉积胶原。在某些情况下，成纤维细胞在创伤部位沉积过量的胶原，（部分或完全地）导致瘢痕。

局部制剂

[0118] 在某些实施方案中，本文中公开了凯莫瑞 C15 肽。本文中进一步公开了包含凯莫瑞 C15 肽和任选的药学上可接受的赋形剂的局部制剂。本文中另外公开了在有需要的个体中治疗炎性皮肤病的方法，包括施用本文中公开的凯莫瑞 C15 肽或者包含本文中公开的凯莫瑞 C15 肽的局部制剂。本文中进一步公开了在有需要的个体中抑制炎性细胞因子或趋化因子的活性的方法，包括施用本文中公开的凯莫瑞 C15 肽或者包含本文中公开的凯莫瑞 C15 肽的局部制剂。在某些实施方案中，本文中还公开了在有需要的个体中抑制炎性细胞因子的核易位或 NFκB 介导的基因转录的方法，包括施用本文中公开的凯莫瑞 C15 肽或者包含本文中公开的凯莫瑞 C15 肽的局部制剂。在一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。在一些实施方案中，该凯莫瑞 C15 肽是凯莫瑞 C15 肽的盐。在一些实施方案中，该凯莫瑞 C15 肽是羧化的。在一些实施方案中，该凯莫瑞 C15 肽是酰胺化的。在一些实施方

案中，该凯莫瑞 C15 肽是环状的。在一些实施方案中，该凯莫瑞 C15 肽与天然存在的凯莫瑞 C15 肽至少 80％、85％、90％、91％、92％、93％、94％、95％、96％、97％、98％、99％、99.5％、99.6％、99.7％、99.8％或 99.9％同源。

[0119] 在一些实施方案中，本文中公开的局部制剂促进凯莫瑞 C15 肽向皮肤的递送。在一些实施方案中，本文中公开的局部制剂促进凯莫瑞 C15 肽向皮肤的递送以用于局部作用（即，局限于皮肤的作用）。在某些情况下，凯莫瑞 C15 肽的局部给药减少或消除了与凯莫瑞 C15 肽全身给药有关的副作用。在一些实施方案中，本文中公开的凯莫瑞 C15 肽局部制剂不会导致全身性作用，或者大大降低任何全身性作用。

[0120] 局部制剂包括但不限于气雾剂、液体、软膏、乳膏、洗液、溶液、悬浮液、乳液、糊剂、凝胶、粉末、油膏、硬膏、涂剂、泡沫、药棒、缓释纳米颗粒、缓释微粒、生物粘合剂、贴剂、绷带和创伤敷料。在一些实施方案中，该制剂包含脂质体、胶束和 / 或微球。在一些实施方案中，药学上可接受的制剂包括任何适合用于人类皮肤或粘膜表面的载体。

软膏

[0121] 本文中公开了包含凯莫瑞 C15 肽和任选的药学上可接受的赋形剂的局部软膏。本文中另外公开了在有需要的个体中治疗炎性皮肤病的方法，包括施用包含本文中公开的凯莫瑞 C15 肽的局部软膏。本文中进一步公开了在有需要的个体中抑制炎性细胞因子或趋化因子的活性的方法，包括施用包含本文中公开的凯莫瑞 C15 肽的局部软膏。在某些实施方案中，本文中还公开了在有需要的个体中抑制炎性细胞因子的核易位或 NF κ B 介导的基因转录的方法，包括施用包含本文中公开的凯莫瑞 C15 肽的局部软膏。在一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。在一些实施方案中，该凯莫瑞 C15 肽是凯莫瑞 C15 肽的盐。在一些实施方案中，该凯莫瑞 C15 肽是羧化的。在一些实施方案中，该凯莫瑞 C15 肽是酰胺化的。在一些实施方案中，该凯莫瑞 C15 肽是环状的。在一些实施方案中，该凯莫瑞 C15 肽与天然存在的凯莫瑞 C15 肽至少 80％、85％、90％、91％、92％、93％、94％、95％、96％、97％、98％、99％、99.5％、99.6％、99.7％、99.8％或 99.9％同源。

[0122] 软膏，如药物制剂领域所公知的，是一般基于石蜡油或其它石油衍生物的半固体制剂。作为软膏，该组合物具有适合于均匀皮肤涂敷的稠度。在一些实施方案中，该软膏基本上是粘性的，以便无论出汗、过湿或环境条件如何均保持与皮肤接触。将要使用的特定软膏基质，如本领域技术人员所理解的，是将会提供最佳的药物递送并且也将提供其它所需特性例如软化性等的基质。同其它载体或赋形剂一样，软膏基质应该是惰性的、稳定的、无刺激的和非致敏的。如在 Remington:The Science and Practice of Pharmacy, 第 19 版 (Easton, Pa.:Mack Publishing Co., 1995) 的 1399-1404 页所述的，软膏基质例如被分为四类：油性基质、可乳化基质、乳剂基质和水溶性基质。油性的软膏基质包括，例如：植物油、从动物获得的脂肪和从石油获得的半固态烃类。可乳化的软膏基质，也称作吸收性软膏基质，含有很少的水或者不含水，并且包括例如硫酸羟基硬脂精、无水羊毛脂和亲水凡士林。乳剂软膏基质是油包水 (W/O) 乳剂或水包油 (O/W) 乳剂，并且包括例如十六醇、单硬脂酸甘油酯、羊毛脂和硬脂酸。一些水溶性软膏基质是由不同分子量的聚乙二醇制备的，进一步的信息再次参见 Remington:The Science and Practice of Pharmacy。在某些情况下，软膏是在体温下软化或熔化的半固体制剂。在某些情况下，软膏再水合皮肤，因此对以水分损失为特征的皮肤病有用。

[0123] 在一些实施方案中，该软膏包含约 0.1-100mg 凯莫瑞 C15 肽 / 克软膏。在一些实施方案中，该软膏包含约 1-10mg 凯莫瑞 C15 肽 / 克软膏。在一些实施方案中，该软膏包含约 1-100mg 凯莫瑞 C15 肽 / 克软膏。在一些实施方案中，该软膏包含约 1-10mg 凯莫瑞 C15 肽 / 克软膏。在一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。

[0124] 在某些实施方案中，该软膏包含凡士林。在一些实施方案中，该软膏包含约 50％的凡士林。在一些实施方案中，该软膏包含辛酸癸酸甘油三酯。在一些实施方案中，该软膏包含约 45％的辛酸癸酸甘油三酯。在一些实施方案中，该软膏包含蜂蜡。在一些实施方案中，该软膏包含约 5％的蜂蜡。在一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。

[0125] 在一些实施方案中，该软膏包含凯莫瑞 C15 肽和凡士林。在一些实施方案中，该软膏包含凯莫瑞 C15 肽和辛酸癸酸甘油三酯。在一些实施方案中，该软膏包含凯莫瑞 C15 肽和蜂蜡。在一些实施方案中，该软膏包含凯莫瑞 C15 肽、凡士林、辛酸癸酸甘油三酯和蜂蜡。在软膏的一个例子中，该软膏包含约 1-10mg 凯莫瑞 C15 肽 / 克软膏、约 50％的凡士林、约 45％的辛酸甘油三酯和约 5％的蜂蜡。在一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。

[0126] 在一些实施方案中，该软膏包含丁基羟基甲苯。在一些实施方案中，该软膏包含约 0.02％ w/w 的丁基羟基甲苯。在一些实施方案中，该软膏包含 PEG。在一些实施方案中，该软膏包含 PEG400。在一些实施方案中，该软膏包含约 15％ w/w 的 PEG400。在一些实施方案中，该软膏包含 Span80。在一些实施方案中，该软膏包含约 2％ w/w 的 Span80。在一些实施方案中，该软膏包含白蜡。在一些实施方案中，该软膏包含约 10％的白蜡。在一些实施方案中，该软膏包含白凡士林。在一些实施方案中，该软膏包含约 71.98％ w/w 的白凡士林。

[0127] 在一些实施方案中，该软膏包含凯莫瑞 C15 肽、白蜡和白凡士林。在一些实施方案中，该软膏包含凯莫瑞 C15 肽、丁基羟基甲苯、PEG400、Span80、白蜡和白凡士林。在软膏的一个例子中，该软膏包含约 1-10mg 凯莫瑞 C15 肽 / 克软膏、约 0.02％ w/w 的丁基羟基甲苯、约 15％ w/w 的 PEG400、约 2％ w/w 的 Span80、约 10％ w/w 的白蜡和约 71.98％ w/w 的白凡士林。在一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。

[0128] 在一些实施方案中，该软膏包含二甲基异山梨醇酯。在一些实施方案中，该软膏包含约 10％ w/w 的二甲基异山梨醇酯。在一些实施方案中，该软膏包含丁基羟基甲苯。在一些实施方案中，该软膏包含约 0.02％ w/w 的丁基羟基甲苯。在一些实施方案中，该软膏包含 Span80。在一些实施方案中，该软膏包含约 2％ w/w。在一些实施方案中，该软膏包含白蜡。在一些实施方案中，该软膏包含约 10％ w/w 的白蜡。在一些实施方案中，该软膏包含白凡士林。在一些实施方案中，该软膏包含约 76.98％ w/w 的白凡士林。

[0129] 在一些实施方案中，该软膏包含凯莫瑞 C15 肽、丁基化二甲基异山梨醇酯、丁基羟基甲苯、Span80、白蜡和白凡士林。在软膏的一个例子中，该软膏包含约 1-10mg 凯莫瑞 C15 肽 / 克软膏、约 10％ w/w 的二甲基异山梨醇酯、约 0.02％ w/w 的丁基羟基甲苯、约 2％ w/w 的 Span80、约 10％ w/w 的白蜡和约 76.98％ w/w 的白凡士林。在一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。

溶液

[0130] 本文中进一步公开了包含凯莫瑞 C15 肽和任选的药学上可接受的赋形剂的局部溶液。本文中另外公开了在有需要的个体中治疗炎性皮肤病的方法，包括施用包含本文中

公开的凯莫瑞C15肽的局部溶液。本文中进一步公开了在有需要的个体中抑制炎性细胞因子或趋化因子的活性的方法，包括施用包含本文中公开的凯莫瑞C15肽的局部溶液。在某些实施方案中，本文中还公开了在有需要的个体中抑制炎性细胞因子的核易位或NFκB介导的基因转录的方法，包括施用包含本文中公开的凯莫瑞C15肽的局部溶液。在一些实施方案中，该凯莫瑞C15肽是人凯莫瑞C15肽。在一些实施方案中，该凯莫瑞C15肽是凯莫瑞C15肽的盐。在一些实施方案中，该凯莫瑞C15肽是羧化的。在一些实施方案中，该凯莫瑞C15肽是酰胺化的。在一些实施方案中，该凯莫瑞C15肽是环状的。在一些实施方案中，该凯莫瑞C15肽与天然存在的凯莫瑞C15肽至少80％、85％、90％、91％、92％、93％、94％、95％、96％、97％、98％、99％、99.5％、99.6％、99.7％、99.8％或99.9％同源。

[0131] 溶液，如本领域所公知的，是包含溶解的材料的均质液体。在某些实施方案中，溶液是基于水或有机溶剂的。在某些实施方案中，溶液包含凯莫瑞C15肽以及提高局部施加的凯莫瑞C15肽向皮肤的渗透的另外的组分。在一些实施方案中，通过用涂药器涂抹、作为滴剂或喷雾剂，将包含凯莫瑞C15肽的溶液局部施加到皮肤。在一些实施方案中，从泵喷药瓶来施加该溶液。在一些实施方案中，从滴眼管来施加该溶液。

[0132] 在一些实施方案中，该溶液包含约0.1-100mg凯莫瑞C15肽/ml溶液。在一些实施方案中，该溶液包含约1-10mg凯莫瑞C15肽/ml溶液。在一些实施方案中，该溶液包含约1-100mg凯莫瑞C15肽/ml溶液。在一些实施方案中，该溶液包含约1-10mg凯莫瑞C15肽/ml溶液。在一些实施方案中，该凯莫瑞C15肽是人凯莫瑞C15肽。

[0133] 在一些实施方案中，该溶液包含肉豆蔻酸异丙酯。在一些实施方案中，该溶液包含醇。在一些实施方案中，该溶液包含十一烯酸。在一些实施方案中，该溶液包含十二烷基硫酸钠。

[0134] 在一些实施方案中，该溶液包含凯莫瑞C15肽、肉豆蔻酸异丙酯、醇、十一烯酸和十二烷基硫酸钠。在该溶液的一个例子中，该溶液含有约1-10mg凯莫瑞C15肽/ml溶液、肉豆蔻酸异丙酯、醇、十一烯酸和十二烷基硫酸钠。在一些实施方案中，该凯莫瑞C15肽是人凯莫瑞C15肽。

[0135] 在一些实施方案中，该溶液包含肉豆蔻酸异丙酯。在一些实施方案中，该溶液包含约45％的肉豆蔻酸异丙酯。在一些实施方案中，该溶液包含肉豆蔻酸异丙酯醇。在一些实施方案中，该溶液包含约45％的肉豆蔻酸异丙酯醇。在一些实施方案中，该溶液包含十一烯酸。在一些实施方案中，该溶液包含约5％的十一烯酸。在一些实施方案中，该溶液包含十二烷基硫酸钠。在一些实施方案中，该溶液包含约5％的十二烷基硫酸钠。

[0136] 在一些实施方案中，该溶液包含凯莫瑞C15肽、肉豆蔻酸异丙酯、醇、十一烯酸和十二烷基硫酸钠。在该溶液的另一个例子中，该溶液包含约1-10mg凯莫瑞C15肽/ml溶液、约45％的肉豆蔻酸异丙酯、约45％的醇、约5％的十一烯酸和约5％的十二烷基硫酸钠。在一些实施方案中，该凯莫瑞C15肽是人凯莫瑞C15肽。在一些实施方案中，从泵喷药瓶来施加该溶液。

[0137] 在一些实施方案中，该溶液包含凯莫瑞C15肽、DMSO和水。在该溶液的另一个例子中，该溶液包含约1-10mg凯莫瑞C15肽/ml溶液、约50％的DMSO和约50％的水。在一些实施方案中，该凯莫瑞C15肽是人凯莫瑞C15肽。在一些实施方案中，从泵喷药瓶来施加该溶液。

[0138] 在溶液的另一个例子中，该溶液包含约 1-10mg 凯莫瑞 C15 肽 /ml 在 DMSO 中的溶液。在一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。在一些实施方案中，从泵喷药瓶来施加该溶液。

[0139] 在一些实施方案中，该溶液包含二甲基异山梨醇酯。在一些实施方案中，该溶液包含约 15％ w/w 的二甲基异山梨醇酯。在一些实施方案中，该溶液包含 Transcutol。在一些实施方案中，该溶液包含约 25％ w/w 的 Transcutol。在一些实施方案中，该溶液包含己二醇。在一些实施方案中，该溶液包含约 12％ w/w 的己二醇。在一些实施方案中，该溶液包含丙二醇。在一些实施方案中，该溶液包含约 5％ w/w 的丙二醇。

[0140] 在一些实施方案中，该溶液包含二甲基异山梨醇酯、Transcutol、己二醇和丙二醇。在溶液的另一个例子中，该溶液包含约 1-10mg 凯莫瑞 C15 肽 /ml 溶液、约 15％ w/w 的二甲基异山梨醇酯、约 25％ w/w 的 Transcutol、约 12％ w/w 的己二醇、约 5％ w/w 的丙二醇、适量 25％三乙醇胺调至 pH4.5 和水加至 100％。在一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。在一些实施方案中，从泵喷药瓶来施加该溶液。

[0141] 在溶液的另一个例子中，该溶液包含约 1-10mg 凯莫瑞 C15 肽 /ml 溶液、约 15％ w/w 的二甲基异山梨醇酯、约 25％ w/w 的 Transcutol、约 12％ w/w 的己二醇、约 5％ w/w 的丙二醇、适量 25％三乙醇胺调至 pH6.0 和水加至 100％。在一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。在一些实施方案中，从泵喷药瓶来施加该溶液。

乳膏和洗液

[0142] 本文中进一步公开了包含凯莫瑞 C15 肽和任选的药学上可接受的赋形剂的局部乳膏或洗液。本文中另外公开了在有需要的个体中治疗炎性皮肤病的方法，包括施用包含本文中公开的凯莫瑞 C15 肽的局部乳膏或洗液。本文中进一步公开了在有需要的个体中抑制炎性细胞因子或趋化因子的活性的方法，包括施用包含本文中公开的凯莫瑞 C15 肽的局部乳膏或洗液。在某些实施方案中，本文中还公开了在有需要的个体中抑制炎性细胞因子的核易位或 NF κ B 介导的基因转录的方法，包括施用包含本文中公开的凯莫瑞 C15 肽的局部乳膏或洗液。在一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。在一些实施方案中，该凯莫瑞 C15 肽是凯莫瑞 C15 肽的盐。在一些实施方案中，该凯莫瑞 C15 肽是羧化的。在一些实施方案中，该凯莫瑞 C15 肽是酰胺化的。在一些实施方案中，该凯莫瑞 C15 肽是环状的。在一些实施方案中，该凯莫瑞 C15 肽与天然存在的凯莫瑞 C15 肽至少 80％、85％、90％、91％、92％、93％、94％、95％、96％、97％、98％、99％、99.5％、99.6％、99.7％、99.8％或 99.9％同源。

[0143] 乳膏，也如本领域所公知的，是粘性液体或半固体乳剂，是水包油或油包水的。乳膏底物是可水洗的，并且含有油相、乳化剂和水相。油相，也称作“内部”相，通常由凡士林和脂肪醇如十六醇或十八醇组成。水相在体积上通常超过油相，虽然不是必须的，并且通常包含湿润剂。在乳膏制剂中的乳化剂通常是非离子的、阴离子的、阳离子的或两性表面活性剂。在某些情况下，乳膏是半固体（例如，软固体或粘稠液体）制剂，其包括分散在水包油乳液或油包水乳液中的凯莫瑞 C15 肽。在某些实施方案中，本文中公开了凯莫瑞 C15 肽的局部制剂，其中该局部制剂是洗液的形式。在某些情况下，洗液是液体乳液（例如，水包油乳液或油包水乳液）。在一些实施方案中，洗液和 / 或乳膏的疏水性组分来源于动物（例如，羊毛脂、鳕鱼肝油和龙涎香）、植物（例如，红花油、蓖麻油、椰子油、棉籽油、鲱油、棕榈仁油、

棕榈油、花生油、大豆油、菜籽油、亚麻籽油、米糠油、松油、芝麻油或葵花籽油）或石油（例如，矿物油或石油胶）。

[0144] 在某些情况下，洗液和乳膏对皮肤病具有“干燥”效果（例如，一些或全部从病变处渗出的流体可以与软膏混溶），且因此对以流体渗出为特征的皮肤病是有用的。

[0145] 在一些实施方案中，该乳膏包含约 0.1-100mg 凯莫瑞 C15 肽 /ml 乳膏。在一些实施方案中，该乳膏包含约 1-10mg 凯莫瑞 C15 肽 /ml 乳膏。在一些实施方案中，该乳膏包含约 1-100mg 凯莫瑞 C15 肽 /ml 乳膏。在一些实施方案中，该乳膏包含约 1-10mg 凯莫瑞 C15 肽 /ml 乳膏。在一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。

[0146] 在一些实施方案中，该洗液包含约 0.1-100mg 凯莫瑞 C15 肽 /ml 洗液。在一些实施方案中，该洗液包含约 1-10mg 凯莫瑞 C15 肽 /ml 洗液。在一些实施方案中，该洗液包含约 1-100mg 凯莫瑞 C15 肽 /ml 洗液。在一些实施方案中，该洗液包含约 1-10mg 凯莫瑞 C15 肽 /ml 洗液。在一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。

[0147] 在一些实施方案中，该洗液包含二甲基异山梨醇酯。在一些实施方案中，该洗液包含约 13％ w/w 的二甲基异山梨醇酯。在一些实施方案中，该洗液包含 Transcutol。在一些实施方案中，该洗液包含约 20％ w/w 的 Transcutol。在一些实施方案中，该洗液包含己二醇。在一些实施方案中，该洗液包含约 10％ w/w 的己二醇。在一些实施方案中，该洗液包含丙二醇。在一些实施方案中，该洗液包含约 4％ w/w 的丙二醇。在一些实施方案中，该洗液包含对羟基苯甲酸甲酯。在一些实施方案中，该洗液包含约 0.015％ w/w 的对羟基苯甲酸甲酯。在一些实施方案中，该洗液包含对羟基苯甲酸丙酯。在一些实施方案中，该洗液包含约 0.05％ w/w 的对羟基苯甲酸丙酯。在一些实施方案中，该洗液包含 EDTA。在一些实施方案中，该洗液包含约 0.01％ w/w 的 EDTA。在一些实施方案中，该洗液包含 Carbopol Ultrez10。在一些实施方案中，该洗液包含约 0.5％ w/w 的 Carbopol Ultrez10。在一些实施方案中，该洗液包含 Penmulen TR-1。在一些实施方案中，该洗液包含约 0.2％ w/w 的 Penmulen TR-1。在一些实施方案中，该洗液包含肉豆蔻酸异丙酯。在一些实施方案中，该洗液包含约 3％ w/w 的肉豆蔻酸异丙酯。在一些实施方案中，该洗液包含油醇。在一些实施方案中，该洗液包含约 5％ w/w 的油醇。在一些实施方案中，该洗液包含约 0.2％ w/w 的丁基羟基甲苯。在一些实施方案中，该洗液包含白凡士林。在一些实施方案中，该洗液包含约 5％ w/w 的白凡士林。在一些实施方案中，用三乙醇胺将该洗液的 pH 值调节到约 4.0 至 6.0。在一些实施方案中，用三乙醇胺将该洗液的 pH 值调节到约 4.0 至 6.0。

[0148] 在一些实施方案中，该洗液包含凯莫瑞 C15 肽、二甲基异山梨醇酯、Transcutol、己二醇、丙二醇、对羟基苯甲酸甲酯、对羟基苯甲酸丙酯、EDTA、Carbopol Ultrez10、Penmulen TR-1 和丁基羟基甲苯。在一些实施方案中，该洗液包含凯莫瑞 C15 肽、二甲基异山梨醇酯、Transcutol、己二醇、丙二醇、对羟基苯甲酸甲酯、对羟基苯甲酸丙酯、EDTA、Carbopol Ultrez10、Penmulen TR-1、肉豆蔻酸异丙酯、油醇、丁基羟基甲苯和白凡士林。在一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。

[0149] 在该洗液的一个例子中，该洗液包含约 1-10mg 凯莫瑞 C15 肽 /ml 洗液、约 13％ w/w 的二甲基异山梨醇酯、约 20％ w/w 的 Transcutol、约 10％ w/w 的己二醇、约 4％ w/w 的丙二醇、约 0.015％ w/w 的对羟基苯甲酸甲酯、约 0.05％ w/w 的对羟基苯甲酸丙酯、约 0.01％ w/w 的 EDTA、约 0.5％ w/w 的 Carbopol Ultrez10、约 0.2％ w/w 的 Penmulen TR-1、约 3％

w/w 的肉豆蔻酸异丙酯、约 5% w/w 的油醇、约 0.2% w/w 的丁基羟基甲苯、约 5% w/w 的白凡士林、适量 25%三乙醇胺调至 pH6.0 和水加至 100%。在一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。

[0150] 在一些实施方案中，该洗液包含十六醇。在一些实施方案中，该洗液包含约 2% w/w 的十六醇。在一些实施方案中，该洗液包含轻质矿物油。在一些实施方案中，该洗液包含约 5.5% w/w 的轻质矿物油。在一些实施方案中，该洗液包含油酸。在一些实施方案中，该洗液包含约 5% w/w 的油酸。

[0151] 在一些实施方案中，该洗液包含凯莫瑞 C15 肽、二甲基异山梨醇酯、Transcutol、己二醇、丙二醇、对羟基苯甲酸甲酯、对羟基苯甲酸丙酯、EDTA、Carbopol Ultrez10、Penmulen TR-1、十六醇、轻质矿物油、油酸、丁基羟基甲苯。在一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。

[0152] 在该洗液的另一个例子中，该洗液包含约 1-10mg 凯莫瑞 C15 肽 /ml 洗液、约 13% w/w 的二甲基异山梨醇酯、约 20% w/w 的 Transcutol、约 10% w/w 的己二醇、约 4% w/w 的丙二醇、约 0.015% w/w 的对羟基苯甲酸甲酯、约 0.05% w/w 的对羟基苯甲酸丙酯、约 0.01% w/w 的 EDTA、约 0.3% w/w 的 Carbopol Ultrez10、约 0.2% w/w 的 Penmulen TR-1、约 2% w/w 的十六醇、约 5.5% w/w 的轻质矿物油、约 5% w/w 的油酸、0.2% w/w 的丁基羟基甲苯、适量 25%三乙醇胺调至 pH6.0 和水加至 100%。在一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。在一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。

凝胶

[0153] 本文中进一步公开了包含凯莫瑞 C15 肽和任选的药学上可接受的赋形剂的局部凝胶。本文中另外公开了在有需要的个体中治疗炎性皮肤病的方法，包括施用包含本文中公开的凯莫瑞 C15 肽的局部凝胶。本文中进一步公开了在有需要的个体中抑制炎性细胞因子或趋化因子的活性的方法，包括施用包含本文中公开的凯莫瑞 C15 肽的局部凝胶。在某些实施方案中，本文中还公开了在有需要的个体中抑制炎性细胞因子的核易位或 NFκB 介导的基因转录的方法，包括施用包含本文中公开的凯莫瑞 C15 肽的局部凝胶。在一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。在一些实施方案中，该凯莫瑞 C15 肽是凯莫瑞 C15 肽的盐。在一些实施方案中，该凯莫瑞 C15 肽是羧化的。在一些实施方案中，该凯莫瑞 C15 肽是酰胺化的。在一些实施方案中，该凯莫瑞 C15 肽是环状的。在一些实施方案中，该凯莫瑞 C15 肽与天然存在的凯莫瑞 C15 肽至少 80%、85%、90%、91%、92%、93%、94%、95%、96%、97%、98%、99%、99.5%、99.6%、99.7%、99.8%或 99.9%同源。

[0154] 凝胶是半固体的、悬浮型体系，并且是本领域公知的。本文中使用的凝胶形成剂可以是在药物领域中一般用于局部半固体剂型的任何胶凝剂。单相凝胶含有在整个载液中基本上均一分布的有机大分子，载液一般是水性的，但也可以含有醇和任选的油。为了制备均一的凝胶，可以加入分散剂如醇或甘油，或者可以通过滴定、机械混合或搅拌或其组合来分散胶凝剂。胶凝剂的量变化很大，基于组合物的总重量，通常从约 0.1 重量%至 2.0 重量%变化。该凝胶形成剂也可以通过共聚原理起效。在碱性 pH 下，在水的存在下，卡波姆经历交联，并形成凝胶样结构。聚合度取决于 pH 值。在阈值 pH 下，由聚合物级达到的粘性最大。在某些情况下，凝胶是半固体（或半刚性的）体系，由分散在液体中的有机大分子的分散体组成。在某些情况下，凝胶是水溶性的，并且使用温水或盐水除去。在某些情况下，凝胶再

水合皮肤，因此对以水分损失为特征的皮肤病有用。

[0155] 在一些实施方案中，该凝胶包含约 0.1-100mg 凯莫瑞 C15 肽 /ml 凝胶。在一些实施方案中，该凝胶包含约 1-10mg 凯莫瑞 C15 肽 /ml 凝胶。在一些实施方案中，该凝胶包含约 1-100mg 凯莫瑞 C15 肽 /ml 凝胶。在一些实施方案中，该凝胶包含约 1-10mg 凯莫瑞 C15 肽 /ml 凝胶。在一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。

[0156] 在一些实施方案中，该洗液包含二甲基异山梨醇酯。在一些实施方案中，该洗液包含约 15％ w/w 的二甲基异山梨醇酯。在一些实施方案中，该洗液包含 Transcutol。在一些实施方案中，该洗液包含约 25％ w/w 的 Transcutol。在一些实施方案中，该洗液包含己二醇。在一些实施方案中，该洗液包含约 12％ w/w 的己二醇。在一些实施方案中，该洗液包含丙二醇。在一些实施方案中，该洗液包含约 5％ w/w 的丙二醇。在一些实施方案中，该洗液包含对羟基苯甲酸甲酯。在一些实施方案中，该洗液包含约 0.015％ w/w 的对羟基苯甲酸甲酯。在一些实施方案中，该洗液包含对羟基苯甲酸丙酯。在一些实施方案中，该洗液包含约 0.05％ w/w 的对羟基苯甲酸丙酯。在一些实施方案中，该凝胶包含 EDTA。在一些实施方案中，该凝胶包含约 0.01％ w/w 的 EDTA。在一些实施方案中，该凝胶包含 Penmulen TR-1。在一些实施方案中，该凝胶包含约 0.5％ w/w 的 Penmulen TR-1。在一些实施方案中，该凝胶包含羟乙基纤维素。在一些实施方案中，该凝胶包含约 1％ w/w 的羟乙基纤维素。

[0157] 在一些实施方案中，该凝胶包含凯莫瑞 C15 肽、二甲基异山梨醇酯、Transcutol、己二醇、丙二醇、对羟基苯甲酸甲酯、对羟基苯甲酸丙酯和 EDTA。在一些实施方案中，该凝胶包含凯莫瑞 C15 肽、二甲基异山梨醇酯、Transcutol、己二醇、丙二醇、对羟基苯甲酸甲酯、对羟基苯甲酸丙酯、EDTA 和 Penmulen TR-1。在一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。

[0158] 在凝胶的一个例子中，该凝胶包含约 1-10mg 凯莫瑞 C15 肽 /ml 凝胶、约 15％ w/w 的二甲基异山梨醇酯、约 25％ w/w 的 Transcutol、约 12％ w/w 的己二醇、约 5％ w/w 的丙二醇、约 0.015％ w/w 的对羟基苯甲酸甲酯、约 0.05％ w/w 的对羟基苯甲酸丙酯、约 0.01％ w/w 的 EDTA、约 0.5％ w/w 的 Penmulen TR-1、适量 25％三乙醇胺调至 pH6.0 和水加至 100％。在一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。

[0159] 在一些实施方案中，该凝胶包含凯莫瑞 C15 肽、二甲基异山梨醇酯、Transcutol、己二醇、丙二醇、对羟基苯甲酸甲酯、对羟基苯甲酸丙酯、EDTA 和羟乙基纤维素。在一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。

[0160] 在凝胶的另一个例子中，该凝胶包含约 1-10mg 凯莫瑞 C15 肽 /ml 凝胶、约 15％ w/w 的二甲基异山梨醇酯、约 25％ w/w 的 Transcutol、约 12％ w/w 的己二醇、约 5％ w/w 的丙二醇、约 0.015％ w/w 的对羟基苯甲酸甲酯、约 0.05％ w/w 的对羟基苯甲酸丙酯、约 0.01％ w/w 的 EDTA、约 1％ w/w 的羟乙基纤维素、适量 25％三乙醇胺调至 pH4.5 和水加至 100％。在一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。

糊剂

[0161] 本文中公开了包含凯莫瑞 C15 肽和任选的药学上可接受的赋形剂的局部糊剂。本文中另外公开了在有需要的个体中治疗炎性皮肤病的方法，包括施用包含本文中公开的凯莫瑞 C15 肽的局部糊剂。本文中进一步公开了在有需要的个体中抑制炎性细胞因子或趋化因子的活性的方法，包括施用包含本文中公开的凯莫瑞 C15 肽的局部糊剂。在某些实施

方案中，本文中还公开了在有需要的个体中抑制炎性细胞因子的核易位或 NF κ B 介导的基因转录的方法，包括施用包含本文中公开的凯莫瑞 C15 肽的局部糊剂。在一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。在一些实施方案中，该凯莫瑞 C15 肽是凯莫瑞 C15 肽的盐。在一些实施方案中，该凯莫瑞 C15 肽是羧化的。在一些实施方案中，该凯莫瑞 C15 肽是酰胺化的。在一些实施方案中，该凯莫瑞 C15 肽是环状的。在一些实施方案中，该凯莫瑞 C15 肽与天然存在的凯莫瑞 C15 肽至少 80％、85％、90％、91％、92％、93％、94％、95％、96％、97％、98％、99％、99.5％、99.6％、99.7％、99.8％或 99.9％同源。

[0162] 糊剂是半固体剂型，其中活性剂悬浮在合适的基质中。取决于基质的属性，糊剂分为脂肪糊剂或由单相含水凝胶制得的糊剂。脂肪糊剂中的基质通常是凡士林或亲水性凡士林等。由单相含水凝胶制得的糊剂通常掺有羧甲基纤维素等作为基质。在某些情况下，糊剂含有至少 20％的固体。在某些情况下，糊剂是在体温下不流动的软膏。在某些情况下，糊剂再水合皮肤，因此对以水分损失为特征的皮肤病有用。在某些情况下，糊剂作为覆盖它们所施加的区域的防护涂层。

[0163] 在一些实施方案中，该溶液包含约 0.1-100mg 凯莫瑞 C15 肽 / 克糊剂。在一些实施方案中，该溶液包含约 1-10mg 凯莫瑞 C15 肽 / 克糊剂。在一些实施方案中，该溶液包含约 1-100mg 凯莫瑞 C15 肽 / 克糊剂。在一些实施方案中，该溶液包含约 1-10mg 凯莫瑞 C15 肽 / 克糊剂。在一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。

硬膏

[0164] 本文中公开了包含凯莫瑞 C15 肽和任选的药学上可接受的赋形剂的局部硬膏。本文中另外公开了在有需要的个体中治疗炎性皮肤病的方法，包括施用包含本文中公开的凯莫瑞 C15 肽的局部硬膏。本文中进一步公开了在有需要的个体中抑制炎性细胞因子或趋化因子的活性的方法，包括施用包含本文中公开的凯莫瑞 C15 肽的局部硬膏。在某些实施方案中，本文中还公开了在有需要的个体中抑制炎性细胞因子的核易位或 NF κ B 介导的基因转录的方法，包括施用包含本文中公开的凯莫瑞 C15 肽的局部硬膏。在一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。在一些实施方案中，该凯莫瑞 C15 肽是凯莫瑞 C15 肽的盐。在一些实施方案中，该凯莫瑞 C15 肽是羧化的。在一些实施方案中，该凯莫瑞 C15 肽是酰胺化的。在一些实施方案中，该凯莫瑞 C15 肽是环状的。在一些实施方案中，该凯莫瑞 C15 肽与天然存在的凯莫瑞 C15 肽至少 80％、85％、90％、91％、92％、93％、94％、95％、96％、97％、98％、99％、99.5％、99.6％、99.7％、99.8％或 99.9％同源。

[0165] 硬膏由直接涂抹在身体上或者在浸透到基底材料如布中之后涂抹在身体上的糊状混合物组成。在一些实施方案中，将包括本发明的药理学活性组合物在内的药物溶解或分散在硬膏中，以制备含药硬膏。

[0166] 在一些实施方案中，该硬膏包含约 0.1-100mg 凯莫瑞 C15 肽 / 克硬膏。在一些实施方案中，该硬膏包含约 1-10mg 凯莫瑞 C15 肽 / 克硬膏。在一些实施方案中，该硬膏包含约 1-100mg 凯莫瑞 C15 肽 / 克硬膏。在一些实施方案中，该硬膏包含约 1-10mg 凯莫瑞 C15 肽 / 克硬膏。在一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。

药棒

[0167] 本文中公开了包含凯莫瑞 C15 肽和任选的药学上可接受的赋形剂的局部药棒。本文中另外公开了在有需要的个体中治疗炎性皮肤病的方法，包括施用包含本文中公开的凯

莫瑞 C15 肽的局部药棒。本文中进一步公开了在有需要的个体中抑制炎性细胞因子或趋化因子的活性的方法，包括施用包含本文中公开的凯莫瑞 C15 肽的局部药棒。在某些实施方案中，本文中还公开了在有需要的个体中抑制炎性细胞因子的核易位或 NFκB 介导的基因转录的方法，包括施用包含本文中公开的凯莫瑞 C15 肽的局部药棒。在一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。在一些实施方案中，该凯莫瑞 C15 肽是凯莫瑞 C15 肽的盐。在一些实施方案中，该凯莫瑞 C15 肽是羧化的。在一些实施方案中，该凯莫瑞 C15 肽是酰胺化的。在一些实施方案中，该凯莫瑞 C15 肽是环状的。在一些实施方案中，该凯莫瑞 C15 肽与天然存在的凯莫瑞 C15 肽至少 80％、85％、90％、91％、92％、93％、94％、95％、96％、97％、98％、99％、99.5％、99.6％、99.7％、99.8％或 99.9％同源。

[0168] 在某些情况下，药棒是在室温下熔化的固体剂型。在一些实施方案中，药棒包含蜡、聚合物、树脂、熔合成硬质团块 (firm mass) 的干固体和 / 或熔合晶体。在一些实施方案中，凯莫瑞 C15 肽的局部制剂是止血笔的形式 ( 即，通过以下步骤制备的药棒 :(1) 加热晶体，直至它们失去其结晶水并变得熔融 ;和 (2) 将熔融的晶体倒入模具中，并使其硬化 )。在一些实施方案中，凯莫瑞 C15 肽的局部制剂是药棒的形式，其中该药棒包含蜡 ( 例如，将蜡熔化并注入合适的模具中，在其中它们固化成药棒的形式 )。

[0169] 在一些实施方案中，凯莫瑞 C15 肽的局部制剂是药棒的形式，其中该药棒包含熔化的基质 ( 即，在体温下软化的基质 )。熔化基质的例子包括但不限于 :蜡、油、聚合物和凝胶。在一些实施方案中，凯莫瑞 C15 肽的局部制剂是药棒的形式，其中该药棒包含润湿的基质 ( 即，通过加入水分而活化的基质 )。

[0170] 在一些实施方案中，该溶液包含约 0.1-100mg 凯莫瑞 C15 肽 / 克药棒。在一些实施方案中，该溶液包含约 1-10mg 凯莫瑞 C15 肽 / 克药棒。在一些实施方案中，该溶液包含约 1-100mg 凯莫瑞 C15 肽 / 克药棒。在一些实施方案中，该溶液包含约 1-10mg 凯莫瑞 C15 肽 / 克药棒。在一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。

生物粘合剂

[0171] 本文中公开了包含凯莫瑞 C15 肽和任选的药学上可接受的赋形剂的局部生物粘合剂。本文中另外公开了在有需要的个体中治疗炎性皮肤病的方法，包括施用包含本文中公开的凯莫瑞 C15 肽的局部生物粘合剂。本文中进一步公开了在有需要的个体中抑制炎性细胞因子或趋化因子的活性的方法，包括施用包含本文中公开的凯莫瑞 C15 肽的局部生物粘合剂。在某些实施方案中，本文中还公开了在有需要的个体中抑制炎性细胞因子的核易位或 NFκB 介导的基因转录的方法，包括施用包含本文中公开的凯莫瑞 C15 肽的局部生物粘合剂。在一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。在一些实施方案中，该凯莫瑞 C15 肽是凯莫瑞 C15 肽的盐。在一些实施方案中，该凯莫瑞 C15 肽是羧化的。在一些实施方案中，该凯莫瑞 C15 肽是酰胺化的。在一些实施方案中，该凯莫瑞 C15 肽是环状的。在一些实施方案中，该凯莫瑞 C15 肽与天然存在的凯莫瑞 C15 肽至少 80％、85％、90％、91％、92％、93％、94％、95％、96％、97％、98％、99％、99.5％、99.6％、99.7％、99.8％或 99.9％同源。

[0172] 生物粘合剂是粘附到身体组织表面的制剂。聚合物生物粘合剂制剂是本领域公知的 ;例如，参见 Heller 等人，"Biodegradable polymers as drug delivery systems", in Chasin, M. and Langer, R., eds. :Dekker, N. Y., pp. 121-161 (1990) 和美国专

利号 6,201,065。合适的非聚合物生物粘合剂也是本领域已知的，包括某些脂肪酸酯（美国专利号 6,228,383）。

[0173] 在某些实施方案中，本文中公开了凯莫瑞 C15 肽的局部制剂，其中该局部制剂通过贴剂来给药。在一些实施方案中，本文中公开的局部制剂被溶解和 / 或分散在聚合物或粘合剂中。在一些实施方案中，本文中公开的贴剂构建成用于连续、脉冲或按需递送凯莫瑞 C15 肽。

[0174] 在一些实施方案中，该生物粘合剂包含约 0.1-100mg 的凯莫瑞 C15 肽。在一些实施方案中，该生物粘合剂包含约 1-10mg 的凯莫瑞 C15 肽。在一些实施方案中，该生物粘合剂包含约 1-100mg 的凯莫瑞 C15 肽。在一些实施方案中，该生物粘合剂包含约 1-10mg 的凯莫瑞 C15 肽。在一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。

贴剂、创伤敷料和绷带

[0175] 本文中公开了包含凯莫瑞 C15 肽和任选的药学上可接受的赋形剂的贴剂、创伤敷料或绷带。本文中另外公开了在有需要的个体中治疗炎性皮肤病的方法，包括施用包含本文中公开的凯莫瑞 C15 肽的贴剂、创伤敷料或绷带。本文中进一步公开了在有需要的个体中抑制炎性细胞因子或趋化因子的活性的方法，包括施用包含本文中公开的凯莫瑞 C15 肽的贴剂、创伤敷料或绷带。在某些实施方案中，本文中还公开了在有需要的个体中抑制炎性细胞因子的核易位或 NF κ B 介导的基因转录的方法，包括施用包含本文中公开的凯莫瑞 C15 肽的贴剂、创伤敷料或绷带。在一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。在一些实施方案中，该凯莫瑞 C15 肽是凯莫瑞 C15 肽的盐。在一些实施方案中，该凯莫瑞 C15 肽是羧化的。在一些实施方案中，该凯莫瑞 C15 肽是酰胺化的。在一些实施方案中，该凯莫瑞 C15 肽是环状的。在一些实施方案中，该凯莫瑞 C15 肽与天然存在的凯莫瑞 C15 肽至少 80％、85％、90％、91％、92％、93％、94％、95％、96％、97％、98％、99％、99.5％、99.6％、99.7％、99.8％或 99.9％同源。

[0176] 创伤敷料、贴剂和绷带包括但不限于：纱布、透明膜敷料、水凝胶、聚氨酯泡沫敷料、水胶体和藻酸盐。在某些情况下，创伤敷料 (1) 维持伤口中的水分、(2) 是半渗透性的、(3) 是半闭合性的、(4) 允许自溶清创、(5) 防护外部污染物、(6) 吸收渗出的流体和 / 或 (7) 允许创伤可视化。

[0177] 在一些实施方案中，该贴剂、创伤敷料或绷带包含约 0.1-100mg 的凯莫瑞 C15 肽。在一些实施方案中，该贴剂、创伤敷料或绷带包含约 1-10mg 的凯莫瑞 C15 肽。在一些实施方案中，该贴剂、创伤敷料或绷带包含约 1-100mg 的凯莫瑞 C15 肽。在一些实施方案中，该贴剂、创伤敷料或绷带包含约 1-10mg 的凯莫瑞 C15 肽。在一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。

皮肤病学赋形剂

[0178] 本文中公开了包含凯莫瑞 C15 肽和任选的药学上可接受的赋形剂的局部制剂。本文中另外公开了在有需要的个体中治疗炎性皮肤病的方法，包括施用本文中公开的凯莫瑞 C15 肽或者包含本文中公开的凯莫瑞 C15 肽和药学上可接受的赋形剂载体的局部制剂。本文中进一步公开了在有需要的个体中抑制炎性细胞因子或趋化因子的活性的方法，包括施用本文中公开的凯莫瑞 C15 肽或者包含本文中公开的凯莫瑞 C15 肽和药学上可接受的赋形剂的局部制剂。在某些实施方案中，本文中还公开了在有需要的个体中抑制炎性细胞因子

的核易位或 NF κ B 介导的基因转录的方法，包括施用本文中公开的凯莫瑞 C15 肽或者包含本文中公开的凯莫瑞 C15 肽和药学上可接受的赋形剂的局部制剂。在一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。在一些实施方案中，该凯莫瑞 C15 肽是凯莫瑞 C15 肽的盐。在一些实施方案中，该凯莫瑞 C15 肽是羧化的。在一些实施方案中，该凯莫瑞 C15 肽是酰胺化的。在一些实施方案中，该凯莫瑞 C15 肽是环状的。在一些实施方案中，该凯莫瑞 C15 肽与天然存在的凯莫瑞 C15 肽至少 80％、85％、90％、91％、92％、93％、94％、95％、96％、97％、98％、99％、99.5％、99.6％、99.7％、99.8％或 99.9％同源。

[0179] 在一些实施方案中，本文中公开的局部制剂包含一种或多种惰性赋形剂，其包括但不限于水、缓冲的水溶液、表面活性剂、挥发性液体、淀粉、多元醇、成粒剂、微晶纤维素、稀释剂、润滑剂、酸、碱、盐、乳液（比如，油 / 水乳胶）、油（比如，矿物油和植物油）、湿润剂、螯合剂、抗氧化剂、无菌溶液、络合剂和崩解剂。

[0180] 在一些实施方案中，本文中描述的局部制剂包含一种或多种通常用在皮肤护理行业中的化妆品或药物试剂。这类试剂的例子例如描述在 CTFA Cosmetic Ingredient Handbook, 第七版 , 1997 和第八版 , 2000 中，通过引用将其整体并入本文。这类试剂的类别的例子包括但不限于 :研磨剂、吸收剂、美学组分（比如香料、颜料、染料 / 着色剂、精油、皮肤增感剂、收敛剂等等（例如丁香油、薄荷醇、樟脑、桉树油、丁子香酚、乳酸薄荷酯、金缕梅馏出物））、抗痤疮剂、抗结块剂、消泡剂、抗微生物剂（例如，丁基氨基甲酸碘代丙酯）、抗氧化剂、粘合剂、生物添加剂、缓冲剂、填充剂、螯合剂、化学添加剂、化妆品杀生物剂、变性剂、药物收敛剂、外部止痛剂、成膜剂或材料、遮光剂、pH 调节剂、推进剂、还原剂、多价螯合剂、皮肤漂白及增白剂（例如对苯二酚、曲酸、抗坏血酸、磷酸抗坏血酸酯镁、抗坏血酸基葡糖胺）、皮肤调节剂（例如保湿剂）、皮肤舒缓和 / 或愈合剂（例如，泛醇及其衍生物、真芦荟 (aloe vera)、泛酸及其衍生物、尿囊素、没药醇和甘草酸二钾）、护肤剂（例如防晒剂或紫外线吸收剂或散射剂）、皮肤处理剂、增稠剂以及维生素及其衍生物。在一些实施方案中，凯莫瑞 C15 肽的局部制剂包含一种或多种这样的试剂。

[0181] 在一些实施方案中，本文中描述的局部制剂包含胶凝（或增稠）剂。在一些实施方案中，本文中公开的局部制剂进一步包含约 0.1％至约 5％、更优选约 0.1％至约 3％、最优选约 0.25％至约 2％的胶凝剂。在某些实施方案中，本文中公开的局部制剂的粘性在约 100 至约 500000cP、约 100cP 至约 1,000cP、约 500cP 至约 1500cP、约 1000cP 至约 3000cP、约 2000cP 至约 8,000cP、约 4,000cP 至约 10,000cP、约 10,000cP 至约 50,000cP 的范围内。

[0182] 用于制备凝胶局部制剂的合适的胶凝剂包括但不限于 :纤维素、纤维素衍生物、纤维素醚（例如，羧甲基纤维素、乙基纤维素、羟乙基纤维素、羟甲基纤维素、羟丙基甲基纤维素、羟丙基纤维素、甲基纤维素）、瓜尔胶、黄原胶、刺槐豆胶、藻酸盐（例如，藻酸）、硅酸盐、淀粉、西黄蓍胶、羧乙烯聚合物、角叉菜胶、石蜡、凡士林、阿拉伯胶（阿拉伯树胶）、琼脂、硅酸镁铝、海藻酸钠、硬脂酸钠、墨角藻、膨润土、卡波姆、角叉菜胶、聚羧乙烯、黄原胶、纤维素、微晶纤维素 (MCC)、角豆胶、角叉菜、右旋糖、帚叉藻聚糖、明胶、印度胶、瓜尔胶、锂蒙脱石、乳糖、蔗糖、麦芽糖糊精、甘露醇、山梨糖醇、蜂蜜、玉米淀粉、小麦淀粉、米淀粉、马铃薯淀粉、明胶、梧桐胶、聚乙二醇（例如，PEG200-4500）、黄蓍树胶、乙基纤维素、乙基羟乙基纤维素、乙基甲基纤维素、甲基纤维素、羟乙基纤维素、羟乙基甲基纤维素、羟丙基纤维素、聚（甲基丙烯酸羟乙酯）、氧化聚明胶、果胶、聚明胶肽、聚维酮、碳酸丙烯酯、甲基乙烯基醚 /

马来酸酐共聚物 (PVM/MA)、聚 ( 甲基丙烯酸甲氧基乙酯 )、聚 ( 甲基丙烯酸甲氧基乙氧基乙酯 )、羟丙基纤维素、羟丙基甲基纤维素 (HPMC)、羧甲基纤维素钠 (CMC)、二氧化硅、聚乙烯吡咯烷酮 (PVP :聚维酮 ) 或它们的组合。

[0183] 在一些实施方案中，本文中描述的局部制剂包含软化剂。软化剂包括但不限于 ：蓖麻油酯、可可脂酯、红花油酯、棉籽油酯、玉米油酯、橄榄油酯、鳕鱼肝油酯、杏仁油酯、鳄梨油酯、棕榈油酯、芝麻油酯、角鲨烯酯、菊井油酯、大豆油酯、乙酰化单酸甘油酯、乙氧基单硬脂酸甘油酯、月桂酸己酯、月桂酸异己酯、棕榈酸异己酯、棕榈酸异丙酯、棕榈酸甲酯、油酸癸酯、油酸异癸酯、硬脂酸十六酯硬脂酸癸酯、异硬脂酸异丙酯、异硬脂酸甲酯、己二酸二异丙酯、己二酸二异己酯、己二酸二己基癸酯、癸二酸二异丙酯、乳酸月桂酯、乳酸十四酯和乳酸十六酯、肉豆蔻酸油酯、硬脂酸油酯和油酸油酯、壬酸、月桂酸、肉豆蔻酸、棕榈酸、硬脂酸、异硬脂酸、羟基硬脂酸、油酸、亚油酸、蓖麻油酸、花生酸、山嵛酸、芥酸、月桂醇、肉豆蔻醇、鲸蜡醇、十六醇、硬脂醇、异硬脂醇、羟基硬脂醇、油醇、蓖麻油醇、山嵛醇、瓢儿菜醇、2- 辛基十二醇、羊毛脂和羊毛脂衍生物、蜂蜡、鲸蜡、肉豆蔻酸十四酯、硬脂酰硬脂酸酯、巴西棕榈蜡、小烛树蜡、卵磷脂和胆固醇。

[0184] 在一些实施方案中，本文中描述的局部制剂包含抗氧化剂。抗氧化剂包括但不限于没食子酸的丙酯、辛酯和十二烷基酯、丁基化羟基苯甲醚 (BHA，通常作为邻位和间位异构体的混合物来购买 )、绿茶提取物、尿酸、半胱氨酸、丙酮酸盐、去甲二氢愈创木酸、抗坏血酸、抗坏血酸盐 ( 如抗坏血酸棕榈酸酯和抗坏血酸钠 )、抗坏血酸基葡糖胺、维生素 E( 即，生育酚，例如 α - 生育酚 )、维生素 E 的衍生物 ( 例如，醋酸生育酚 )、类视黄醇 ( 如视黄酸、视黄醇、反式视黄醇、顺式视黄醇、反式视黄醇和顺式视黄醇的混合物、3- 脱氢视黄醇 ) 和维生素 A 的衍生物 ( 如乙酸视黄酯、视黄醛和棕榈酸视黄酯，也称为 tetinyl palmitate)、柠檬酸钠、亚硫酸钠、番茄红素、花青素 (anthocyanids)、生物类黄酮 ( 例如橙皮素、柚皮素、芦丁和槲皮素 )、超氧化物歧化酶、谷胱甘肽过氧化物酶、丁基羟基甲苯 (BHT)、吲哚 -3- 甲醇、碧萝芷、褪黑素、萝卜硫素、孕烯醇酮、硫辛酸和 4- 羟基 -5- 甲基 -3[2H]- 呋喃酮。

[0185] 在一些实施方案中，本文中描述的局部制剂包含皮肤保护剂。示例性的皮肤保护剂包括但不限于防晒剂、抗痤疮添加剂、抗皱和抗皮肤萎缩剂。作为皮肤保护剂的合适的防晒剂包括 ：2- 乙基己基对甲氧基肉桂酸酯、2- 乙基己基 N,N- 二甲基 - 对 - 氨基苯甲酸酯、对氨基苯甲酸、2- 苯基苯并咪唑 -5- 磺酸、氰双苯丙烯酸辛酯 (octocrylene)、氧苯酮、水杨酸单甲酯 (homomethyl salicylate)、水杨酸辛酯、4,4'- 甲氧基 - 叔丁基二苯甲酰甲烷、4- 异丙基二苯甲酰甲烷、3- 苯亚甲基樟脑、3-(4- 甲基苯亚甲基 ) 樟脑、邻氨基苯甲酸酯 / 盐 (anthanilates)、超细二氧化钛、氧化锌、氧化铁、二氧化硅、2,4- 二羟基二苯甲酮的 4-N,N-(2- 乙基己基 ) 甲基氨基苯甲酸酯、4- 羟基二苯甲酰甲烷的 4-N,N-(2- 乙基己基 )- 甲基氨基苯甲酸酯、2- 羟基 -4-(2- 羟基乙氧基 ) 二苯甲酮的 4-N,N-(2- 乙基己基 ) 甲基氨基苯甲酸酯和 4-(2- 羟基乙氧基 ) 二苯甲酰甲烷的 4-N,N-(2- 乙基己基 )- 甲基氨基苯甲酸酯。合适的抗痤疮剂包括 ：水杨酸 ；5- 辛酰水杨酸 ；间苯二酚 ；类视黄醇，如视黄酸及其衍生物 ；除半胱氨酸之外的含硫的 D 和 L 氨基酸 ；硫辛酸 ；抗生素和抗微生物剂，比如过氧化苯甲酰、羟甲辛吡酮、四环素、2,4,4'- 三氯 -2'- 羟基二苯醚、3,4,4'- 三氯均二苯脲 (3,4,4'-trichlorobanilide)、壬二酸、苯氧乙醇、苯氧丙醇、苯氧异丙醇、乙酸乙酯、克林霉素和甲氯环素 (melclocycline) ；类黄酮 ；和胆盐，比如鲨胆甾醇硫酸脂、脱氧胆酸盐

和胆酸盐。抗皱和抗皮肤萎缩剂的例子是视黄酸及其衍生物、视黄醇、视黄酯、水杨酸及其衍生物、除半胱氨酸外的含硫的 D 和 L 氨基酸、α - 羟酸（例如，羟基乙酸和乳酸）、植酸、硫辛酸和溶血磷脂酸。

[0186] 在一些实施方案中，本文中描述的局部制剂包含刺激缓和添加剂，以最小化或消除由组合物的渗透增强基底或其它组分引起的皮肤刺激或皮肤损害的可能性。示例性的刺激缓和添加剂包括但不限于：α - 生育酚；单胺氧化酶抑制剂，特别是苯基醇，例如 2- 苯基 -1- 乙醇；甘油；水杨酸和水杨酸盐 / 酯；抗坏血酸和抗坏血酸盐 / 酯；离子载体，比如莫能星；两亲性胺；氯化铵；N- 乙酰半胱氨酸；顺式尿刊酸；辣椒素；和氯喹。

[0187] 在一些实施方案，本文中描述的局部制剂包含干燥感改性剂，它是当加入到乳液中时、当乳液干燥时赋予皮肤以“干燥感”的试剂。示例性的干燥感改性剂包括但不限于：滑石、高岭土、白垩、氧化锌、硅酮液、无机盐如硫酸钡、表面处理的二氧化硅、沉淀二氧化硅、煅制二氧化硅，例如，可从 Degussa Inc.，New York，N.Y.U.S.A 获得的 Aerosil。另一种干燥感改性剂是在美国专利号 6,488,916 中公开的类型的表氯醇交联的甘油基淀粉。

[0188] 在一些实施方案中，本文中描述的局部制剂包含抗微生物剂，以防止存储期间的变质，即，抑制诸如酵母和霉菌的微生物的生长。合适的抗微生物剂一般选自：对羟基苯甲酸的甲酯和丙酯（即，对羟基苯甲酸甲酯和对羟基苯甲酸丙酯）、苯甲酸钠、山梨酸、咪脲、黄铁矿 (purite)、过氧化物、过硼酸盐及其组合。

[0189] 在一些实施方案中，本文中描述的局部制剂包含美学剂。美学剂的例子包括香料、颜料、着色剂、精油、皮肤增感剂和收敛剂。合适的美学剂包括丁香油、薄荷醇、樟脑、桉树油、丁子香酚、乳酸甲酯、没药醇、金缕梅馏出物和绿茶提出物。

[0190] 在一些实施方案中，本文中描述的局部制剂包含香料。香料是可以赋予在美学上令人愉悦的香味的芳香族物质。典型的香料包括从植物来源（即，玫瑰花瓣、栀子花、茉莉花等等）提取的芳香材料，它们可以单独或任意组合地使用以制备精油。在一些实施方案中，为了复合香料制备乙醇提取物。在一些例子中，该香料是合成制备的香料。一种或多种香料可以任选地按约 0.001 至约 5 重量百分比或约 0.01 至约 0.5 重量百分比的量包含在防晒组合物中。在一些实施方案中，如果需要的话使用另外的防腐剂，包括例如公知的防腐剂组合物，例如苯甲醇、苯乙醇和苯甲酸、羟基苯 (diazolydinyl)、尿素、氯苯甘醚、氨基甲酸碘代丙炔酯和氨基甲酸丁酯等等。

[0191] 在一些实施方案中，本文中描述的局部制剂包含表面活性剂。可以用于形成本文中提供的药物组合物和剂型的表面活性剂包括但不限于：亲水性表面活性剂、亲脂性表面活性剂及其混合物。在一些实施方案，使用亲水性表面活性剂的混合物。在一些实施方案，使用亲脂性表面活性剂的混合物。在一些实施方案中，使用至少一种亲水性表面活性剂和至少一种亲脂性表面活性剂的混合物。

[0192] 在某些实施方案中，该表面活性剂是任何合适的无毒化合物，它对药物是非反应性的，并且大大降低药物、赋形剂和给药部位之间的表面张力。示例性的表面活性剂包括但不限于：可以按商品名 Mednique6322 和 Emersol6321（来自 Cognis Corp.，Cincinnati，Ohio）获得的油酸；氯化十六烷基吡啶（来自 Arrow Chemical，Inc. Westwood，N.J.）；可以按商品名 Epikuron200（来自 Lucas Meyer Decatur，Ill.）获得的大豆磷脂；可以按商品名吐温 20（来自 ICI Specialty Chemicals，Wilmington，Del.）获

得的聚氧化乙烯 (20) 脱水山梨醇单月桂酸酯；可以按商品名吐温 60（来自 ICI）获得的聚氧化乙烯 (20) 脱水山梨醇单硬脂酸酯；可以按商品名吐温 80（来自 ICI）获得的聚氧化乙烯 (20) 脱水山梨醇单油酸酯；可以按商品名 Brij76（来自 ICI）获得的聚氧化乙烯 (10) 硬脂酰醚；可以按商品名 Brij92（来自 ICI）获得的聚氧化乙烯 (2) 油烯基醚；可以按商品名 Tetronic150R1（来自 BASF）获得的聚氧化乙烯 - 聚氧化丙烯 - 乙二胺嵌段共聚物；可以按商品名 Pluronic L-92、Pluronic L-121 和 Pluronic F68（来自 BASF）获得的聚氧化丙烯 - 聚氧化乙烯嵌段共聚物；可以按商品名 Alkasurf CO-40（来自 Rhone-Poulenc Mississauga Ontario, Canada）获得的蓖麻油乙氧基化物；和它们的混合物。

[0193] 在一些实施方案中，合适的亲水性表面活性剂具有至少为 10 的 HLB 值，而合适的亲脂性表面活性剂具有约 10 或小于约 10 的 HLB 值。用来表征非离子两亲性化合物的相对亲水性和疏水性的一个经验参数是亲水 - 亲脂平衡值（“HLB”值）。具有较低 HLB 值的表面活性剂是更亲脂或疏水的，并且在油中具有更大的溶解度；而具有较高 HLB 值的表面活性剂是更亲水的，并且在水溶液中具有更大的溶解度。亲水性表面活性剂通常认为是 HLB 值大于约 10 的那些化合物，以及通常不适用该 HLB 量度的阴离子、阳离子或两性离子化合物。同样地，亲脂性（疏水性）表面活性剂是 HLB 值等于或小于约 10 的化合物。表面活性剂的 HLB 值是通常用来配制工业的、药物的或化妆品乳液的指导。

[0194] 在提供的局部制剂中使用的亲水性表面活性剂是离子的或非离子的。合适的离子型表面活性剂包括但不限于：烷基铵盐；梭链孢酸盐；氨基酸、寡肽和多肽的脂肪酸衍生物；氨基酸、寡肽和多肽的甘油酯衍生物；卵磷脂和氢化卵磷脂；溶血卵磷脂和氢化溶血卵磷脂；磷脂及其衍生物；溶血磷脂及其衍生物；肉碱脂肪酸酯盐；烷基硫酸酯的盐；脂肪酸盐；多库酯钠；酰基乳酸酯；单甘油酯和二甘油酯的单乙酰化和二乙酰化酒石酸酯；琥珀酰化的单甘油酯和二甘油酯；单甘油酯和二甘油酯的柠檬酸酯；和它们的混合物。

[0195] 示例性的离子型表面活性剂包括卵磷脂、溶血卵磷脂、磷脂、溶血磷脂及其衍生物；肉碱脂肪酸酯盐；烷基硫酸酯的盐；脂肪酸盐；多库酯钠；酰基乳酸酯；单甘油酯和二甘油酯的单乙酰化和二乙酰化酒石酸酯；琥珀酰化的单甘油酯和二甘油酯；单甘油酯和二甘油酯的柠檬酸酯；和它们的混合物。

[0196] 在一些实施方案中，离子型表面活性剂是以下物质的离子化形式：卵磷脂、溶血卵磷脂、磷脂酰胆碱、磷脂酰乙醇胺、磷脂酰甘油、磷脂酸、磷脂酰丝氨酸、溶血磷脂酰胆碱、溶血磷脂酰乙醇胺、溶血磷脂酰甘油、溶血磷脂酸、溶血磷脂酰丝氨酸、PEG- 磷脂酰乙醇胺、PVP- 磷脂酰乙醇胺、脂肪酸的乳酰酯、硬脂酰 -2- 乳酸酯、硬脂酰乳酸酯、琥珀酸单甘油酯、单 / 二甘油酯的单 / 二乙酰化酒石酸酯、单 / 二甘油酯的柠檬酸酯、胆酰肌氨酸 (cholylsarcosine)、己酸酯、辛酸酯、癸酸酯、月桂酸酯、肉豆蔻酸酯、棕榈酸酯、油酸酯、蓖麻油酸酯、亚油酸酯、亚麻酸酯、硬脂酸酯、月桂基硫酸酯、十四烷基 (teracecyl) 硫酸酯、多库酯、月桂酰肉碱、棕榈酰肉碱、肉豆蔻酰肉碱，和它们的盐和混合物。

[0197] 示例性的亲水性非离子型表面活性剂包括但不限于：烷基葡糖苷；烷基麦芽糖苷；烷基硫葡糖苷；月桂基聚乙二醇甘油酯；聚氧化烯烷基醚，如聚乙二醇烷基醚；聚氧化烯烷基酚，如聚乙二醇烷基酚；聚氧化烯烷基酚脂肪酸酯，如聚乙二醇脂肪酸单酯和聚乙二醇脂肪酸二酯；聚乙二醇甘油脂肪酸酯；聚甘油脂肪酸酯；聚氧化烯脱水山梨醇脂肪酸酯，如聚乙二醇脱水山梨醇脂肪酸酯；多元醇与由甘油酯、植物油、氢化植物油、脂肪酸和固醇

组成的组的至少一个成员的亲水性酯交换产物；聚氧化乙烯固醇、其衍生物和类似物；聚氧乙烯化维生素及其衍生物；聚氧化乙烯－聚氧化丙烯嵌段共聚物；和它们的混合物；聚乙二醇脱水山梨醇脂肪酸酯和多元醇与由甘油三酯、植物油和氢化植物油组成的组的至少一个成员的亲水性酯交换产物。在一些实施方案中，该多元醇是甘油、乙二醇、聚乙二醇、山梨糖醇、丙二醇、季戊四醇或糖类。

[0198] 其它示例性的亲水性非离子型表面活性剂包括而不限于：PEG-10 月桂酸酯、PEG-12 月桂酸酯、PEG-20 月桂酸酯、PEG-32 月桂酸酯、PEG-32 二月桂酸酯、PEG-12 油酸酯、PEG-15 油酸酯、PEG-20 油酸酯、PEG-20 二油酸酯、PEG-32 油酸酯、PEG-200 油酸酯、PEG-400 油酸酯、PEG-15 硬脂酸酯、PEG-32 二硬脂酸酯、PEG-40 硬脂酸酯、PEG-100 硬脂酸酯、PEG-20 二月桂酸酯、PEG-25 甘油三油酸酯、PEG-32 二油酸酯、PEG-20 甘油月桂酸酯、PEG-30 甘油月桂酸酯、PEG-20 甘油硬脂酸酯、PEG-20 甘油基油酸酯、PEG-30 甘油基油酸酯、PEG-30 甘油月桂酸酯、PEG-40 甘油月桂酸酯、PEG-40 棕榈仁油、PEG-50 氢化蓖麻油、PEG-40 蓖麻油、PEG-35 蓖麻油、PEG-60 蓖麻油、PEG-40 氢化蓖麻油、PEG-60 氢化蓖麻油、PEG-60 玉米油、PEG-6 癸酸／辛酸甘油酯、PEG-8 癸酸／辛酸甘油酯、聚甘油基－10 月桂酸酯、PEG-30 胆固醇、PEG-25 植物固醇、PEG-30 大豆甾醇、PEG-20 三油酸酯、PEG-40 脱水山梨醇油酸酯、PEG-80 脱水山梨醇月桂酸酯、聚山梨醇酯 20、聚山梨醇酯 80、POE-9 月桂基醚、POE-23 月桂基醚、POE-10 油基醚、POE-20 油基醚、POE-20 硬脂酰醚、生育酚 PEG-100 琥珀酸酯、PEG-24 胆固醇、聚甘油基 -10 油酸酯、吐温 40、吐温 60、蔗糖单硬脂酸酯、蔗糖单月桂酸酯、蔗糖单棕榈酸酯、PEG10-100 壬基酚系列、PEG15-100 辛基酚系列和泊洛沙姆。

[0199] 示例性的合适的亲脂性表面活性剂包括但不限于：脂肪醇；甘油脂肪酸酯；乙酰化甘油脂肪酸酯；低级醇脂肪酸酯；丙二醇脂肪酸酯；脱水山梨醇脂肪酸酯；聚乙二醇脱水山梨醇脂肪酸酯；固醇和固醇衍生物；聚氧乙烯化固醇和固醇衍生物；聚乙二醇烷基醚；糖酯；糖醚；单甘油酯和二甘油酯的乳酸衍生物；多元醇与由甘油酯、植物油、氢化植物油、脂肪酸和固醇组成的组的至少一个成员的疏水性酯交换产物；油溶性维生素／维生素衍生物；和它们的混合物。在这个组中，亲脂性表面活性剂包括甘油脂肪酸酯、丙二醇脂肪酸酯和它们的混合物，或者是多元醇与由植物油、氢化植物油和甘油三酯组成的组的至少一个成员的疏水性酯交换产物。

[0200] 在一些实施方案中，表面活性剂用于并不排斥使用它的本文中提供的任何制剂中。在一些实施方案中，基于制剂的总重量，表面活性剂的量为约 0.0001 重量％至 1 重量％，特别是约 0.001 重量％至 0.1 重量％。在一些实施方案，不使用表面活性剂或者使用有限类别的表面活性剂是合意的。在一些实施方案中，提供的局部制剂可以不含或基本上不含表面活性剂，即含有小于大约 0.0001 重量％的表面活性剂。如果使用如上所述的 cromone，尤其是这样。其它合适的表面活性剂／乳化剂是本领域技术人员公知的，并且在《CTFA 国际化妆品成分辞典和手册 (CTFA International Cosmetic Ingredient Dictionary and Handbook)》第 2 卷，第 7 版 (1997) 中列出。

[0201] 其它示例性的合适的水性载体包括但不限于林格氏溶液和等渗氯化钠。在一些实施方案中，水性悬浮液包括悬浮剂（例如纤维素衍生物、海藻酸钠、聚乙烯吡咯烷酮和西黄蓍胶）和湿润剂（例如卵磷脂）。用于水性悬浮液的合适的防腐剂包括对羟基苯甲酸乙酯和正丙酯。

[0202] 可用来形成本文中提供的药物组合物和剂型的示例性螯合剂包括但不限于：乙二胺四乙酸 (EDTA)、EDTA 二钠、依地酸二钠钙、EDTA 三钠、白蛋白、转铁蛋白、去铁敏 (desferoxamine)、得斯芬 (desferal)、甲磺酸去铁敏、EDTA 四钠和 EDTA 二钾、偏硅酸钠或其中任意的组合。在一些实施方案中，向本发明的制剂中加入高达约 0.1％ W/V 的螯合剂，例如 EDTA 或其盐。

[0203] 可用于形成本文中提供的药物组合物和剂型的示例性防腐剂包括但不限于：purite、过氧化物、过硼酸盐、咪唑烷基脲、重氮烷基脲、苯氧乙醇、铵鎓 (alkonium) 氯化物（包括苯扎氯铵）、对羟基苯甲酸甲酯、对羟基苯甲酸乙酯和对羟基苯甲酸丙酯。在其它实施方案中，用于本发明组合物的合适的防腐剂包括：苯扎氯铵、黄铁矿 (purite)、过氧化物、过硼酸盐、硫柳汞、氯丁醇、对羟基苯甲酸甲酯、对羟苯甲酸丙酯、苯乙醇、依地酸二钠、山梨酸、Onamer M 或本领域技术人员所知的其它试剂。在本发明的一些实施方案中，以 0.004％至 0.02％ W/V 的水平使用这样的防腐剂。

[0204] 可以用于形成提供的药物组合物和剂型的示例性润滑剂包括但不限于：硬脂酸钙、硬脂酸镁、矿物油、轻质矿物油、甘油、山梨糖醇、甘露醇、聚乙二醇、其它二醇、硬脂酸、十二烷基硫酸钠、滑石、氢化植物油（例如，花生油、棉籽油、向日葵油、芝麻油、橄榄油、玉米油和大豆油）、硬脂酸锌、油酸乙酯、月桂酸乙酯、琼脂或其混合物。

[0205] 可以用于形成提供的药物组合物和剂型的示例性增稠剂包括但不限于：肉豆蔻酸异丙酯、棕榈酸异丙酯、新戊酸异癸酯、角鲨烯、矿物油、$C_{12}$-$C_{15}$ 苯甲酸酯和氢化聚异丁烯。在一些实施方案中，不会破坏最终产品中的其它化合物的试剂（例如非离子增稠剂）是合意的。另外的增稠剂的选择是本领域技术人员熟知的。

[0206] 本文中公开的药物局部制剂以任何适当的方法来配制。可想到任何合适的技术、载体和 / 或赋形剂用于与本文中公开的凯莫瑞 C15 肽一起使用。关于本文所述的药物局部制剂的概述，参见：Remington:The Science and Practice of Pharmacy, 第 19 版 (Easton, Pa.:Mack Publishing Company, 1995)；Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania1975；Liberman, H.A. 和 Lachman, L. 编，Pharmaceutical Dosage Forms, Marcel Decker, New York, N.Y., 1980；和 Pharmaceutical Dosage Forms and Drug Delivery Systems, 第 7 版 (Lippincott Williams&Wilkins1999)，为了这些公开内容通过参考将它们并入本文。

局部渗透增强剂

[0207] 在一些实施方案中，本文中描述的局部制剂包含局部渗透增强剂。药物局部递送到皮肤提供了许多益处。对于患者，这是舒适的、便利的且非侵入性的。避免了在口服治疗中可能遇到的可变的吸收和代谢速率，并且也消除了其它固有的不便（例如，胃肠刺激、在有些情况下需要与食物一起给药或者在其它情况下不与食物一起给药）。这样的局部治疗避免了引起高的全身药物水平和可随之而来的可能的副作用，即，抑制其它生物过程中细胞因子的释放或 NF-κB 活性。

[0208] 然而，将药物局部递送到皮肤通常是具有挑战性的。皮肤是结构复杂的、相对较厚的膜。分子要从环境移动进入并穿过无损伤的皮肤，必须首先穿透角质层和在其表面上的任何材料。角质层是覆盖大部分躯体的大约 10-15 微米厚的层，它由致密的、高度角质化的细胞组成。在这些细胞中的高度角质化以及它们的致密堆积，被认为是在大多数情况下产

生对于药物渗透而言基本不可透过的屏障的最重要的因素。对于许多药物，在不利用一些提高皮肤透过性的手段的情况下，穿过皮肤的渗透速率极低。由于许多炎性皮肤病患者的角质层通常比正常皮肤更厚，因此特别难以实现局部药物向皮肤受影响区域内的渗入。

[0209] 为了增加药物穿透皮肤的程度和速率，已经尝试了各种途径，每个都包括使用化学渗透增强剂或物理渗透增强剂。皮肤渗透的物理增强包括，例如电泳技术，如离子电渗疗法。还已经研究了利用超声（或“声透疗法”）作为物理渗透增强剂。化学渗透增强剂更常使用。它们是如下的化合物：其随同药物一起（或者，在有些情况下，在给药之前）局部施用，以增加角质层的渗透性，从而提供药物穿过皮肤的增强的渗入。理想地，这样的化学渗透增强剂（或“透过增强剂”，如本文中提到的化合物）是无害的并且仅仅用来促进药物扩散穿过角质层的化合物。

[0210] 各种提高皮肤渗透性的化合物是本领域已知的，并且描述在相关的教科书和文献中。已经用来提高皮肤渗透性的化合物包括：亚砜，比如二甲亚砜 (DMSO) 和癸甲基亚砜 ($C_{10}$MSO)；醚，比如二甘醇单乙醚（可以作为 Transcutol™ 商购获得）和二甘醇单甲醚；表面活性剂，比如月桂酸钠、十二烷基硫酸钠、溴化十六烷基三甲基铵、苯扎氯铵、泊洛沙姆 (231、182、184)、吐温 (20、40、60、80) 和卵磷脂（美国专利号 4,783,450）；1- 取代的氮杂环庚烷 -2- 酮，特别是 1- 正 - 十二烷基氮杂环庚烷 -1- 酮（可以按商标 Azone™ 从 Nelson Research&Development Co., Irvine, Calif. 获得；参见美国专利号 3,989,816、4,316,893、4,405,616 和 4,557,934）；醇，比如乙醇、丙醇、辛醇、苯甲醇等等；脂肪酸，比如月桂酸、油酸和戊酸；脂肪酸酯，比如肉豆蔻酸异丙酯、棕榈酸异丙酯、丙酸甲酯和油酸乙酯；多元醇及其酯，比如丙二醇、乙二醇、甘油、丁二醇、聚乙二醇和聚乙二醇单月桂酸酯 (PEGML；参见，例如美国专利号 4,568,343)；酰胺及其它含氮化合物，比如脲、二甲基乙酰胺 (DMA)、二甲基甲酰胺 (DMF)、2- 吡咯烷酮、1- 甲基 -2- 吡咯烷酮、乙醇胺、二乙醇胺和三乙醇胺；萜烯；烷酮；和有机酸，特别是水杨酸和水杨酸盐、柠檬酸和琥珀酸。《经皮渗透增强剂 (Percutaneous Penetration Enhancers)》(Smith 等人编，CRC Press, 1995) 一书提供了关于大量化学和物理增强剂的领域和进一步的背景资料的优异综述。

[0211] 长期以来一直认为，强碱如 NaOH 不适合作为透过增强剂，因为它们会损伤皮肤。现在已经发现，通过将皮肤暴露于皮肤接触制剂或贴剂中的碱或碱溶液，可以提高各种药物的皮肤渗透性，而不引起皮肤损伤。可以使用多种碱或碱浓度来获得皮肤上的溶液的期望 pH。因此，选择该 pH，以使其足够低而不引起皮肤损伤，但又足够高以提高皮肤对于各种活性剂的渗透性。因此，重要的是，优化在任何贴剂或制剂中的碱的量，以便增加药物穿过身体表面的通量，同时使皮肤损伤的任何可能性最小化。在一些实施方案中，这意味着，在与本发明制剂或药物递送系统相接触的身体表面处的 pH 在大约 pH8.0 至约 pH13.0、约 pH8.0 至约 pH11.5、约 pH8.5 至约 pH11.5、或约 pH8.5 至约 pH10.5 的范围内。在一些实施方案中，该 pH 在约 pH9.5 至约 pH11.5，或约 pH10.0 至约 pH11.5 的范围内。

[0212] 在一个实施方案中，在皮肤表面处的 pH 是主要的设计考虑因素，即，设计组合物或体系，以便在皮肤表面提供期望的 pH。在某些情况下，无水制剂和透皮体系不具有可测量的 pH，并且设计该制剂或体系以便在皮肤表面提供目标 pH。来自身体表面的水分可以迁移到制剂或体系中，溶解碱，从而将碱释放到溶液中，这随后将在身体表面提供期望的目标 pH。在某些情况下，亲水性组合物是合乎需要的。此外，当使用水性制剂时，在某些情况下，

在将它施加到皮肤上之后，该制剂的 pH 随着时间而改变。例如，在某些情况下，在施加到身体表面之后，凝胶、溶液、软膏等经历水分的净损失，也即，损失的水量大于从身体表面收到的水量。在这种情况下，该制剂的 pH 在某些情况下不同于它在制备时的 pH。在一些实施方案中，通过设计水性制剂，可轻易地纠正这个问题，从而在身体表面提供目标 pH。

[0213] 在其它实施方案中，包含在递送系统中的制剂或药物组合物的 pH 会在大约 pH8.0 至约 pH13.0、约 pH8.0 至约 pH11.5、约 pH8.5 至约 pH11.5、或约 pH8.5 至约 pH10.5 的范围内。在其它实施方案中，该 pH 会在约 pH9.5 至约 pH11.5 或约 pH10.0 至约 pH11.5 的范围内。在本发明的一个实施方案中，该制剂的 pH 高于身体表面处的 pH。例如，如果使用水性制剂，来自身体表面的水分可以稀释该制剂，从而在身体表面提供不同的 pH，它一般低于制剂本身的 pH。

[0214] 在一个实施方案中，使身体表面暴露于碱或碱溶液充分的一段时间，以便在身体表面提供高的 pH，从而在皮肤或粘膜中生成药物穿过通道。预计药物通量与溶液强度和暴露时间成正比。然而，希望的是要平衡药物通量的最大化和皮肤损伤的最小化。这可以通过多种方式来完成。例如，在一些实施方案中，通过选择在 8.0 至 13.0 范围内的较低 pH，通过使皮肤暴露于该制剂或体系更短的一段时间，或者通过包含至少一种刺激缓和添加剂，将皮肤损伤最小化。或者，可以建议患者改变每次后续给药的施加位置。

[0215] 虽然下面阐明了某些量，但是应当理解，对于本文中描述的所有无机和有机碱，任意这种碱的最佳量将取决于该碱的强弱及其分子量以及其它因素，例如在施用的活性剂中可离子化位点的数目和在该制剂或贴剂中是否存在任何酸性物质。本领域技术人员可以轻易地确定任何具体碱的最佳量，使得增强的程度最佳化，同时身体表面损伤的可能性得到消除或至少基本上最小化。

[0216] 示例性的无机碱是无机氢氧化物、无机氧化物、弱酸的无机盐和它们的组合。一些无机碱是其水溶液具有高 pH 的无机碱，并且作为食物或药物添加剂是可接受的。这类无机碱的例子包括：氢氧化铵、氢氧化钠、氢氧化钾、氢氧化钙、氢氧化镁、氧化镁、氧化钙、$Ca(OH)_2$、醋酸钠、硼酸钠、偏硼酸钠、碳酸钠、碳酸氢钠、磷酸钠、碳酸钾、碳酸氢钾、柠檬酸钾、乙酸钾、磷酸钾和磷酸铵和它们的组合。

[0217] 无机氢氧化物包括例如氢氧化铵、碱金属氢氧化物和碱土金属氢氧化物和它们的混合物。一些无机氢氧化物包括：氢氧化铵；单价碱金属氢氧化物，比如氢氧化钠和氢氧化钾；二价碱土金属氢氧化物，比如氢氧化钙和氢氧化镁；和它们的组合。

[0218] 在本发明组合物和体系中包含的无机氢氧化物的量一般占局部施加的制剂或药物递送系统或贴剂的药物储库的约 0.3-7.0W/V%、约 0.5-4.0W/V%、约 0.5-3.0W/V% 或约 0.75-2.0W/V%。

[0219] 无机氧化物包括例如氧化镁、氧化钙等等。

[0220] 在一些实施方案中，在本发明组合物和体系中包含的无机氧化物的量基本上高于以上对于无机氢氧化物所述的量。在一些情况下，它高达 20wt%，在某些情况下高达 25wt% 或更高，但通常在约 2-20wt% 的范围内。在一些实施方案中，考虑任何碱可中和物质的存在，来调节这些量。

[0221] 弱酸的无机盐包括：磷酸铵（二碱价的）；弱酸的碱金属盐，比如醋酸钠、硼酸钠、偏硼酸钠、碳酸钠、碳酸氢钠、磷酸钠（三碱价的）、磷酸钠（二碱价的）、碳酸钾、碳酸氢钾、

柠檬酸钾、乙酸钾、磷酸钾（二碱价的）、磷酸钾（三碱价的）；弱酸的碱土金属盐，比如磷酸镁和磷酸钙；等等，和它们的组合。

[0222] 适合用于本发明的有机碱是具有氨基、胺基、肟、氰基、芳香族或非芳香族含氮杂环、脲基及其组合的化合物。更具体地说，合适的有机碱的例子是含氮碱类，其包括但不限于伯胺、仲胺、叔胺、脒、胍、羟胺、氰基胍、氰基脒、肟、含氰基（--CN）的基团、芳香族和非芳香族含氮杂环、脲和它们的混合物。在一些实施方案中，该有机碱是伯胺、仲胺、叔胺、芳香族和非芳香族含氮杂环和它们的混合物。

[0223] 对于本文中所有的渗透增强碱，任意特定试剂的最佳量将取决于该碱的强弱、该碱的分子量以及其它因素，例如在施用的药物中可离子化位点的数目和在该制剂或贴剂中的任何其它的酸性物质。通过确保在施加制剂后该制剂在皮肤表面有效提供约 pH7.5 至约 pH13.0、约 pH8.0 至约 pH11.5 或约 pH8.5 至约 pH10.5 的 pH，本领域技术人员可以轻易地确定任意特定试剂的最佳量。在一些实施方案中，该 pH 在约 pH9.5 至约 pH11.5 或约 pH10.0 至约 pH11.5 的范围内。这转而确保了治疗程度最大化，同时使身体表面损伤的可能性消除或至少基本最小化。

[0224] 在鼻内给药的情况下，在一些实施方案中，这样的溶液或悬浮液相对于鼻分泌物是等渗的，并且具有大致相同的 pH，例如从约 pH4.0 至约 pH7.4 或约 pH6.0 至约 pH7.0。缓冲液应该是生理上相容的，并且包括（只是举例来说）磷酸盐缓冲液。例如，代表性的鼻血管收缩剂被描述成被缓冲至约 6.2 的 pH(Remington's Pharmaceutical Sciences, 第 16 版，Arthur Osol 编，第 1445 页 (1980))。本领域技术人员可以轻易地确定对鼻和 / 或上呼吸道给药无害的水溶液的适当的盐水含量和 pH。适用于鼻内给药的制剂的一个例子是用磷酸二氢钠缓冲至约 6.0 至约 8.0 的 pH 的水溶液，其包含约 1% W/V 的 LFA-1 拮抗剂、高达约 0.1% W/V 的 EDTA 和任选的高达约 0.4% w/w 的对羟基苯甲酸甲酯和高达约 0.02% w/w 的对羟基苯甲酸丙酯。

[0225] 其它渗透增强剂将是局部药物递送领域的普通技术人员已知的，和 / 或在相关教科书和文献中描述。参见，例如《经皮渗透增强剂 (Percutaneous Penetration Enhancers)》Smith 等人编 (CRC Press, 1995)。

[0226] 在某些实施方案中，本文中公开了凯莫瑞 C15 肽的局部制剂，其中该局部制剂包含渗透增强剂。渗透增强剂包括但不限于：月桂基硫酸钠、月桂酸钠、聚氧化乙烯 -20- 十六基醚、月桂醇聚醚 -9、十二烷基硫酸钠、磺基琥珀酸二辛钠、聚氧化乙烯 -9- 月桂基醚 (PLE)、吐温 80、壬基苯氧基聚乙烯 (NP-POE)、聚山梨醇酯、甘胆酸钠、脱氧胆酸钠、牛磺胆酸钠、牛磺双氢褐霉素钠、甘油双氢褐霉素钠 (sodium glycodihydrofusidate)、油酸、辛酸、单和二甘油酯、月桂酸、酰基胆碱、辛酸、酰基肉碱、癸酸钠、EDTA、柠檬酸、水杨酸盐、DMSO、癸基甲基亚砜、乙醇、异丙醇、丙二醇、聚乙二醇、甘油、丙二醇和二甘醇单乙醚。在一些实施方案中，凯莫瑞 C15 的局部制剂含有渗透增强剂。在一些实施方案中，凯莫瑞 C15 的局部制剂不含渗透增强剂。在一些实施方案中，凯莫瑞 C15 的局部制剂含有 DMSO。在一些实施方案中，凯莫瑞 C15 的局部制剂不含 DMSO。

联合治疗

[0227] 在一些实施方案中，除凯莫瑞 C15 肽之外，该局部制剂还包含至少一种另外的治疗剂。在一些实施方案中，该另外的治疗剂是抗氧化剂、抗炎剂、抗微生物剂、抗血管生成

剂、抗凋亡剂、血管内皮生长因子抑制剂、抗病毒剂、钙依赖磷酸酶抑制剂、皮质类固醇或免疫调节剂。在一些实施方案中，包含凯莫瑞 C15 肽的局部制剂是皮质类固醇。在一些实施方案中，该皮质类固醇是局部皮质类固醇。与凯莫瑞 C15 肽一起使用的药剂在本文的联合治疗部分中进一步描述。

给药和剂量

[0228] 在某些实施方案中，本文中公开了凯莫瑞 C15 肽。本文中进一步公开了包含凯莫瑞 C15 肽和任选的药学上可接受的赋形剂的局部制剂。本文中另外公开了在有需要的个体中治疗炎性皮肤病的方法，包括施用本文中公开的凯莫瑞 C15 肽或者包含本文中公开的凯莫瑞 C15 肽的局部制剂。本文中进一步公开了在有需要的个体中抑制炎性细胞因子或趋化因子的活性的方法，包括施用本文中公开的凯莫瑞 C15 肽或者包含本文中公开的凯莫瑞 C15 肽的局部制剂。在某些实施方案中，本文中还公开了在有需要的个体中抑制炎性细胞因子的核易位或 NF κ B 介导的基因转录的方法，包括施用本文中公开的凯莫瑞 C15 肽或者包含本文中公开的凯莫瑞 C15 肽的局部制剂。在一些实施方案中，该凯莫瑞 C15 肽是人凯莫瑞 C15 肽。在一些实施方案中，该凯莫瑞 C15 肽是凯莫瑞 C15 肽的盐。在一些实施方案中，该凯莫瑞 C15 肽是羧化的。在一些实施方案中，该凯莫瑞 C15 肽是酰胺化的。在一些实施方案中，该凯莫瑞 C15 肽是环状的。在一些实施方案中，该凯莫瑞 C15 肽与天然存在的凯莫瑞 C15 肽至少 80％、85％、90％、91％、92％、93％、94％、95％、96％、97％、98％、99％、99.5％、99.6％、99.7％、99.8％或 99.9％同源。

[0229] 局部给药的优点包括：将治疗剂直接局部递送到受影响的组织，以及由于低全身生物利用性导致的最小的全身副作用。例如，在一些实施方案中，本文中提供的局部制剂直接施用到皮肤、眼、口、鼻、阴道粘膜或肛门粘膜。本文中提供的局部递送方法特别适合于该制剂的局部给药。合适的制剂和附加的载体在本文中讨论，此外，还描述在 Remington"The Science and Practice of Pharmacy"（第 20 版，Lippincott Williams&Wilkins, Baltimore Md.）中，其教导通过引用全部并入本文。

[0230] 根据本发明的治疗组合物的一个优点是：局部施加特别方便于治疗和预防多种皮肤病状。在一些实施方案中，将治疗组合物非侵入性地直接施加到目标部位。通过局部给药适宜地处理的其它病症包括鼻通道、眼和口的变应性病状。在一些实施方案中，提供的凯莫瑞 C15 肽具有快速的全身清除，使得被全身吸收的任何药物得到快速清除。

[0231] 在一些实施方案中，凯莫瑞 C15 肽的局部浓度是全身浓度的大约 2 倍、3 倍、4 倍、5 倍、10 倍、25 倍、50 倍或 100 倍。在另一个实施方案中，凯莫瑞 C15 肽的局部浓度是全身浓度的 100 倍。在另一个实施方案中，凯莫瑞 C15 肽的局部浓度是全身浓度的 1000 倍。在一个实施方案中，在同一时间点，局部浓度是全身浓度的大约 10000 倍或更高。在一些实施方案中，采用任何本领域已知的方法（例如，ELISA 和 / 或 LCMS/MS）测量治疗剂的浓度。

[0232] 在某些情况下，选择的药学活性组合物的递送方法包括：将本发明的制剂施加到身体表面受到炎性或免疫相关病状或其症状影响的区域。在提供的方法的实施方案中，将该制剂局部施加到皮肤、眼、口、鼻、阴道粘膜或肛门粘膜。在一些实施方案中，将乳膏、软膏、糊剂、硬膏或洗液涂抹在皮肤的受影响区域上，并轻轻擦入。在一些实施方案中，将聚合物的或其它生物粘合制剂涂抹或薄敷在皮肤的受影响区域上。在一些实施方案中，以同样的方式施加溶液，但更典型地用滴管、喷雾器、拭子等来施加，并且小心地施加到皮肤的受

影响区域。在一些实施方案中，将凡士林涂抹在皮肤受影响区域周围的皮肤上，以在治疗期间保护其免受可能的刺激。

[0233] 在一些实施方案中，通过使用递送装置来实现局部递送，该递送装置有利于药剂直接向皮肤组织内的递送，例如是微针注入装置，或者包含皮肤覆盖物 (covering) 的递送装置，借助于该覆盖物的粘着性质，该药剂借此在受影响的皮肤和覆盖物之间保持较长时间。

剂量

[0234] 在某些实施方案中，本文中公开了凯莫瑞 C15 肽的局部制剂，其中施用该局部制剂用于预防性和 / 或治疗性处理。在某些情况下，对于此用途有效的量将取决于疾病、病症或病状的严重程度和病程、以前的治疗、个体的健康状况和对药物的反应以及治疗医师的判断。

[0235] 按照药代动力学曲线来递送该组合物，这导致有效剂量的凯莫瑞 C15 肽的递送。药物的实际有效量可以根据以下因素而变化 ：使用的具体药物或其组合 ；配制的具体组合物 ；给药方式 ；和患者的年龄、体重和状况 ；以及所治疗的症状或病状的严重程度。用于特定患者的剂量可以由本领域普通技术人员利用常规的考虑因素来确定 ( 例如，借助于适当的常规药理学方案 )。为了给药而想到的药物的每日总剂量，以及因而相应组合物中药物的以重量计的浓度，可以广泛地变化，但是在正规开业医生的典型技能范围内。

[0236] 在一些实施方案中，递送凯莫瑞 C15 肽的局部制剂以达到局部治疗有效的浓度。例如，在一些实施方案中，利用在体外剂量滴定研究中足以将与炎症有关的细胞过程抑制至少约 10％、20％、30％、40％、50％、60％、70％、80％、90％的凯莫瑞 C15 肽的局部组织浓度，来达到局部治疗有效浓度。在一些实施方案中，利用在体外剂量滴定研究中足以将与炎症有关的细胞过程抑制至少约 50％的凯莫瑞 C15 肽的局部组织浓度，来达到局部治疗有效浓度。例如，在一些实施方案中，利用在体外在抗原呈递细胞如巨噬细胞或树突细胞中足以将与炎症有关的细胞过程抑制至少约 10％、20％、30％、40％、50％、60％、70％、80％、90％的凯莫瑞 C15 肽的局部组织浓度，来达到局部治疗有效浓度。在一些实施方案中，利用在体外在抗原呈递细胞如巨噬细胞或树突细胞中足以将与炎症有关的细胞过程抑制至少约 50％的凯莫瑞 C15 肽的局部组织浓度，来达到局部治疗有效浓度。在一些实施方案中，在加入凯莫瑞 C15 肽之前、期间或之后，例如通过将细胞与 IFNγ 和 / 或 LPS 接触来刺激该抗原呈递细胞。

[0237] 在一些实施方案中，利用在体外在抗原呈递细胞如巨噬细胞或树突细胞中足以将一种或多种炎性细胞因子的分泌抑制至少约 10％、20％、30％、40％、50％、60％、70％、80％、90％的凯莫瑞 C15 肽的局部组织浓度，来达到局部治疗有效浓度。在一些实施方案中，利用在体外在抗原呈递细胞如巨噬细胞或树突细胞中足以将一种或多种炎性细胞因子的分泌抑制至少约 50％的凯莫瑞 C15 肽的局部组织浓度，来达到局部治疗有效浓度。在一些实施方案中，例如通过将细胞与 IFNγ 和 / 或 LPS 接触来刺激该抗原呈递细胞。在一些实施方案中，在加入凯莫瑞 C15 肽之前、期间或之后，例如通过将细胞与 IFNγ 和 / 或 LPS 接触来刺激该抗原呈递细胞。

[0238] 在一些实施方案中，利用在体外在抗原呈递细胞如巨噬细胞或树突细胞中足以将一种或多种炎性细胞因子的转录抑制至少约 10％、20％、30％、40％、50％、60％、70％、

80％、90％的凯莫瑞 C15 肽的局部组织浓度，来达到局部治疗有效浓度。在一些实施方案中，利用在体外在抗原呈递细胞如巨噬细胞或树突细胞中足以将一种或多种炎性细胞因子的转录抑制至少约 50％的凯莫瑞 C15 肽的局部组织浓度，来达到局部治疗有效浓度。在一些实施方案中，在加入凯莫瑞 C15 肽之前、期间或之后，例如通过将细胞与 IFNγ 和 / 或 LPS 接触来刺激该抗原呈递细胞。在一些实施方案中，该炎性细胞因子是 IL-23、IL-12、TNFα、IL-1β、IL-6 或 RANTES。

[0239] 在一些实施方案中，用大于约 0.1pM-100nM 的凯莫瑞 C15 肽的局部组织浓度来达到局部治疗有效浓度。在一些实施方案中，用大于约 1pM-10nM 的凯莫瑞 C15 肽的局部组织浓度来达到局部治疗有效浓度。在一些实施方案中，用大于约 1pM-1nM 的凯莫瑞 C15 肽的局部组织浓度来达到局部治疗有效浓度。在一些实施方案中，用大于约 1-100pM 的凯莫瑞 C15 肽的局部组织浓度来达到局部治疗有效浓度。在一些实施方案中，用大于约 1-10pM 的凯莫瑞 C15 肽的局部组织浓度来达到局部治疗有效浓度。在一些实施方案中，凯莫瑞 C15 肽在施用于受试者后约 1-12 小时内达到大于约 1nM 的局部组织浓度。在一些实施方案中，凯莫瑞 C15 肽在施用于受试者后约 1-12 小时内达到大于约 10pM 的局部组织浓度。在一些实施方案中，凯莫瑞 C15 肽在施用于受试者后约 1-12 小时内达到大于约 10pM 的局部组织浓度。在一些实施方案中，凯莫瑞 C15 肽在施用于受试者后约 1-12 小时内达到大于约 1pM 的局部组织浓度。

[0240] 在一些实施方案中，达到凯莫瑞 C15 肽的局部治疗有效浓度，同时维持低的全身水平。例如，在一些实施方案中，达到约 1pM-10nM 的局部治疗有效浓度，同时维持小于 1-100pM 的全身药物浓度。例如，在一些实施方案中，达到约 1pM-1nM 的局部治疗有效浓度，同时维持小于 1-100pM 的全身药物浓度。例如，在一些实施方案中，达到约 1-100pM 的局部治疗有效浓度，同时维持小于 1-100pM 的全身药物浓度。

[0241] 例如，在一些实施方案中，达到约 1pM-10nM 的局部治疗有效浓度，同时维持小于 10-100pM 的全身药物浓度。例如，在一些实施方案中，达到约 1pM-1nM 的局部治疗有效浓度，同时维持小于 10-100pM 的全身药物浓度。例如，在一些实施方案中，达到约 1-100pM 的局部治疗有效浓度，同时维持小于 10-100pM 的全身药物浓度。

[0242] 在其它实施方案中，达到约 1pM-10nM 的局部治疗有效浓度，同时维持小于 1000pM 的全身药物浓度。在其它实施方案中，达到约 1pM-10nM 的局部治疗有效浓度，同时维持小于 10pM 的全身药物浓度。在其它实施方案中，达到约 1pM-1nM 的局部治疗有效浓度，同时维持小于 1000pM 的全身药物浓度。在其它实施方案中，达到约 1pM-1nM 的局部治疗有效浓度，同时维持小于 10pM 的全身药物浓度。在其它实施方案中，达到约 1-100pM 的局部治疗有效浓度，同时维持小于 1000pM 的全身药物浓度。在其它实施方案中，达到约 1-100pM 的局部治疗有效浓度，同时维持小于 10pM 的全身药物浓度。

[0243] 在一些实施方案中，采用本领域已知以及在上面公开的多种方法中的任何方法，例如 ELISA 和 / 或 LCMS/MS，由血浆浓度测量该肽的全身浓度。

[0244] 在一些实施方案中，凯莫瑞 C15 肽的有效量是每平方英寸约 0.01-100 毫克的剂量。在一些实施方案中，凯莫瑞 C15 肽的有效量是每平方英寸约 0.01-10 毫克的剂量。在一些实施方案中，凯莫瑞 C15 肽的有效量是每平方英寸约 0.1-100 毫克的剂量。在一些实施方案中，凯莫瑞 C15 肽的有效量是每平方英寸约 0.1-10 毫克的剂量。

[0245] 在一些实施方案中，给药方案取决于许多易于确定的因素，例如受影响区域的大小、皮肤病的严重程度和炎性皮肤病对治疗的响应性，但一般会是每天一次或多次剂量，疗程持续几天到几个月，或者直至实现治愈或者实现炎性皮肤病的大小和/或严重程度的显著降低。在一些实施方案中，另一种给药方案倾向于使用全身生物制剂和/或强效局部药剂来治愈或显著降低炎性皮肤病的大小和/或严重程度，然后向皮肤病部位施用凯莫瑞C15肽，以防止皮肤病的复发(remission)或复原。能快速从体循环中清除的凯莫瑞C15肽局部制剂的局部给药对影响大面积的炎性疾病的患者特别有益。在一些实施方案中，患者能够大面积治疗，而没有显著的免疫抑制和由全身暴露于药物引起的副作用的风险。普通技术人员可以轻易确定最佳的剂量、给药方法和重复率。通常，设想每天一至四次施加该制剂。采用皮肤贴剂，通常在整个药物递送期内，一般在8至72小时的范围内，将该装置保持在身体表面上适当的位置，并且在必要时进行更换。

[0246] 在一些实施方案中，凯莫瑞C15肽的局部制剂以足以发挥治疗效果的量存在，以将免疫相关的或炎性疾病或病症的症状平均减少至少约5%、10%、15%、20%、25%、30%、40%、50%、60%、70%、80%、90%、超过90%，或基本上消除免疫相关的或炎性疾病或病症的症状。对于许多炎性疾病，存在公认的治疗效果临床评价（例如，用于牛皮癣的PASI和/或PGA评分，和用于湿疹的EASI评分）。

[0247] 在一些实施方案中，以单剂量施用凯莫瑞C15肽的局部制剂。在一些实施方案中，施用单剂量的凯莫瑞C15肽以治疗急性病状。在一些实施方案中，当它与用于治疗急性病状的另外的治疗剂共施用时，使用施用单剂量的凯莫瑞C15肽。

[0248] 在一些实施方案中，以多剂量施用凯莫瑞C15肽的局部制剂（其自身或者与一种或多种另外的治疗剂联合）。在一些实施方案中，给药是每天大约一次、两次、三次、四次、五次、六次、七次、八次、九次、十次或多于十次。在一些实施方案中，给药是大约一年一次、一年两次、六个月一次、四个月一次、三个月一次、60天一次、一个月一次、每两周一次、每周一次或每隔一天一次。

[0249] 在一些实施方案中，凯莫瑞C15肽的局部制剂和其它治疗剂一起施用，大约每天一次至大约每天十次。在另一个实施方案中，另外的治疗剂在施用凯莫瑞C15肽局部制剂的同时、之前或之后施用。在另一个实施方案中，凯莫瑞C15肽局部制剂和其它治疗剂的施用持续短于约7天。在又一实施方案中，该共施用持续超过约6、10、14、28天、两个月、六个月或一年。在一些情况下，共施用给药维持必要长的时间，例如用于慢性炎症的给药。

[0250] 在一些实施方案中，每天一次施用凯莫瑞C15肽的局部制剂。在一些实施方案中，每天两次施用凯莫瑞C15肽的局部制剂。在一些实施方案中，每天三次施用凯莫瑞C15肽的局部制剂。在一些实施方案中，在任何时间施用凯莫瑞C15肽的局部制剂。在一些实施方案中，在早晨施用凯莫瑞C15肽的局部制剂。在一些实施方案中，在白天施用凯莫瑞C15肽的局部制剂。在一些实施方案中，在晚上施用凯莫瑞C15肽的局部制剂。在一些实施方案中，在夜里施用凯莫瑞C15肽的局部制剂。

[0251] 在本发明的另一方面，将凯莫瑞C15肽的局部组织浓度在治疗有效水平上维持延长的一段时间。在一些实施方案中，将凯莫瑞C15肽的局部组织浓度在治疗有效水平上维持一定长度的时间，或者在剂量之间维持。在一些例子中，将针对局部给药选择的凯莫瑞C15肽在局部治疗有效水平上维持延长的时间，使受试者获得治疗效果，而无需每天施用多

个剂量。

[0252] 在一些实施方案中，在施用于受试者之后至少约 2 小时、约 4 小时、约 6 小时、约 8 小时、约 10 小时、约 12 小时、约 14 小时、约 16 小时、约 18 小时、约 20 小时、约 22 小时或约 24 小时的时间里，该凯莫瑞 C15 肽具有大于约 1-1000pM 的局部组织浓度。在一些实施方案中，在施用于受试者之后至少约 2 小时、约 4 小时、约 6 小时、约 8 小时、约 10 小时、约 12 小时、约 14 小时、约 16 小时、约 18 小时、约 20 小时、约 22 小时或约 24 小时的时间里，该凯莫瑞 C15 肽具有大于约 1-100pM 的局部组织浓度。在一些实施方案中，在施用于受试者之后至少约 2 小时、约 4 小时、约 6 小时、约 8 小时、约 10 小时、约 12 小时、约 14 小时、约 16 小时、约 18 小时、约 20 小时、约 22 小时或约 24 小时的时间里，该凯莫瑞 C15 肽具有大于约 1-100pM 的局部组织浓度。在一些实施方案中，在施用于受试者之后至少约 2 小时、约 4 小时、约 6 小时、约 8 小时、约 10 小时、约 12 小时、约 14 小时、约 16 小时、约 18 小时、约 20 小时、约 22 小时或约 24 小时的时间里，该凯莫瑞 C15 肽具有大于约 10-100pM 的局部组织浓度。在一些实施方案中，在施用于受试者之后至少约 2 小时、约 4 小时、约 6 小时、约 8 小时、约 10 小时、约 12 小时、约 14 小时、约 16 小时、约 18 小时、约 20 小时、约 22 小时或约 24 小时的时间里，该凯莫瑞 C15 肽具有大于约 1-10pM 的局部组织浓度。

[0253] 在一些实施方案中，该局部制剂的给药持续长达治疗该疾病或病症所需的时间。在一些实施方案中，将本发明的组合物施用超过 1、2、3、4、5、6、7、14 或 28 天。在一些实施方案中，将本发明的组合物施用短于 28、14、7、6、5、4、3、2 或 1 天。在一些实施方案中，不间断地长期施用本发明的组合物，例如为了治疗慢性炎症。

[0254] 在皮肤病没有改善的一些实施方案中，长期施用本文中公开的局部制剂（即，持续延长的一段时间，包括贯穿个体生命的持续时间）。在皮肤病确实得到改善的一些实施方案中，连续给予本文中公开的局部制剂。在一些实施方案中，所施用的活性剂的剂量暂时减少或暂时停止某一长度的时间（即“休药期”）。在一些实施方案中，休药期持续 2 天至 1 年，包括之间的全部整数。在一些实施方案，在休药期期间的剂量减少为约 10％至约 100％，包括之间的全部整数。

[0255] 在皮肤病确实得到改善的一些实施方案中，以维持剂量来施用本文中公开的局部制剂。在皮肤病确实得到改善的一些实施方案中，以降低的频率或降低的剂量来施用本文中公开的局部制剂。

[0256] 在一些实施方案中，为了凯莫瑞 C15 肽的控制释放，配制本文中公开的局部制剂。在一些实施方案中，凯莫瑞 C15 肽释放超过 15 分钟、或 30 分钟、或 1 小时、或 4 小时、或 6 小时、或 12 小时、或 18 小时、或 1 天、或 2 天、或 3 天、或 4 天、或 5 天、或 6 天、或 7 天、或 10 天、或 12 天、或 14 天、或 18 天、或 21 天、或 25 天、或 30 天、或 45 天、或 2 个月或 3 个月或 4 个月或 5 个月或 6 个月或 9 个月或 1 年的时期。

联合治疗

[0257] 在某些实施方案中，本文中公开了凯莫瑞 C15 肽。本文中进一步公开了包含凯莫瑞 C15 肽和任选的药学上可接受的赋形剂的局部制剂。本文中另外公开了在有需要的个体中治疗炎性皮肤病的方法，包括施用本文中公开的凯莫瑞 C15 肽或者包含本文中公开的凯莫瑞 C15 肽的局部制剂。本文中进一步公开了在有需要的个体中抑制炎性细胞因子或趋化因子的活性的方法，包括施用本文中公开的凯莫瑞 C15 肽或者包含本文中公开的凯莫瑞

C15肽的局部制剂。在某些实施方案中，本文中还公开了在有需要的个体中抑制炎性细胞因子的核易位或NFκB介导的基因转录的方法，包括施用本文中公开的凯莫瑞C15肽或者包含本文中公开的凯莫瑞C15肽的局部制剂。在一些实施方案中，该凯莫瑞C15肽是人凯莫瑞C15肽。在一些实施方案中，该凯莫瑞C15肽是凯莫瑞C15肽的盐。在一些实施方案中，该凯莫瑞C15肽是羧化的。在一些实施方案中，该凯莫瑞C15肽是酰胺化的。在一些实施方案中，该凯莫瑞C15肽是环状的。在一些实施方案中，该凯莫瑞C15肽与天然存在的凯莫瑞C15肽至少80％、85％、90％、91％、92％、93％、94％、95％、96％、97％、98％、99％、99.5％、99.6％、99.7％、99.8％或99.9％同源。在一些实施方案中，上述方法或制剂进一步包含另外的治疗剂。

[0258] 在一些实施方案中，该另外的治疗剂治疗炎性皮肤病。在一些实施方案中，该另外的治疗剂调节凯莫瑞C15肽的副作用。在有些情况下，该疾病状态的病理学事件的特点是削弱的自身调节、细胞凋亡、局部缺血、新血管形成和炎性刺激的组合。在一些实施方案中，凯莫瑞C15肽和另外的治疗剂的组合产生累加或协同效应。

[0259] 在一些实施方案中，该另外的治疗剂是抗氧化剂、抗炎剂、抗微生物剂（包括抗菌剂）、抗组胺剂、肥大细胞稳定剂、抗病毒和抗真菌剂、抗血管生成剂、抗凋亡剂、润滑剂和/或促分泌剂。

[0260] 白细胞粘附和新血管形成的过程诱导了炎症。在一些实施方案中，抗炎剂与凯莫瑞C15肽联合地、在其之前、在其之后或伴随地给药。在一些实施方案中，该抗炎剂选自皮质类固醇相关的药物，包括但不限于：地塞米松、氟米龙、甲羟松、倍他米松、曲安西龙、曲安奈德、泼尼松、泼尼松龙、氢化可的松、利美索龙，以及它们的药学上可接受的盐，泼尼卡酯、地夫可特、卤米松、替可的松、泼尼立定、泼尼松龙戊酸酯、帕拉米松、甲泼尼龙、甲泼尼松、马泼尼酮、异氟泼尼龙、醋酸卤泼尼松、哈西缩松、福莫可他、氟氢缩松、氟泼尼龙、醋酸氟泼尼定（fluprednidine acetate）、醋酸甲氟龙、氟可龙、氟考丁酯、醋酸氟轻松、氟轻松、氟尼缩松、氟米松、氟氢可的松、氟氯奈德（fluclorinide）、甘草次酸、二氟泼尼酯、二氟可龙、双醋酸二氟拉松、去羟米松（脱氧米塞松）、地奈德、地西龙、可的伐唑、皮质酮、可的松、氯泼尼醇、氯可托龙、氯倍他松、氯倍他索、氯泼尼松、咖啡醇、布地奈德、倍氯米松、安西奈德、别孕烷丙酮化合物、阿氯米松、21-乙酰氧基孕烯醇酮、曲洛奈德、醋酸二氟拉松、脱酰可的发唑、RU-26988、布地奈德、脱酰可的发唑等等。在一些实施方案中，该抗炎剂选自5-氨基水杨酸酯（5-ASA）化合物，例如柳氮磺吡啶（Azulfidine）、奥沙拉秦（Dipentum）和美沙拉秦（例子包括：Pentasa、Asacol、Dipentum、Colazal、Rowasa灌肠剂和Canasa栓剂）。在一些实施方案，该抗炎剂选自环孢菌素相关的药物（例如，钙依赖磷酸酶拮抗剂），包括但限于：环孢菌素家族的成员和其它相关的钙依赖磷酸酶拮抗剂，包括西罗莫司、他克莫司（tacorlimus）和吡美莫司。在一些实施方案中，该抗炎剂选自NSAIDs，包括但不限于：醋氨酚、阿西美辛、醋氯芬酸、阿明洛芬、氨芬酸、苄达酸、苯噁洛芬、溴芬酸、布氯酸、布替布芬、卡洛芬、塞来昔布、桂美辛、氯吡酸、双氯芬酸、依托度酸、艾托考昔、联苯乙酸、芬克洛酸、芬布芬、非诺洛芬、芬替酸、氟诺洛芬、氟比洛芬、异丁芬酸、布洛芬、吲哚美辛、三苯唑酸、伊索昔康、伊索克酸、吲哚洛芬、酮洛芬、氯那唑酸、氯索洛芬、甲芬那酸、甲氯芬那酸、美洛昔康、甲嗪酸、莫苯唑酸、咪洛芬、萘普生、尼氟灭（niflumic）、奥沙普秦、pirozolac、吡洛芬、普拉洛芬、丙替嗪酸、罗非昔布、水杨酸及其衍生物（即，例如阿司匹林）、舒林酸、舒洛芬、琥布

宗、噻洛芬酸 (triaprofenic acid)、托美丁、伐地考昔、联苯丁酸、希莫洛芬、扎托洛芬、佐美酸、阿司匹林、阿西美辛 (acemetcin)、丁丙二苯肼、carprofenac、环氯茚酸、二氟尼柳、恩芬那酸、芬度柳、氟芬那酸、氟尼辛、龙胆酸、酮咯酸、美沙拉秦、它们的前药，等等。在一些实施方案中，使用免疫调节剂，例如 6- 巯基嘌呤 (6-MP)、硫唑嘌呤 (Imuran)、氨甲喋呤 (Rheumatrex、Trexall)、Stelara、英夫利昔单抗 (Remicade) 和阿达木单抗 (Humira)。

[0261] 在一些实施方案中，另外的治疗剂是血管内皮生长因子 (VEGF) 抑制剂，例如 1) 抗 VEGF 或其受体的中和单克隆抗体 ;2)VEGF 受体的小分子酪氨酸激酶抑制剂 ;3) 可溶性 VEGF 受体，其作为 VEGF 的诱饵受体 ;和 4) 核酶，其特异性靶向 VEGF。针对 VEGF 具有活性的抗体的一些例子是，例如 Lucentis( 雷珠单抗 ) 和 Avastin( 贝伐珠单抗 )。寡核苷酸药物的一个例子是，例如 Macugen( 哌加他尼钠注射剂 )。小分子酪氨酸激酶抑制剂包括，例如帕唑帕尼、索拉非尼、索坦等等。

[0262] 可用于与凯莫瑞 C15 肽联合地、在其之前、在其之后或伴随给药的一类治疗剂是抗组胺剂，包括烷基胺、乙醇胺和吩噻嗪类，例如，马来酸氯苯那敏、单宁酸氯苯那敏、盐酸苯海拉明、盐酸异丙嗪、阿伐斯汀、马来酸阿扎他定、盐酸氮卓斯汀、马来酸溴苯那敏、马来酸卡比沙明、盐酸西替利嗪、富马酸氯马斯汀、盐酸赛庚啶、地氯雷他定、马来酸右溴苯那敏、马来酸右氯苯那敏、茶苯海明 (dimenhydriunate)、盐酸苯海拉明、富马酸依美斯汀、盐酸非索非那定、盐酸羟嗪、富马酸酮替芬、氯雷他定、盐酸氯苯甲嗪、盐酸奥洛他定、酒石酸苯茚胺、喹硫平、柠檬酸曲吡那敏、盐酸曲吡那敏和盐酸曲普利啶。

[0263] 可用于与凯莫瑞 C15 肽联合地、在其之前、在其之后或伴随给药的一类治疗剂是肥大细胞稳定剂，例如色甘酸钠和奈多罗米。

[0264] 在某些情况下，在细胞中诱发氧化应激，其具有由免疫或炎性疾病诱导的受损的自动调节和局部缺血过程。在一些实施方案中，抗氧化剂可用于与凯莫瑞 C15 肽联合地、在其之前、在其之后或伴随给药。在本发明方法中有用的合适的抗氧化剂的例子包括但不限于 :抗坏血酸、生育酚、生育三烯酚、类胡萝卜素、谷胱甘肽、α- 硫辛酸、泛醇、生物类黄酮、肉碱和超氧化物歧化酶模拟物，例如，2,2,6,6- 四甲基 -1- 哌啶氧基 (TEMPO)、DOXYL、PROXYL 硝基氧化合物 ;4- 羟基 -2,2,6,6- 四甲基 -1- 哌啶氧基 (TEMPOL)、M-40401、M-40403、M-40407、M-40419、M-40484、M-40587、M-40588 等。

[0265] 在一些实施方案中，提供这样的方法，其中抗凋亡治疗剂与凯莫瑞 C15 肽联合地、在其之前、在其之后或伴随给药。合适的抗凋亡剂的例子是，例如胱天蛋白酶、组织蛋白酶和 TNF-α 的抑制剂。

[0266] 可用于与凯莫瑞 C15 肽联合地、在其之前、在其之后或伴随给药的一类治疗剂是抗微生物剂。合适的抗微生物化合物包括但不限于 :青霉素类，例如阿莫西林、氨苄西林、阿洛西林、羧苄西林、氯唑西林、双氯西林、氟氯西林、美洛西林、萘夫西林、青霉素、哌拉西林、替卡西林等 ;β- 内酰胺酶抑制剂 ;碳青霉烯类，例如，厄他培南、亚胺培南、美罗培南等 ;头孢菌素类，例如，头孢克洛、头孢孟多、头孢西丁、头孢丙烯、头孢呋辛 (ceftiroxime)、头孢克肟、头孢地尼、头孢托仑、头孢哌酮、头孢噻肟、头孢泊肟、头孢羟氨苄、头孢他定、头孢布坦、头孢唑肟、头孢曲松 (ceffiriaxone)、头孢唑啉、头孢克肟、头孢氨苄、头孢吡肟等 ;喹诺酮类，例如，环丙沙星、依诺沙星、加替沙星、左氧氟沙星、洛美沙星、莫西沙星 (morifloxacin)、诺氟沙星、氧氟沙星、曲伐沙星等 ;大环内酯类，例如，阿奇霉素、克拉霉

素、地红霉素、红霉素、米尔倍霉素、醋竹桃霉素等；单环 β-内酰胺类 (monbactams)，例如 LFA-1 拮抗剂等；四环素类，例如，地美环素、多西环素、米诺环素、土霉素、四环素等；氨基糖苷类，例如，阿米卡星、庆大霉素、卡那霉素、新霉素、奈替米星、巴龙霉素、链霉素、托普霉素等；碳头孢烯，例如氯碳头孢等；链阳菌素类；磺胺类，例如，磺胺米隆 (mefanide)、偶氮磺胺、磺胺醋酰、磺胺甲二唑、磺胺、柳氮磺吡啶、磺胺异噁唑、甲氧苄啶、甲氧苄啶-磺胺甲噁唑等；其它抗微生物剂，例如甲硝唑；和联合药物，例如，磺胺甲噁唑和甲氧苄啶等。

[0267] 其它抗微生物剂包括抗病毒剂类别。抗病毒剂包括但不限于治疗剂，例如进入抑制剂、逆转录酶抑制剂、核苷或核苷酸类似物、蛋白酶抑制剂和病毒从宿主细胞释放的抑制剂。此组中的一些说明性的治疗剂包括但不限于：阿巴卡韦、阿昔洛韦、阿德福韦、金刚烷胺、安普那韦、阿比朵尔、阿扎那韦、atripla、溴夫定、西多福韦、可比韦、达芦那韦、地拉韦啶、去羟肌苷、二十二醇、依度尿苷、依法韦仑、恩曲他滨、恩夫韦肽、恩替卡韦、泛昔洛韦、福米韦生、膦甲酸、膦乙酸、更昔洛韦、加德西 (gardasil)、伊巴他滨、immunovir、碘苷、咪喹莫特、茚地那韦、肌苷、III 型干扰素、II 型干扰素、I 型干扰素、干扰素、拉米夫定、洛匹那韦、洛韦胺、马拉韦罗、吗啉胍、奈非那韦、奈韦拉平、nexavir、奥司他韦、喷昔洛韦、帕拉米韦、普可那利、鬼臼毒素、拉替拉韦、利巴韦林、金刚乙胺、利托那韦、沙奎那韦、司他夫定、替诺福韦、替诺福韦酯、替拉那韦、曲氟尿苷、三协唯、曲金刚胺、特鲁瓦达 (truvada)、伐昔洛韦、缬更昔洛韦、维立韦罗、阿糖腺苷、伟拉咪定 (viramidine)、扎西他滨、扎那米韦、齐多夫定等。

[0268] 在一些实施方案中，施用到皮肤的制剂包含一种或多种抗微生物剂或抗生素剂。

[0269] 在一些实施方案中，与凯莫瑞 C15 肽给药联合地、在其之前、伴随地或者在其之后施用促分泌剂。在一些实施方案中，增加眼中粘蛋白或其它流体的产生是有益的。例子包括但不限于地夸磷索 (Diquafasol)、瑞巴派特 (Rebamipide) 和类花生酸 (Eicosanoid)15-(S)-HETE。

实施例

[0270] 下面的实施例是说明性的，并且不限制本文中描述的制剂和方法的范围。

实施例 1：hC-15 对人巨噬细胞的细胞因子分泌的影响

[0271] 在本实施例中，考察人凯莫瑞 C15 抑制从激活的人巨噬细胞分泌细胞因子的能力。对于该实验，比较人凯莫瑞 C15 肽 AGEDPHSFYFPGQFA 和人凯莫瑞 C17 肽 AGEDPHSFYFPGQFAFS 的活性。利用 BOP 与 FMOC 保护的氨基酸的偶联以及最终用 TFA 从树脂上切割，通过固相合成来合成 C15 和 C17 肽。通过利用水 / 乙腈梯度的反相 C18 色谱法来将肽纯化。

[0272] 人巨噬细胞来源于从 3 个供体获得的人 CD14+ 单核细胞。在第一天，将分离的单核细胞解冻，并对于每组一式三份地以 $5\times10^5$ 个细胞 /ml 的细胞浓度接种在 24 孔细胞培养皿的每孔 1ml RPMI1640GlutaMAX™ 培养基（补充有 10％ FBS、100U/ml 青霉素、100μg/ml 链霉素、0.05μM 巯基乙醇、1％ NEAA 和 1％丙酮酸钠）中。向每个孔中加入 M-CSF，以达到 25ng/ml 的终浓度。细胞在 37℃与 5％ $CO_2$ 下生长 7 天，以使细胞分化成巨噬细胞。在 4 天后更换培养基和 M-CSF。

[0273] 在分化后，除去含有 M-CSF 的培养基。将细胞清洗，并将载体对照、地塞米松、C15 或 C17 加入到合适的孔中。在加入之前，将测试肽溶解于 50％ DMSO/ 水中。加入

C-15(MW1669 ;16.7mg/ml) 至 1pM、10pM 或 100 的终浓度 ;加入 C17(MW1904 ;19.0mg/ml) 至 1μM 的终浓度。加入地塞米松至 1μM 的终浓度。在加入到孔中之后,将培养板在 37℃与 5% $CO_2$ 下孵育 1 小时。将等体积的完全培养基加入到未处理的孔。在整个试验期间,将对照或测试处理维持在正确的浓度下。

[0274] 然后,将 IFNγ(终浓度 20ng/ml) 加入到合适的孔。在加入 IFNγ 后,将培养板在 37℃和 5% $CO_2$ 下孵育 4 小时。在 IFNγ 刺激期间维持载体对照、测试处理或地塞米松的浓度。然后,将 LPS(终浓度 10ng/ml) 加入到合适的孔。在加入 LPS 后,将培养板在 37℃和 5% $CO_2$ 下孵育 15 小时。在 6 小时后,将约 60μl 的培养上清液从所有的孔中除去,并在 -80℃下储存以用于分析。在 LPS 刺激期间维持载体对照、测试处理或地塞米松的浓度。

[0275] 在 LPS 刺激后 15 小时时,收获剩余的细胞培养上清液,并在 -80℃下储存直至分析。维持载体对照、测试处理或地塞米松的浓度,直至培养结束。

[0276] 使用 Luminex® 技术 (Procarta 人细胞因子试剂盒 ;Panomics),按照厂商说明书,对在 LPS 加入后 6 小时和 15 小时取出的细胞培养上清液测定 RANTES、TNFα、IL-1β、IL-6、IL-10、IL-12p40(与 IL-12 和 IL-23 共有的亚单位) 和 IL-15(阴性对照) 的产生。

[0277] 在刺激后 16 小时 IL-1β 和 RANTES 浓度的结果示于图 1A 和 1B 中。图 1C 显示 RANTES 表达在 6 小时和 15 小时时间点之间的差异。图 1D 显示在 16 小时时的 IL-10 表达。正如所预期的,没有观察到 IL-15 的抑制。

[0278] 在低至 1pM 的剂量下,在刺激后 16 小时时,人凯莫瑞 C15 肽显示出对人巨噬细胞分泌 IL-1β 和 RANTES 的强烈抑制 (分别是大约 45%和 65%)(图 1A 和 1B)。对于新合成的 RANTES(即,在 6 小时和 15 小时时间点之间的差异),该抑制为大约 90%。在刺激后 16 小时时,人凯莫瑞 C15 肽也显示出对人巨噬细胞分泌 IL-12p40 的强烈抑制 (大约 55%)(图 1D)。地塞米松也表现出对 IL-1β 和 RANTES 分泌的抑制 (对于 1μM 的剂量,分别是大约 30%和 50%),但其效果小于 C15 的效果。地塞米松对 IL-12p40 分泌的抑制比 C15 稍强 (图 1D)。地塞米松也有力地抑制 (约 70%)IL-10(它是抗炎细胞因子) 的产生,而 C15 只产生 IL-10 的适度下降 (约 25%)(图 1D)。因为 IL-10 是天然抗炎剂,抑制 IL-10 是不希望的。人凯莫瑞 C17 肽即使在 1μM 下也未表现出对细胞因子产生的任何显著抑制。总之,通过在百万分之一的剂量下显示出对炎性细胞因子水平的类似效果,人凯莫瑞 C15 肽表现出比地塞米松优异的效力。

实施例 2 :对于 ChemR23 或 GPR1 激动剂或拮抗剂活性的分析

[0279] 除了不是 G 蛋白偶联受体的 CCRL2 之外,凯莫瑞还与两种 G 蛋白偶联受体 ChemR23(CMKLR1) 和 GPR1 结合。为了确定凯莫瑞 C15 肽的作用方式,考查了凯莫瑞肽充当 GCPR 的拮抗剂或激动剂的能力。

[0280] 在该实验中,将人凯莫瑞 C15 肽 AGEDPHSFYFPGQFA 的激动剂和 / 或拮抗剂活性与小鼠凯莫瑞 C15 肽 AGEDPHGYFLPGQFA、人凯莫瑞 C16 肽 AGEDPHSFYFPGQFAF 和人凯莫瑞 C17 肽 AGEDPHSFYFPGQFAFS 的活性进行比较。

[0281] 使用 DiscoveRx PathHunter™ eXpress GPCR 活性试验来测试凯莫瑞肽针对 GPCR ChemR23 和 GPR1 的激动剂和拮抗剂活性。测试了两种试验形式 :PathHunter β-抑制蛋白试验和 Hit Hunter cAMP Hunter 试验。

PathHunter β-抑制蛋白试验

[0282] PathHunter β-抑制蛋白试验采用由DiscoveRx开发的、被称作互补的技术来以均质的、非成像试验形式监测GPCR的活化，该技术使用酶片段互补(EFC)试验，以β-半乳糖苷酶(β-Gal)作为功能报道分子。所述酶被分成在细胞中表达为融合蛋白的两个互补的部分。酶受体(EA)与β-抑制蛋白融合，而ProLink供体肽与目标GPCR融合。在GPCR刺激后，β-抑制蛋白募集到受体以进行脱敏，使β-Gal的两个片段聚拢在一起并允许发生互补。这将产生活性酶，其可转化化学发光底物，并产生在标准微板阅读器上可检测的输出信号。

[0283] 该试验涉及CHO细胞系，该CHO细胞系表达1)目标GPCR(例如ChemR23或GPR1)，其具有与受体的C-末端融合的β-gal酶片段；和2)与主β-gal酶融合的β-抑制蛋白。当所述激动剂与受体结合时，β-抑制蛋白募集到受体，并且来自GPCR的片段补足该β-gal酶，从而形成功能性β-gal酶。然后加入底物，并产生荧光，来检测β-抑制蛋白募集。

[0284] 采用的方案是DiscoveRx PathHunter™概况分析(profiling)服务所采用的标准方案。简言之，按照标准程序将PathHunter细胞系从冰箱贮存物扩展到T25烧瓶中，并在测定前将其维持在选择性生长培养基中。一旦确认细胞是健康的并且正常生长，就利用细胞解离试剂将细胞从烧瓶传代，并接种到白壁、透明底384-孔微板中进行化合物概况分析。为了进行概况分析，在20μL总体积中以每孔5000个细胞的密度接种细胞，并使之在加入化合物之前贴壁并复苏过夜。

[0285] 对于激动剂试验，产生化合物原液的中间稀释液，使得可以向每个孔中加入5μL的5X化合物，其中最终DMSO浓度为总体积的1%。为了以激动剂模式对化合物进行概况分析，在化合物的存在下将细胞在37℃下培养90分钟。

[0286] 对于拮抗剂试验，在概况分析的上午完成激动剂剂量曲线，以确定下列使用化合物的拮抗剂测试的EC80值。向存在相同浓度的载体的每个孔中加入5μL的5X激动剂(即，凯莫瑞)。直接由激动剂剂量曲线来确定EC80激动剂浓度。对于拮抗剂测定，将细胞与拮抗剂一起预孵育，之后在EC80浓度下进行激动剂激发：将4.5μL的5X化合物加至细胞，并在37℃下孵育30分钟。将5.5μL的6X EC80激动剂加至细胞，并在37℃下孵育90分钟。

[0287] 对于激动剂和拮抗剂试验，分别通过单次加入12.5或15μL(50% v/v)的PathHunter检测试剂混合物，随后在室温下孵育1小时后，来产生测定信号。在信号产生后，采用用于化学发光信号检测的PerkinElmer Envision™仪器读取微板。

[0288] 使用GraphPad Prism或Activity Base来绘制在存在及不存在化合物的情况下的剂量曲线。对于激动剂模式试验，利用下列公式计算活性百分比：%活性＝100% x(测试样品的平均RLU-载体对照的平均RLU)/(对照配体的平均MAX RLU-载体对照的平均RLU))。对于拮抗剂模式试验，利用下列公式计算抑制百分比：%抑制＝100% x(1-测试样品的平均RLU-载体对照的平均RLU)/(EC80对照的平均RLU-载体对照的平均RLU))。

Hit Hunter cAMP Hunter试验

[0289] DiscoveRx已经开发了一组细胞系，它们稳定地表达通过cAMP发信号的非标记的GPCR。该Hit Hunter cAMP Hunter试验采用由DiscoveRx开发的、被称作互补的技术，以均质的、非成像试验形式监测经由Gi和Gs第二信使信号传导的GPCR活化。其使用酶片段互补(EFC)试验，以β-半乳糖苷酶(β-Gal)作为功能报道分子。该酶被分成两个互补的

部分。原标记 (Pro-Label) 供体肽与 cAMP 融合，并且在该试验中与细胞产生的 cAMP 竞争结合 cAMP 特异性抗体。通过 EA 与任何未结合的 ED-cAMP 的互补，形成活性 β-Gal。该活性酶可转化化学发光底物，以产生在标准微板阅读器上可检测的输出信号。

[0290] 采用的方案是DiscoveRx PathHunter™概况分析服务所采用的标准方案。简言之，按照标准程序将 cAMP Hunter 细胞系从冰箱贮存物扩展到 T25 烧瓶中，并在测定前将其维持在选择性生长培养基中。一旦确认细胞是健康的并且正常生长，就利用细胞解离试剂缓冲剂将细胞从烧瓶传代，并接种到白壁、透明底 384- 孔微板中进行化合物概况分析。为了进行概况分析，在 20μL 总体积中以每孔 10000 个细胞的密度接种细胞，并使之在加入化合物之前贴壁并复苏过夜。第二天采用如下所示的方案处理细胞。利用DiscoveRx HitHunter cAMP XS+ 试验来确定 cAMP 的调节。

[0291] 对于激动剂试验，从细胞吸出培养基，并替换为 15μL2:1HBSS/Hepes :cAMP XS+Ab 试剂。产生化合物原液的中间稀释液，使得可以向每个孔中加入 5μL 的 4X 化合物，其中最终载体浓度为总体积的 1%。为了以激动剂模式对化合物进行概况分析，在化合物的存在下将细胞在 37℃下孵育 30 分钟。

[0292] 对于拮抗剂试验，从细胞吸出培养基，并替换为 10μL1:1HBSS/Hepes :cAMP XS+Ab 试剂。完成激动剂剂量曲线，以确定下列使用化合物的拮抗剂测试的 EC80 值。向存在相同浓度的载体的每个孔中加入 5μL 的 4X 激动剂（即，凯莫瑞）。直接由激动剂剂量曲线来确定 EC80 激动剂浓度。对于拮抗剂测定，细胞与拮抗剂一起预孵育，之后在 EC 浓度下进行激动剂激发。将 5μL 的 4X 化合物加至细胞，并在 37℃下孵育 30 分钟。将 5μL 的 4X EC80 激动剂加至细胞，并在 37℃下孵育 30 分钟。

[0293] 通过与 20μL cAMP XS+ED/CL 裂解混合物孵育 1 小时，之后与 20μL cAMP XS+EA 试剂在室温下孵育 3 小时，来产生测定信号。在信号产生后，利用用于化学发光信号检测的 PerkinElmer Envision™ 仪器读取微板。

[0294] 使用 GraphPad Prism 或 Activity Base 来绘制在存在及不存在化合物的情况下的剂量曲线。对于激动剂模式试验，利用下列公式计算活性百分比：%活性＝ 100% x( 测试样品的平均 RLU- 载体对照的平均 RLU)/(MAX 对照的平均 RLU- 载体对照的平均 RLU))。对于拮抗剂模式试验，利用下列公式计算抑制百分比：%抑制＝ 100% x(1- 测试样品的平均 RLU- 载体对照的平均 RLU)/(EC80 对照的平均 RLU- 载体对照的平均 RLU))。

[0295] 在以下的表 1 中提供了 GPR1 和 CMKLR1PathHunter Biosensor 细胞系的数据的概要。

表 1.GPR1 和 CMKLR1PathHunter Biosensor 数据

| GPCR | 化合物 ID | [EC50](M) | 最大活性 % | 等级次序 | [IC50](M) | 最大抑制 % |
|---|---|---|---|---|---|---|
| GPR1 | mC15 | 3.7E-06 | 27.8% | 4 | >1.0E-5 | 0% |
| | C15 (人) | 1.7E-02 | 10.6% | 3 | >1.0E-5 | 0% |
| | C16 (人) | 2.1E-09 | 87.9% | 2 | >1.0E-5 | 0% |
| | C17 (人) | 1.5E-09 | 80.9% | 1 | >1.0E-5 | 0% |
| CPCR | 化合物 ID | [EC50](M) | 最大活性 % | 等级次序 | [IC50](M) | 最大抑制 % |
| ChemR23 | mC15 | >1.0E-06 | 0.4% | 3 | >1.0E-5 | 0% |
| | C15 (人) | >1.0E-5 | 0.8% | 3 | >1.0E-5 | 0% |
| | C16 (人) | 2.9E-08 | 98.6% | 1 | >1.0E-5 | 0% |
| | C17 (人) | 4.8E-07 | 67.5% | 2 | >1.0E-5 | 0% |

[0296] 在以下的表 2 中提供了小鼠 ChemR23PathHunter 和人 ChemR23cAMP Hunter Biosensor 细胞系的数据的概要。PathHunter Biosensor 细胞系。

表 2. ChemR23 PathHunter 和人 ChemR23 cAMP Hunter Biosensor 数据

| 化合物名称 | 试验名称 | 试验形式 | 测定目标 | 结果类型 | RC50(uM) |
|---|---|---|---|---|---|
| hrChemerin | 抑制蛋白 | 激动剂 | mChemR23 | EC50 | 0.0015405 |
| hr Chemerin | cAMP | 激动剂 | ChemR23 | EC50 | 0.0040557 |
| mC15 | 抑制蛋白 | 激动剂 | ChemR23 | EC50 | >10 |
| mC15 | 抑制蛋白 | 拮抗剂 | m ChemR23 | IC50 | >10 |
| mC15 | cAMP | 拮抗剂 | ChemR23 | IC50 | >10 |
| C15(人) | 抑制蛋白 | 激动剂 | m ChemR23 | EC50 | >10 |
| C15(人) | 抑制蛋白 | 拮抗剂 | m ChemR23 | IC50 | 9.6635 |
| C15(人) | cAMP | 拮抗剂 | ChemR23 | IC50 | >10 |
| C16(人) | 抑制蛋白 | 激动剂 | m ChemR23 | EC50 | 0.038472 |
| C16(人) | 抑制蛋白 | 拮抗剂 | m ChemR23 | IC50 | >10 |
| C16(人) | cAMP | 拮抗剂 | ChemR23 | IC50 | >10 |

| | | | | | |
|---|---|---|---|---|---|
| C17(人) | 抑制蛋白 | 激动剂 | m ChemR23 | EC50 | 0.84015 |
| C17(人) | 抑制蛋白 | 拮抗剂 | m ChemR23 | IC50 | >10 |
| C17(人) | cAMP | 拮抗剂 | ChemR23 | IC50 | >10 |

[0297] 在图 2A 和 2B 中示出了 ChemR23 和 GPR1 受体的激动剂剂量响应曲线。如在上表和图中所示，人或小鼠凯莫瑞 C15 肽都不能充当人 ChemR23 或 GPR1 的激动剂。如期望的那样，凯莫瑞对两种受体表现出强激动剂活性。此外，人凯莫瑞 C16 和 C17 肽都表现出激动剂活性。

[0298] 对于拮抗剂试验，将凯莫瑞刺激到 80％最大信号，并与凯莫瑞肽拮抗。在图 2C 和 2D 中示出了 ChemR23 和 GPR1 受体的拮抗剂剂量响应曲线。如在上表和图中所示，人或小鼠凯莫瑞 C15 肽都不能充当人 ChemR23 或 GPR1 的拮抗剂。

实施例 3：FYFP 基序中的丙氨酸置换对 C15 抗炎活性的影响

[0299] 蛋白磷酸酶 2A 的 B 亚单位包含 FYFP 基序，该基序类似于人凯莫瑞 C15 肽中的 FYFP 基序。该 FYFP 基序在物种之间保守，并且对于与 PP2A 核心酶的结合至关重要 (Davis AJ 等人，J Biol Chem. 2008；283:16104-14)。人野生型 PP2A B- 亚单位 PR70 包含氨基酸序列 IPTFYFPRGRP。

[0300] 在该实验中，考察了人凯莫瑞 C15 肽中的 FYFP 基序对于抗炎活性的重要性。将人凯莫瑞 C15 肽 AGEDPHSFYFPGQFA 的能力与具有氨基酸序列 AGEDPHGYFAPGQFA 的置换凯莫瑞 C15 肽（其中将肽中的第二个苯丙氨酸改变为丙氨酸）的能力进行比较。如实施例 1 所述进行该实验。测试了 0.1pM、0.5pM 和 1pM 浓度的 C15 和 C15 突变肽。如实施例 1 所述确定细胞因子表达。

[0301] 图 3 显示了在 C15 和 C15 丙氨酸置换的肽的存在下，TNFα 和 RANTES 表达的抑制百分比。如图中所示，C15 肽能够分别抑制 61％和 47％的 TNFα 和 RANTES 表达。相反，突变 C15 多肽不能抑制任一种细胞因子的表达。此数据表明，FYFP 基序对于凯莫瑞 C15 肽的抗炎性质是重要的。

实施例 4：人凯莫瑞 C15 肽的软膏制剂

[0302] 在本实施例中，将人凯莫瑞 C15 肽如下配制成软膏：

表 3

| 组分 | 量 |
|---|---|
| 人凯莫瑞 C15 肽 | 2.6+/-0.8mg/g 软膏 |
| 白凡士林 | 50％ |
| 辛酸癸酸甘油三酯 | 45％ |
| 蜂蜡 | 5％ |

[0303] 在软膏的另外的实例中，如下配制人凯莫瑞 C15 肽：

表 4

| 组分（% w/w） | 软膏 2728-74 | 软膏 2728-75 |
|---|---|---|
| 人凯莫瑞 C15 肽 | 2.6+/-0.8mg/g 软膏 | 2.6+/-0.8mg/g 软膏 |
| 二甲基异山梨醇酯 | - | 10% |
| 丁基羟基甲苯 | 0.02% | 0.02% |
| PEG400 | 15% | - |
| Span80 | 2% | 2% |
| 白蜡 | 10% | 10% |
| 白凡士林 | 71.98% | 76.98$ |

实施例 5：人凯莫瑞 C15 肽的凝胶制剂

[0304] 在本实施例中，将人凯莫瑞 C15 肽如下配制成凝胶：

表 5

| 组分（% w/w） | 凝胶 2728-60 | 凝胶 2728-76 |
|---|---|---|
| 人凯莫瑞 C15 肽 | 2.6+/-0.8mg/ml 凝胶 | 2.6+/-0.8mg/ml 凝胶 |
| 二甲基异山梨醇酯 | 15% | 15% |
| Transcutol | 25% | 25% |
| 己二醇 | 12% | 12% |
| 丙二醇 | 5% | 5% |
| 对羟基苯甲酸甲酯 | 0.15% | 0.15% |
| 对羟基苯甲酸丙酯 | 0.05% | 0.05% |
| EDTA | 0.01% | 0.01% |
| 羟乙基纤维素 | - | 1% |
| Penmulen TR-1 | 0.5% | - |
| 25%三乙醇胺 | 适量至 pH6.0 | 适量至 pH4.5 |
| 水 | 适量至 100% | 适量至 100% |

实施例 6：人凯莫瑞 C16 肽的洗液制剂

[0305] 在本实施例中，将人凯莫瑞 C15 肽如下配制成洗液：

表 6

| 组分 (% w/w) | 洗液 2728-77 | 洗液 2728-72 |
|---|---|---|
| 人凯莫瑞 C15 肽 | 2.6+/-0.8mg/ml 洗液 | 2.6+/-0.8mg/ml 洗液 |
| 二甲基异山梨醇酯 | 13% | 13% |
| Transcutol | 20% | 20% |
| 己二醇 | 10% | 10% |
| 丙二醇 | 4% | 4% |
| 对羟基苯甲酸甲酯 | 0.15% | 0.15% |
| 对羟基苯甲酸丙酯 | 0.05% | 0.05% |
| EDTA | 0.01% | 0.01% |
| Carbopol Ultrez10 | 0.5% | 0.3% |
| Penmulen TR-1 | 0.2% | 0.2% |
| 肉豆蔻酸异丙酯 | 3% | - |
| 油醇 | 5% | - |
| 十六醇 | - | 2% |
| 轻质矿物油 | - | 5.5% |
| 油酸 | - | 5% |
| 丁基羟基甲苯 | 0.2% | 0.2% |
| 白凡士林 | 5% | - |
| 25%三乙醇胺 | 适量至 pH6.0 | 适量至 pH6.0 |
| 水 | 适量至 100% | 适量至 100% |

实施例 7 :人凯莫瑞 C17 肽的溶液制剂

[0306] 在本实施例中,将人凯莫瑞 C15 肽如下配制成溶液 :

表 7

| 组分(% w/w) | 溶液 2728-79 | 溶液 2728-81 | 溶液 2728-80 | 溶液 A |
|---|---|---|---|---|
| 人凯莫瑞 C15 肽 | 2.6 +/- 0.8 mg/ml 溶液 | 2.6 +/- 0.8 mg/ml 溶液 | 2.6 +/- 0.8 mg/ml 溶液 | 2.6 +/- 0.8 mg/ml 溶液 |
| 二甲基异山梨醇酯 | 15% | 15% | - | |
| Transcutol | 25% | 25% | - | |
| 己二醇 | 12% | 12% | - | |
| 丙二醇 | 5% | 5% | - | |
| DMSO | - | - | 99% | |
| 25%三乙醇胺 | 适量至 pH 4.5 | 适量至 pH 6.0 | - | |
| 肉豆蔻酸异丙酯 | | | | 45% |
| 醇 | | | | 45% |
| 十一烯酸 | | | | 5% |
| 十二烷基硫酸钠 | | | | 5% |
| 水 | 适量至 100% | 适量至 100% | - | |

实施例 8：人凯莫瑞 C15 肽的皮肤稳定性和渗透性

[0307] 在本实施例中，考察了人凯莫瑞 C15 肽在人类皮肤中保持稳定以及穿透人类皮肤的能力。测试了 DMSO 形式和包含该 C15 肽的软膏。

凯莫瑞 C15 肽软膏

[0308] 本研究的目的是，确定人凯莫瑞 C15 肽是否会扩散穿过在 Franz 池中保持在流通条件下的体外人类皮肤，其中以软膏的形式施用该 C15 肽。如实施例 4 所述将人凯莫瑞 C15 肽制备为软膏。该 C15 软膏的 10％溶液在施加到皮肤之前即刻制备。将从腹部整形术获得的女性人类皮肤维持在组织培养基和抗生素中，并在 3 天内使用。

[0309] 在静态条件下 (n ＝ 3) 使用标准的 Franz 扩散池 (LGA, Berkeley, CA)。将大约 200μl 的 10％软膏溶液转移到该皮肤的表面，并用药刀分布在表面上。然后应用薄衬 (liner) 向皮肤表面施加 5 分钟的轻微压力，之后将该扩散池堵塞，并保持 24 小时。此后，通过用药刀在皮肤表面上刮擦来回收该软膏，并将保留的材料转移至 50/50 的水－氯仿溶液。然后，通过加热将表皮和真皮分离，并将表皮用 50/50 水－氯仿溶液抽提。然后，将该表皮转移到第二个管中，并在含有 0.1％蛋白酶抑制剂的 PBS 中均匀化。将真皮切碎并在含有 0.1％蛋白酶抑制剂的 PBS 中均匀化。回收该受体流体 (receptor fluid)，并在真空下浓缩。将不含 C15 的软膏施加到皮肤，并且以相同的方式对皮肤进行取样，作为对照 (n ＝ 2)。

[0310] 通过 HPLC 来确定 C15 从给药材料、表皮和受体流体中的回收。通过 LC/MS 来确定表皮中的 C15 浓度。利用下列反相 HPLC 条件来分析皮肤表面和表皮回收物和表皮匀浆样品：

表 8

| | |
|---|---|
| HPLC | Shimadzu 20A系统 |
| 流动相 | A-0.1%的甲酸水溶液<br>B-0.1%在乙腈中的甲酸 |
| 柱 | Phenomenex Gemini™ C18柱(目录号00B-4439-E0, 4.6 × 50 mm, 3 μm) |
| 注入体积 | 5μl |
| 梯度 | 80% A + 20% B至10% A + 90 % B (0-3 分钟) 和10% A + 90% B (3-3.5分钟) |
| 流速 | 800 μl/min |
| 检测 | 在1.92分钟时在275 nm处的峰高 |
| LLQ | 150 ng/ml |

采用下面的 LC/MS/MS 条件来分析真皮样品：

表 9

| | |
|---|---|
| HPLC | 具有Shimadzu SIL-HTc自动进样器的Shimadzu VP系统 |
| 流动相 | A-0.2%的甲酸水溶液<br>B-0.2%在乙腈中的甲酸 |
| 柱 | 2.1 × 10 mm Peeke Scientific Duragel G C18保护柱 |
| 注入体积 | 100 μl |
| 梯度 | 5% B (0.5分钟) 然后 5-95% B (2分钟) |
| 流速 | 400 μl/min |
| 质谱仪 | Applied Biosystems/MDS SCIEC API 3000 |
| 接口 | TurbolonSpray (ESI), 于400°C |
| 软件 | Analyst v1.4.1 |
| 极性 | 阳离子 |
| Q1/Q3 离子 | 对于C15为803.7/120.4<br>对于苯海拉明 (I.S.)为256.2/167.2<br>对于右美沙芬(I.S.)为272.1/215.2 |
| LLQ | 10 ng/ml |

[0311] 用样品回收和提取法来获得良好的质量平衡。氯仿可能已经移除一些起初已经穿透表皮的 C15。在表皮和真皮中测量到少量的 C15。合起来，两个区室占施加剂量的不到 1%。

表 10

| 施加的C15 mg | 皮肤表面 mg | % | 表皮 mg | % | 真皮匀浆 ng | % | 受体流体 | 总% |
|---|---|---|---|---|---|---|---|---|
| 2.19 | 0.74 | 33.6 | 1.53 | 70.2 | 0 | 0.00 | <LLQ | 103.8 |
| 3.52 | 1.17 | 33.3 | 2.25 | 64.1 | 77.4 | 0.02 | <LLQ | 97.4 |
| 2.06 | 0.83 | 40.6 | 1.45 | 71.2 | 238.2 | 0.12 | <LLQ | 111.8 |

50% DMSO 溶液研究

[0312] 本研究的目的是，确定通过使用 50%的 DMSO 水溶液，人凯莫瑞 C15 肽是否会扩散穿过在 Franz 池中保持在流通条件下的体外人类皮肤。50% DMSO 被认为是对于渗透增强

而言可接受的最大量。

[0313] 在该研究中使用的样品是储存在 -20℃下的小鼠和人凯莫瑞 C15 肽。使用的皮肤样品是从乳房成形术获得的女性人类皮肤。将冷冻样品在 -20℃下储存 30 天。在组织培养基和抗生素中获得新鲜样品，并在 3 天内使用。

稳定性研究：

[0314] 进行初步研究，比较人 C15 与小鼠 C15 的稳定性。制备冷冻和新鲜人类皮肤的匀浆，来评价 C15 在皮肤中的降解。将冷冻或新鲜的人类皮肤分别切碎并在 3ml 水中均匀化，并分离上清液。将上清液与小鼠或人 C15 的溶液混合，以产生 0.5mg/ml 的 C15 溶液。将每种溶液在 37℃下孵育，并在 0、1、2 和 24 小时时取样以进行 C15 分析（图 3）。

[0315] 在该试验中，人 C15 比小鼠 C15 更稳定。C15 的降解在冷冻皮肤的匀浆中比在新鲜皮肤的匀浆中明显更低。在 24 小时后，C15 在冷冻和新鲜皮肤的匀浆中的降解分别是 25％和 98％。基于这些发现，制备人 C15 的 2％溶液，用于扩散池试验。

Franz 池研究：

[0316] 用 Franz 池进行 C15 的皮肤渗透的两项研究：

1. 将小鼠 C15 在 50％ DMSO 水溶液中的 1％溶液施加到之前冷冻的人类皮肤上，以开展 HPLC 方法，用于后续使用人 C15 的试验。这一式三份进行。

2. 将人 C15 在 50％ DMSO 水溶液中的 2％溶液施加到新鲜人类皮肤和表皮、真皮上，并分析受体流体的 C15。

[0317] 将皮肤清洗、吸干、切成圆形片，并在施加 C15 之前在 Franz 池中适应 2 小时。使用带有水夹套的流通扩散池，其暴露 2.54$cm^2$ 的皮肤区域。将该池维持在 37℃，在静态条件下操作，并在 700rpm 下搅拌 24 小时。用 PBS(pH ＝ 7.0) 作为受体流体。在实验当天制备 C15 在 50％ DMSO 水溶液中的溶液。

[0318] 将 400μl 的每种 C15 溶液以 100μl 的等份移液到皮肤表面上，并用石蜡膜密封扩散池。一式三份运行扩散池，其中一个对照由只用载体处理的皮肤组成。在 24 小时结束时收集受体流体（约 5mL)，并在分析之前通过蒸发进行浓缩。将皮肤吸干、用胶带剥离三次，以除去残留的 C15，并在 50℃下热分离到表皮和真皮中。将表皮在 5％ TCA 中超声处理 10 分钟，并分析上清液。将真皮切碎并在 5％ TCA 中均匀化，并浓缩和分析上清液。

[0319] 对于小鼠 C15 实验，只分析受体流体。

[0320] 开展反相 HPLC 方法以定量人 C15(Shimamura 等人，2009)。利用 Phenomenex Gemini™ C18 柱（目录号 00B-4439-E0，4.6×50mm，3μm)，在 40℃下在 Shimadzu20A 体系中完成分离。流动相与 (A)0.1％的甲酸水溶液和 (B) 含 0.1％甲酸的乙腈混合。利用 80％ A+20％ B 至 10％ A+90％ B(0-3 分钟）和 10％ A+90％ B(3-3.5 分钟）的梯度体系，以 0.8ml/min 的流速进行分离。注入体积为 5μl。在 275nm 处监测该洗脱液。以色谱图中的单峰观察到人 C15，保留时间在大约 1.8 分钟。通过外标校准来完成人 C15 的量化。以施加剂量的吸收％来表示人 C15 的结果。参见表 11。

[0321] 在来自每项研究的受体流体中测量到非常低的 C15 水平。利用冷冻的人类皮肤和小鼠 C15(0.3％)，C15 受体流体水平最高。在受体流体和表皮中检测到人 C15。真皮样品观察到在 1.8 分钟处的宽峰，但无法与背景峰区分开。（表 11)。人 C15 在新鲜人类皮肤中的 HPLC 结果和吸收％ (n ＝ 3)。

表 11

| 样品 | 峰面积 1.7-1.8min | 净C15(μg) | 穿过皮肤的总C15 (μg) | 在皮肤区室中的% C15 |
|---|---|---|---|---|
| 皮肤1受体流体 | 255 | 0.0053 | 1.26 | 0.02% |
| 皮肤2受体流体 | 1587 | 0.0332 | 7.34 | 0.09% |
| 皮肤3受体流体 | 84 ND | 0.0018 | 0.42 | 0.01% |
| 对照受体流体 | | | | |
| 皮肤1表皮 | 165899 | 3.50 | 700.72 | 8.76% |
| 皮肤2表皮 | 139517 | 2.95 | 590.32 | 7.38% |
| 皮肤3表皮 | 49493 | 1.07 | 213.58 | 2.67% |
| 对照表皮 | ND | | | |
| 皮肤1真皮 | 宽峰 | | | |
| 皮肤2真皮 | 宽峰 | | | |
| 皮肤3真皮 | 宽峰 | | | |
| 对照真皮 | 宽峰 | | | |

[0322] 在体外流通条件下，利用 50％ DMSO 水溶液的渗透增强，人 C15 穿透人类皮肤。在受体流体中检测到低水平，然而在表皮中且最可能在表皮中检测到较高的水平。

[0323] 来自上述两项 Franz 池研究的结果总结在下表中。该研究表明，可以穿过角质层向真皮或更远处递送治疗相关水平的 C15（例如，>1nM）。渗透增强剂（例如 DMSO）可能不是实现向真皮的递送所必须的。

表 12

| 样品 | DMSO (50%) [C15] | 软膏 [C15] |
|---|---|---|
| 皮肤 1 表皮 (2.54 $cm^2$)<br>皮肤 2 表皮(2.54 $cm^2$)<br>皮肤 3 表皮(2.54 $cm^2$) | 419,400 nM<br>353,500 nM<br>127,000 nM | 953,000 nM<br>1,406,000 nM<br>906,000 nM |
| 皮肤 1 真皮 (2.54 $cm^2$)<br>皮肤 2 真皮 (2.54 $cm^2$)<br>皮肤 3 真皮 (2.54 $cm^2$) | NA*<br>NA*<br>NA* | 48 nM<br>149 nM<br>NS* |
| 皮肤 1 受体流体(5 mL)<br>皮肤 2 受体流体(5 mL)<br>皮肤 3 受体流体(5 mL) | 151 nM<br>888 nM<br>50 nM | <10 nM<br><10 nM<br><10 nM |
| *NA 没有分析的可能，干扰 HPLC 检测<br>*NS 没有样品<br>研究概述：将在 DMSO（50%水溶液）或软膏（50%凡士林、45%椰子油、5%蜂蜡，没有渗透增强剂）中配制的 huC15 施加到新鲜人类皮肤。在 24 小时后，用 HPLC 或 LCMS/MS（软膏）来分析表皮、真皮和受体流体的 C15。 | | |

实施例 9 :在牛皮癣患者中的微斑 (Microplaque) 试验

[0324] 微斑试验已经成功用于评价牛皮癣的局部治疗。微斑试验使得能够直接比较不同局部治疗和直接向牛皮癣病变的给药。将具有 6 个洞的模板附着到病变处。患者每天访视诊所，以向金属盘上施加特定的药物剂量，之后将每个金属盘施加到特定的斑点，然后将胳膊包好并保持在封闭下，直至进行下次给药。多个制剂、对照以及活性比较物（如果需要的话）可以全部容纳在一个斑块上。一种典型的微板试验涉及 12-15 名患者，持续 2 周。

[0325] 为了确定 C15 作为牛皮癣局部治疗的临床效力和生物利用性，在稳定斑块状牛皮癣患者中进行 C15 的两种原型局部制剂的 0 期微量给药研究。在示例性的微量给药研究中，进行微斑试验，其中对于 15 名受试者中的每一名，向一个稳定斑块上的六个测试斑点 (2cm 直径）中的每一个每天施加配制的药物，持续 10 至 21 天。此形式允许在 2 种制剂和 3 个浓度下测试 C15，对于每种制剂使用对照，并使用中等强度的类固醇（地塞米松）或戊酸倍他米松 (betamethasone Valorate) 作为活性比较物。

[0326] 在该研究中，每个群组中的所有患者每天接受 0.2ml 的每种测试物的施加，该每种测试物施加到六个均匀测试部位的一个上，切成水胶体敷料，放置在每名患者的研究斑块上。在门诊时间，由研究者在临床环境下施加测试物。在施加每个剂量后，将研究斑用另外的敷料封闭，直至下次诊所访视。相对于在牛皮癣中比较典型的 2/3 期研究设计，在封闭情况下过量地递送药物可大大提高该制剂的性能和药物效力。即使是诸如具有缓慢起效（在自给药的患者中，4-6 周）和非常温和的效力的维生素 D 类似物的药物，在该微斑试验中也已经证明有可测量的改善。受试者在治疗后到诊所观察以进行状况评估。除去该水胶

体敷料，获得所治疗的斑块的数字图像，对所治疗的部位进行临床评分，进行身体检查，并收集供安全性实验室使用的样品。在基线时、在预先确定的研究期间的时间段和在最后一次给药之后，记录每个治疗部位的总临床评分 (TCS)。TCS 是红斑 (0-3)、等级 (0-3) 和厚度 (0-3) 的总和。对于每个指标 :0 ＝没有，1 ＝轻度、2 ＝中度、3 ＝重度。TCS 的可能范围是 0 至 9。此外，在基线时、在预先确定的研究期间的时间段和在最后一次给药之后，记录动态严重性评分 (DSS)，该 DDS 比较每个部位与邻近的牛皮癣斑块的未治疗区域。DDS 是 5 分体系 :-1 ＝恶化 ;0 ＝未改变 ;1 ＝轻微改善 ;2 ＝明显改善但未完全清除 ;3 ＝完全清除。利用描述统计学（包括平均值、标准差、中值、最小值、最大值和相对于基线的变化百分比）来评价 TCS 和 DSS 的效力量度。列出在研究期间报告的所有不良事件，包括局部和全身事件，来记录过程、严重程度和结果。按照治疗组、严重程度和与研究药物的关系来总结所有非请求的不良事件。

[0327] 可以设计另外的微量给药研究，来进一步探索另外的制剂，以便为 2 期研究提供信息，或者可以延长时间长度以针对温和的活性或缓慢的起效。

[0328] C15 在体外在 15 小时内抑制 40-60％的细胞因子产生 / 分泌。C15 似乎也抑制细胞因子信息生成。最近关于来自牛皮癣患者的累及和非累及皮肤中的 IL-23 水平的一项研究表明，斑块中的 IL-23 水平 2 倍于非累及皮肤中的水平。我们的预期，即 C15 的起效在微斑时间过程中将是可观察的，是基于在 Stelara 的一期研究中获得的结果，其中牛皮癣患者在单剂后两周内在 PASI 评分上显示出 50％的改善。该同一群组的患者在注射后 5 天达到最大血清浓度。Stelara 似乎是通过经由抗体 - 抗原结合来清除 IL-23 并通过抑制 IL23p19 信息而达到其治疗效果。

实施例 10 :C15 在小鼠牛皮癣模型中的活性

[0329] 在本实施例中，在小鼠牛皮癣模型中检测人凯莫瑞 C15 肽的治疗活性。基于用来评价牛皮癣动物模型的临床、组织学、免疫表型和生化标准，K5.Stat3C 重组小鼠类似于人类牛皮癣。K5.Stat3C 小鼠在用 12-0- 十四酰佛波醇 -13- 乙酸酯 (TPA) 局部处理刺激后，在角质形成细胞和表皮增生中组成型表达激活的 Stat2。

[0330] 在示例性方案中，在耳朵上用 TPA（例如，在丙酮中的 3.4nmol 的 TPA) 或丙酮对照物局部处理小鼠以诱发皮肤病变，每周三次，持续 4-8 周。对皮肤样品的实时 PCR 用来证实细胞因子表达的上调，包括 IL-23、IL012、TNF-α、IL-β 和 / 或 IL-6。在诱发皮肤病变之后，每天将包含人凯莫瑞 C15 肽的制剂或载体对照局部施加到皮肤病变处，持续 6-12 天。每天评估病变的改善。预计用包含人凯莫瑞 C15 肽的制剂处理的小鼠将表现出在牛皮癣病变中减少的细胞因子表达和表皮的牛皮癣表型的改善，如通过对来自处理和未处理小鼠的皮肤样品的肉眼观察和组织学检查所评估的。

实施例 11 :接触性超敏反应试验

[0331] 在本实施例中，在接触性超敏反应试验中检测人凯莫瑞 C15 肽的治疗活性，该试验是细胞介导的免疫功能的体内试验和人类变应性接触性皮炎模型。在该试验中，将表皮细胞暴露于外来半抗原，这导致可以测量和定量的迟发型超敏反应。朗格汉斯细胞（它是 Ia+、骨髓来源的表皮细胞）通过向带有 CD4 的 T 淋巴细胞呈递抗原来启动对半抗原的致敏，该 T 淋巴细胞转而又分泌淋巴因子并向反应部位募集其它细胞。

[0332] 接触性超敏反应由传入或初始致敏期和传出或引发期组成。在传出期期间，当表

皮细胞遇到它们之前已经暴露过的特定抗原时，发生局部肿胀（在啮齿动物中），并且在人类中导致皮肤湿疹。

[0333] 在示例性方案中，将小鼠剃毛，并将它们腹部的皮肤暴露于半抗原。在 6 天后（传入期），在传出期开始之前测量基线耳厚度。最后，用半抗原溶液皮内处理耳朵，并在大约 24 小时的时候测量耳厚度。在该研究中使用的模型接触变应原是溶于丙酮 / 橄榄油溶液中的 2,4,6- 三硝基氯苯 (TNCB ；也称作苦基氯）。其它可以使用的示例性变应原包括例如 FITC、噁唑酮 (oxazalone) 和 DNFB。变应原处理后耳厚度的改变可用于计算接触性超敏反应的抑制百分比。在示例性的实施方案中，将小鼠用包含人凯莫瑞 C15 肽的制剂预处理，来考察对变应性应答的防止或抑制。在另外的示例性实施方案中，将半抗原和包含人凯莫瑞 C15 肽的制剂共同施用于小鼠，来考察对变应性应答的防止或抑制。在另外的示例性实施方案中，用半抗原处理小鼠以诱发变应性应答，然后用包含人凯莫瑞 C15 肽的制剂处理，来考察对变应性应答的治疗。预计用人凯莫瑞 C15 肽进行的治疗将导致对变应性应答的预防、抑制和 / 或治疗。

[0334] 本文中描述的实例和实施方案是用于说明的目的，并且给本领域技术人员建议的各种改进或改变将包括在本申请的精神和范围以及所附权利要求书的范围内。本文中使用的章节标题仅用于组织目的，而不应当被解释为限制所描述的主题。

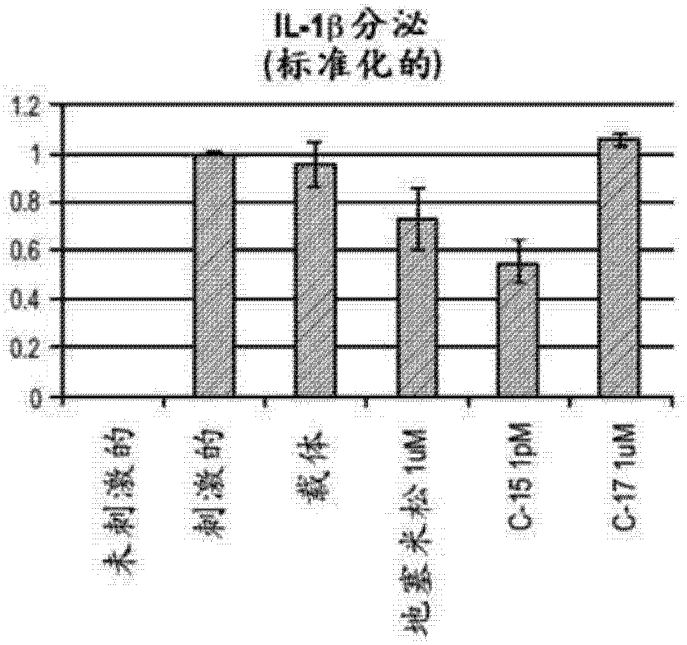

IL-1β分泌
(标准化的)
1.2
1
0.8
0.6
0.4
0.2
0
未刺激的
刺激的
载体
地塞米松1uM
C-15 1pM
C-17 1uM

图 1A

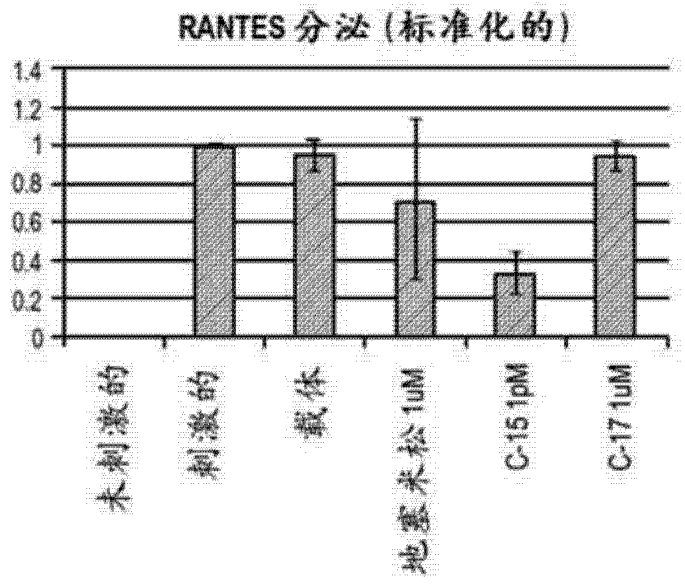

RANTES分泌(标准化的)
1.4
1.2
1
0.8
0.6
0.4
0.2
0
未刺激的
刺激的
载体
地塞米松1uM
C-15 1pM
C-17 1uM

图 1B

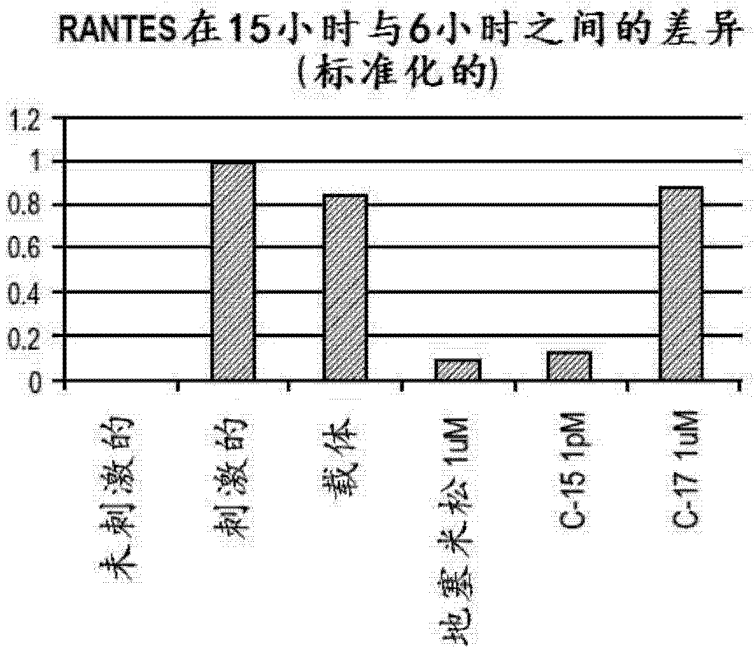

RANTES在15小时与6小时之间的差异
(标准化的)
1.2
1
0.8
0.6
0.4
0.2
0
未刺激的
刺激的
载体
地塞米松1uM
C-15 1pM
C-17 1uM

图 1C

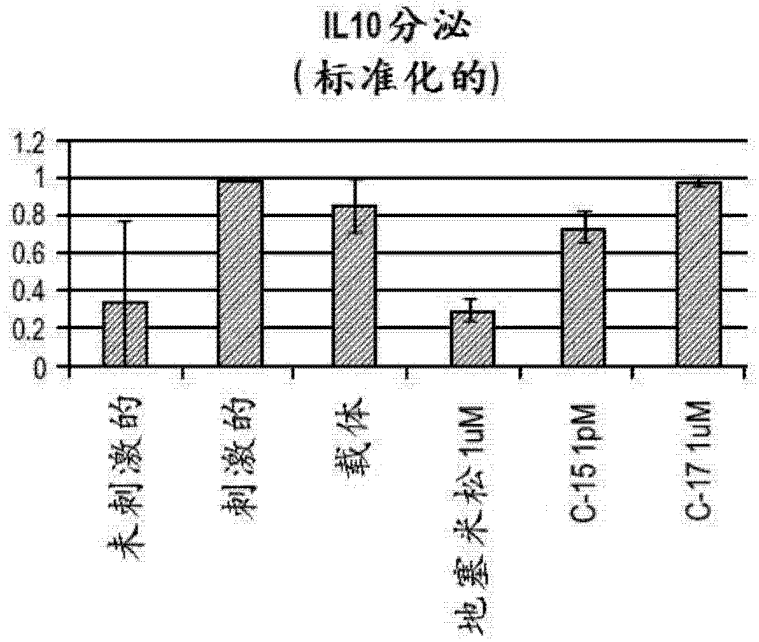

IL10分泌
(标准化的)
1.2
1
0.8
0.6
0.4
0.2
0
未刺激的
刺激的
载体
地塞米松1uM
C-15 1pM
C-17 1uM

图 1D

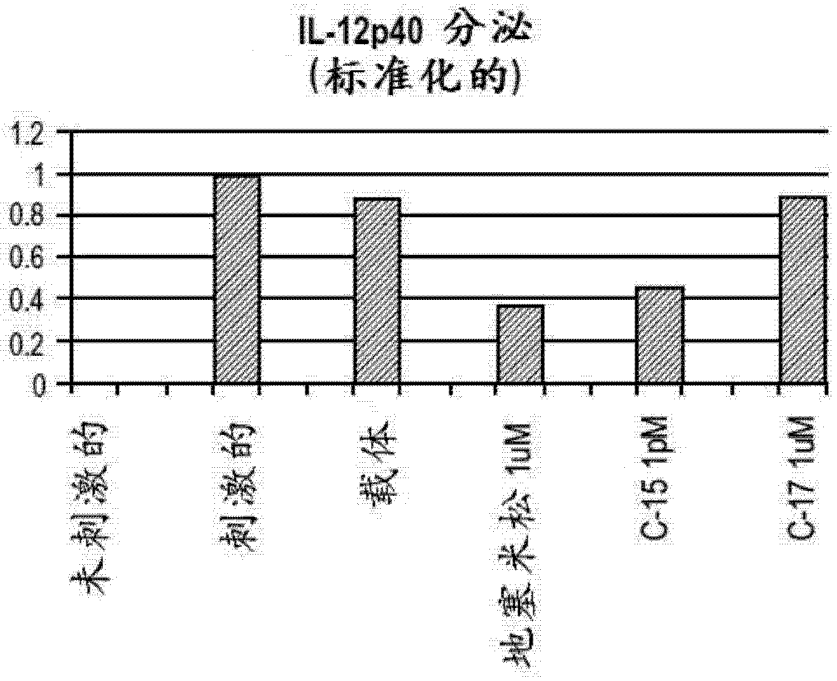

IL-12p40 分泌
(标准化的)
1.2
1
0.8
0.6
0.4
0.2
0
未刺激的
刺激的
载体
地塞米松 1uM
C-15 1pM
C-17 1uM

图 1E

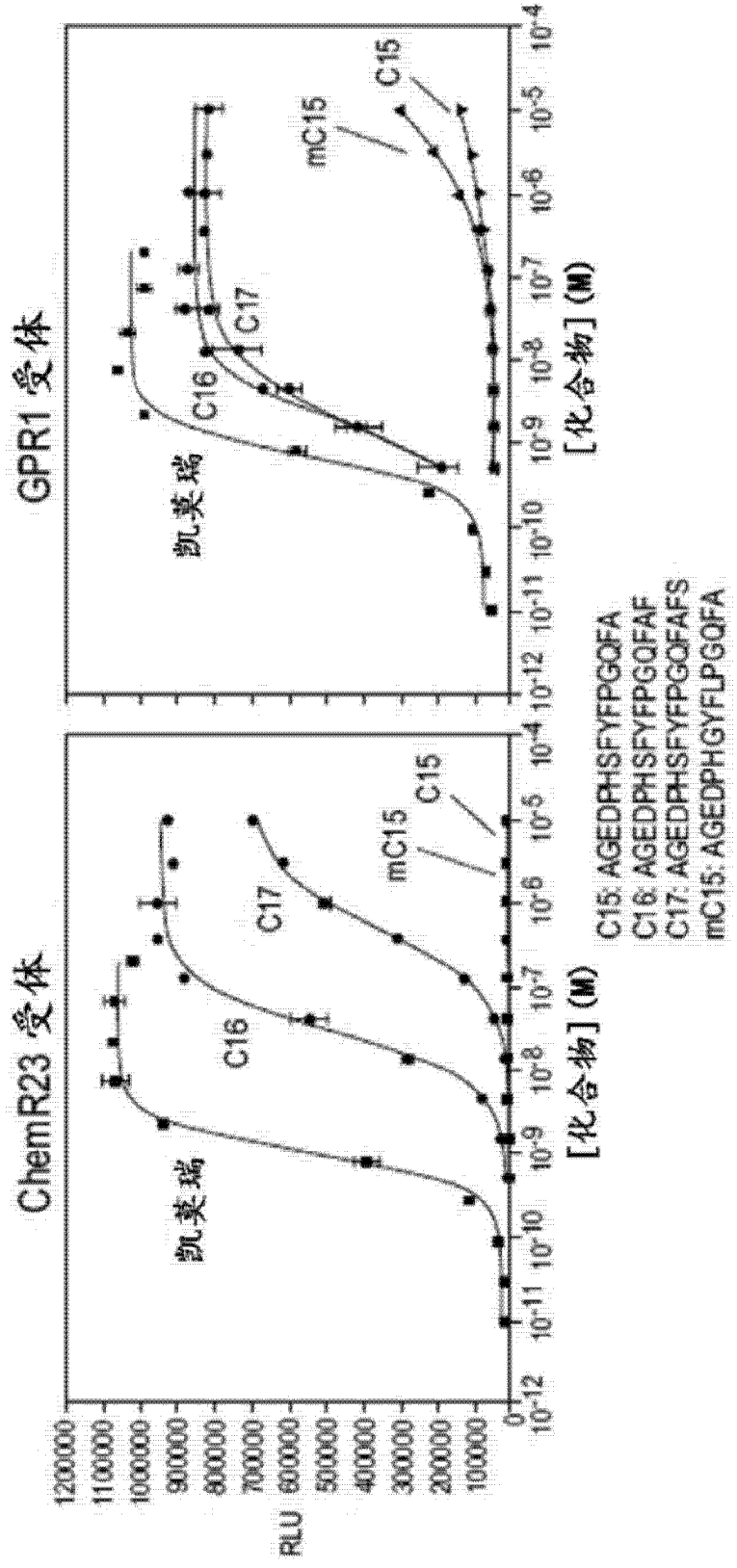

ChemR23 受体
GPR1 受体
凯莱瑞
C16
C17
mC15
C15
RLU
[化合物] (M)
C15: AGEDPHSFYFPGQFA
C16: AGEDPHSFYFPGQFAF
C17: AGEDPHSFYFPGQFAFS
mC15: AGEDPHGYFLPGQFA

图 2A

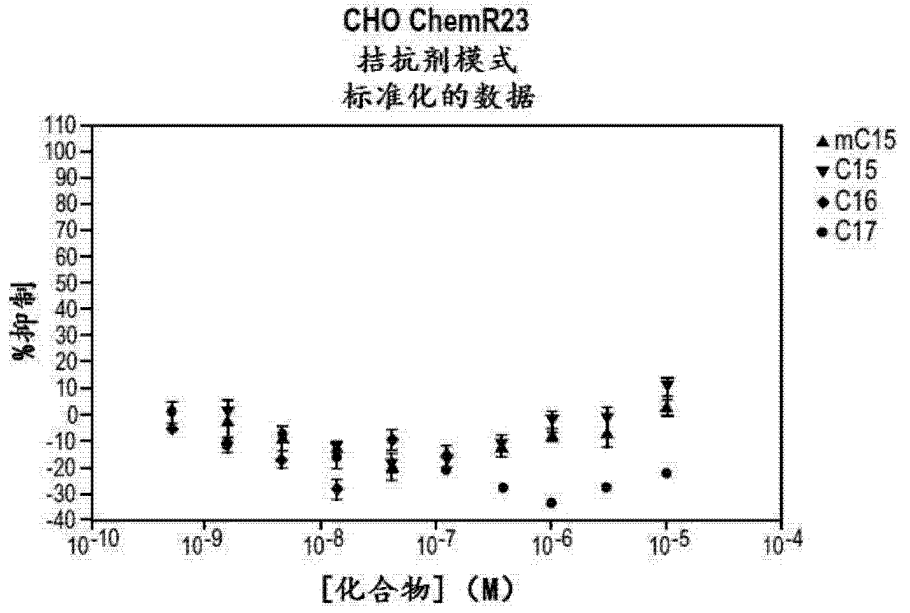

CHO ChemR23
拮抗剂模式
标准化的数据
%抑制
[化合物] (M)
mC15
C15
C16
C17

图 2B

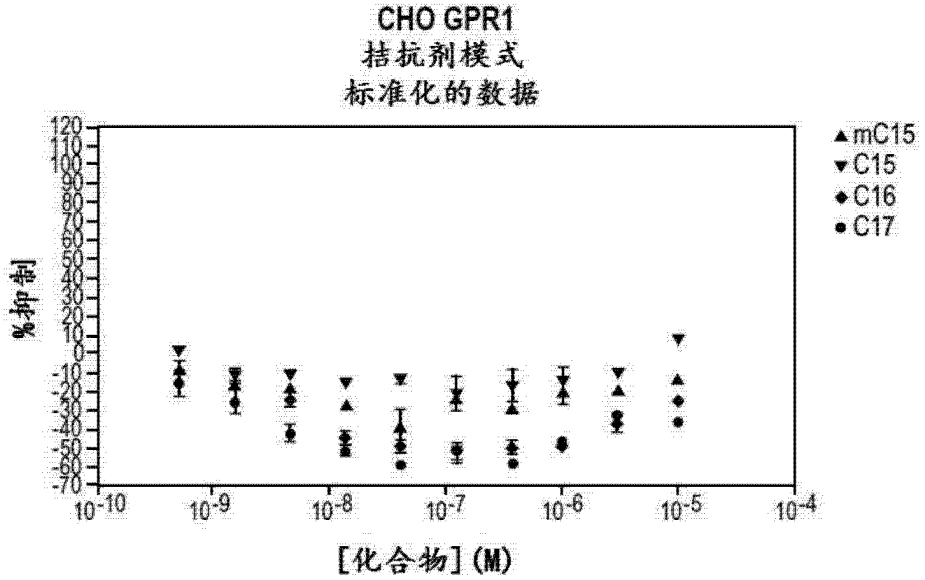

CHO GPR1
拮抗剂模式
标准化的数据
%抑制
[化合物] (M)
mC15
C15
C16
C17

图 2C

C15: AGEDPHSFYFPGQFA
mC15: AGEDPHGYFLPGQFA
C15-A: AGEDPHGYFAPGQFA
B亚单位: P-TFYFP

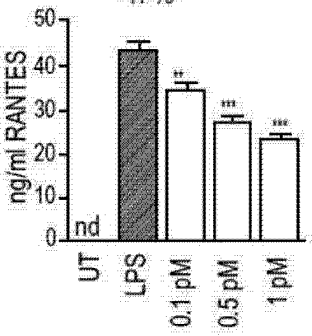
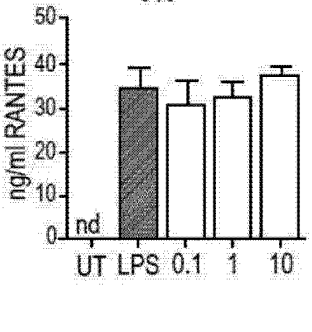
| LPS/IFNγ-诱导的细胞因子表达的抑制百分比 | | |
|---|---|---|
| 细胞因子 | C15 | C15-A |
| TNFα | 61% | 0% |
| RANTES | 47%  C15 | 0%  C15-M |





图 3

## Abstract

Described herein, are topical formulations for treating a dermato logical disease, disorder, or condition. Topical formulation disclosed herein include a therapeutically-effective amount of a human chemerin C15 peptide formulated for dermal administration.