

**CROSS-REFERENCE TO RELATED APPLICATIONS**

[0001] This application claims priority to United States Provisional Patent Application No. 63/583,467, filed September 18, 2023, the entire contents of which are hereby incorporated by reference in their entirety.

**BACKGROUND**

[0002] Topical compositions are commonly utilized in the treatment and/or prevention of dermatological conditions. The present disclosure provides new technologies (e.g., compositions, methods, kits, etc.) that comprise or deliver an active agent (e.g., a PAI-1 inhibitor), their production and use, including in treatment and/or prevention of a variety of diseases, disorders, and/or conditions.

**SUMMARY**

[0003] The present disclosure recognizes a need for improvements in topical compositions for treatment of diseases, disorders, and/or conditions. Among other things, in some embodiments, the present disclosure provides improved compositions that comprise and/or deliver an active agent (e.g., a PAI-1 inhibitor). The present disclosure provides, among other things, compositions formulated for topical application that comprise and/or deliver an active agent (e.g., a PAI-1 inhibitor). In some embodiments, such compositions are useful, for example, in various cosmetic and medical applications.

[0004] Compositions (e.g., original compositions, as described herein) that comprise or deliver an active agent, for example a PAI-1 inhibitor, such as those described in PCT patent application number PCT US2019/050849 filed September 12, 2019, published as WO2020/056160 on March 19, 2020 and entitled "PLASMINOGEN ACTIVATOR INHIBITOR 1 (PAI-1) INHIBITORS AND USES THEREFOR"; and/or in PCT patent application number PCT US2019/050890 filed September 19, 2019, published as WO2020/056191 on March 19, 2020 and entitled "USES OF PLASMINOGEN

ACTIVATOR INHIBITOR 1 (PAI-1) INHIBITORS"; have been successfully used for topical administration of an active agent (e.g., a PAI-1 inhibitor).

[0005] For example, in some embodiments an original composition that comprises and/or delivers an active agent (e.g., a PAI-1 inhibitor) was formulated as an ethanol-based composition. As may be known to those skilled in the art, alcohol-based compositions may be used to topically deliver an active agent more effectively than other compositions (e.g., water-based compositions) because ethanol is a known topical penetration enhancer. However, among other things, it is an insight of the present disclosure that an active agent in an ethanol-based composition (i.e., an ethanol-based composition that comprises and/or delivers said active agent (e.g., a PAI-1 inhibitor)) can settle to the bottom of a container over time. That is, the present disclosure identifies the source of a problem with such ethanol-based compositions. Among other things, the present disclosure provides compositions with reduced ethanol, for example relative to an appropriate reference composition (e.g., an original composition, as described herein). In some embodiments, an improved composition, as described herein, comprises more water relative to such reference (e.g., original) composition that comprises and/or delivers the relevant active agent. In some embodiments, the present disclosure provides a surprising insight that water-based compositions more effectively deliver (e.g., topically) an active agent, when compared to a reference composition (e.g., an original composition (e.g., an alcohol-based composition) that contains a topical penetration enhancer. The present inventors have undertaken extensive studies of this class of composition, and, as described in the Examples, have made important and surprising findings that define certain embodiments and/or classes of such compositions as particularly and unexpectedly useful and/or advantageous.

[0006] Among other things, in some embodiments, the present disclosure provides a composition (e.g., an improved composition, as described herein) that comprises or delivers a PAI-1 inhibitor. In some embodiments, a composition, as described herein, is formulated for topical application to a site of a subject. In some embodiments, a composition, as described herein, is substantially free of ETOH.

[0007] In some embodiments, a site is skin. In some embodiments, a site contains or did contain a plurality of hair follicles. In some embodiments, each hair follicle optionally comprises a hair disposed therein.

**[0008]** In some embodiments, a composition (e.g., an improved composition) is substantially free of all alcohols. In some embodiments, a composition is substantially free of sorbitol.

**[0009]** In some embodiments, not more than 35% of a composition (e.g., an improved composition) by weight is comprised of a penetration enhancer.

In some embodiments, a penetration enhancer is one or more of glycerin, isopropyl myristate and/or propylene glycol. In some embodiments, a composition (e.g., an improved composition) includes glycerin in an amount that is greater than 1% but no more than 15% by weight of the composition. In some embodiments, a composition (e.g., an improved composition) includes glycerin in amount that is 10% by weight of the composition. In some embodiments, a composition (e.g., an improved composition) includes isopropyl myristate in an amount that is less than 15% by weight of a composition as described herein. In some embodiments, a composition includes isopropyl myristate in an amount greater than 1% but no more than 15% by weight of a composition as described herein. In some embodiments, a composition includes isopropyl myristate in an amount that is 10% by weight of a composition as described herein. In some embodiments, a composition (e.g., an improved composition) includes propylene glycol in an amount that is greater than 1% but no more than 15% by weight of the composition. In some embodiments, a composition (e.g., an improved composition) includes propylene glycol in an amount that is 10% by weight of the composition.

**[0010]** In some embodiments, a composition (e.g., an improved composition) includes Steareth 20 in an amount that is greater than 1% but no more than 3% by weight of the composition. In some embodiments, a composition (e.g., an improved composition) includes Steareth 20 in an amount that is 2% by weight of the composition.

**[0011]** In some embodiments, a composition (e.g., an improved composition) includes Tween 80 in an amount that is greater than 1% but no more than 6% by weight of the composition. In some embodiments, a composition (e.g., an improved composition) includes Tween 80 in an amount that is 3.5% by weight of the composition.

**[0012]** In some embodiments, a composition (e.g., an improved composition) includes propyl paraben in an amount that is greater than 0.05% but no more than 0.15% by weight of a composition. In some embodiments, a composition (e.g., an improved

composition) includes propyl paraben in an amount that is 0.10% by weight of a composition.

[0013] In some embodiments, a composition (e.g., an improved composition) includes butylated hydroxyl toluene in an amount that is greater than 0.05% but no more than 0.15% by weight of a composition. In some embodiments, a composition (e.g., an improved composition) includes butylated hydroxyl toluene in an amount that is 0.10% by weight of a composition.

[0014] In some embodiments, a composition (e.g., an improved composition) includes water in an amount that is greater than 15% but no more than 70% by weight of a composition as described herein. In some embodiments, a composition includes water in an amount that is no more than 54% by weight of a composition as described herein.

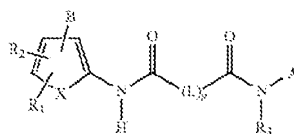
[0015] In some embodiments, a composition (e.g., an improved composition) comprises xanthan gum. In some embodiments, a composition includes xanthan gum in an amount that is greater than 0.1% but no more than 0.3% by weight of a composition as described herein. In some embodiments, a composition includes xanthan gum in an amount that is 0.2% by weight of a composition as described herein.

[0016] In some embodiments, a composition (e.g., an improved composition) includes methyl paraben in an amount that is greater than 0.1% but no more than 0.3% by weight of a composition as described herein. In some embodiments, a composition includes methyl paraben in an amount that is 0.2% by weight of a composition as described herein.

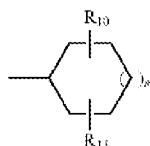
[0017] In some embodiments, a composition (e.g., an improved composition) includes edetate disodium. In some embodiments, a composition includes edetate disodium in an amount that is greater than 0.01% but no more than 0.1% by weight of a composition as described herein. In some embodiments, a composition includes edetate disodium in an amount that is 0.05% by weight of a composition as described herein.

[0018] In some embodiments, a PAI-1 inhibitor is selected from a group consisting of: polypeptides, nucleic acids, lipids, carbohydrates, small molecules, metals, polymers, therapeutic antibodies, fragments of therapeutic antibodies, and/or combinations thereof. In some embodiments, a PAI-1 inhibitor is a 2-aminobenzoic acid analog. In some embodiments, a PAI-1 inhibitor is a 5-chloro-2-aminobenzoic acid analog.

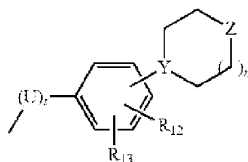
[0019] In some embodiments, a PAI-1 inhibitor is a compound of Formula (1)

**Formula (1)**

[0020] In some embodiments, R<sub>1</sub> and R<sub>2</sub> are the same or different. In some embodiments, each of R<sub>1</sub> and R<sub>2</sub> represents hydrogen, halogen, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, cycloalkenyl, alkynyl, hydroxyl, alkoxy, cycloalkoxy, alkenyloxy, cycloalkenyloxy, aryloxy, aralkyl, aralkyloxy, heterocyclic-alkyl, heterocyclicalkyloxy, aryl optionally having one or two substituents, 5- to 6-membered ring heteroaryl optionally having one or two substituents, or benzo-fused heteroaryl optionally having one or two substituents, amino or carbonyl, each of which is optionally substituted with one or two substituents, or cyano, carboxy, or alkoxy-carbonyl. In some embodiments, R<sub>1</sub> and R<sub>2</sub> are optionally adjoined with each other to form a ring. In some embodiments, R<sub>3</sub> is hydrogen, alkyl, cycloalkyl, or aryl optionally having one or two substituents. In some embodiments, X is -C(R<sub>5</sub>)=C(R<sub>6</sub>)-, -C(R<sub>7</sub>) N-, or -N=C (R<sub>8</sub>)-. In some embodiments, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub> each represents hydrogen, halogen, alkyl optionally having one or two substituents, or alkoxy. In some embodiments, L is alkylene (some carbon atoms in the alkylene optionally form a cycloalkyl ring), alkenylene, alkynylene, cycloalkylene, alkyleneoxyalkylene, alkylene-thioalkylene, alkylene-SO-alkylene, or alkylene-SO<sub>2</sub>-alkylene, each of which is optionally substituted with one or two substituents, or alkylene-N(R<sub>9</sub>)-alkylene optionally substituted with one or two substituents. In some embodiments, R<sub>9</sub> represents hydrogen, or alkyl optionally having one or two substituents. In some embodiments, p represents an integer of 0 or 1. In some embodiments, A is a group represented by any one of the following Formulae (2), (3) or (4):

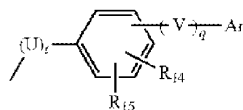
**Formula (2)**

[0021] In some embodiments,  $R_{10}$  and  $R_{11}$  are the same or different. In some embodiments, each of  $R_{10}$  and  $R_{11}$  represents hydrogen or straight- or branched-chain alkyl. In some embodiments,  $m$  represents an integer of 0 to 10.



**Formula (3)**

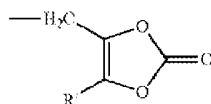
[0022] In some embodiments,  $R_{12}$  and  $R_{13}$  are the same or different. In some embodiments, each of  $R_{12}$  and  $R_{13}$  represents hydrogen, halogen, or alkyl optionally having one or two substituents, cycloalkyl optionally having one or two substituents, or alkoxy optionally having one or two substituents. In some embodiments,  $Y$  represents CH or nitrogen. In some embodiments,  $Z$  represents  $CH_2$ , oxygen, or N-alkyl. In some embodiments,  $n$  represents an integer of 0 to 3. In some embodiments,  $U$  represents alkylene. In some embodiments,  $t$  represents an integer of 0 or 1,



**Formula (4)**

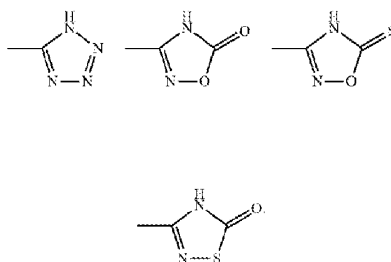
[0023] In some embodiments,  $R_{14}$  and  $R_{15}$  are the same or different. In some embodiments, each of  $R_{14}$  and  $R_{15}$  represents hydrogen, halogen, or alkyl optionally having one or two substituents, cycloalkyl optionally having one or two substituents, or alkoxy optionally having one or two substituents. In some embodiments,  $V$  is alkylene, alkyleneoxyalkylene, oxyalkylene, alkyleneoxy, or oxygen. In some embodiments,  $q$  represents an integer of 0 or 1. In some embodiments,  $U$  and  $t$  are as defined above. In some embodiments,  $Ar$  represents aryl having one or two substituents (such one or two substituents optionally form a ring with a part of carbon atoms in an aryl group), 5- to 6-membered ring aryl group having one or two identical or different heteroatoms optionally having one or two substituents, or benzo-fused heteroaryl optionally having one to three substituents. In some embodiments,  $B$  represents  $COOR_{16}$ . In some embodiments,  $R_{16}$

represents hydrogen, alkyl, aryl or aralkyl, a group represented by  $\text{CH}(\text{R}_{17})\text{O}---\text{COR}_{18}$  or  $---\text{CH}(\text{R}_{17})---\text{O}---\text{CO}---\text{OR}_{18}$ , wherein  $\text{R}_{17}$  is hydrogen or alkyl, and  $\text{R}_{18}$  is alkyl or cycloalkyl, a (5-alkyl-2-oxo-1,3-dioxolen-4-yl)methyl group represented by the following Formula (5):



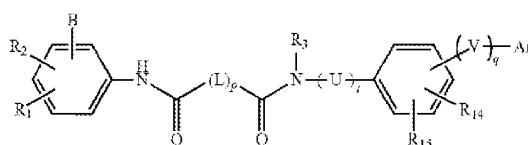
**Formula (5)**

[0024] In some embodiments,  $\text{R}'$  represents alkyl. In some embodiments,  $\text{R}'$  represents a heterocyclic group: a 1H-tetrazol-5-yl group; a 4,5-dihydro-5-oxo-4H-1,2,4-oxadiazol-3-yl group, a 4,5-dihydro-5-thioxo-4H-1,2,4-oxadiazol-3-yl group, or a 4,5-dihydro-5-oxo-1,2,4-thiadiazol-3-yl group, represented by the following Formulae (6), (7), (8) (sequentially from the left), and/or (9) (bottom):



**Formula (6), (7), (8) (sequentially from the left), and (9) (bottom)**

[0025] In some embodiments, a PAI-1 inhibitor is a compound of Formula (10)



**Formula (10)**

[0026] In some embodiments,  $\text{R}_1$  and  $\text{R}_2$  are the same or different. In some embodiments, each of  $\text{R}_1$  and  $\text{R}_2$  represents hydrogen, halogen, alkyl, or aryl optionally having one or two substituents. In some embodiments,  $\text{R}_3$  is hydrogen or alkyl. In some embodiments,  $\text{R}_{14}$  and  $\text{R}_{15}$  are the same or different. In some embodiments, each of  $\text{R}_{14}$  and

R<sub>15</sub> represents hydrogen, alkyl, or halogen. In some embodiments, V is alkylene, oxyalkylene, or oxygen. In some embodiments, Ar is aryl optionally having one or two substituents, aryl group having one or two identical or different heteroatoms optionally having one or two substituents, or benzofused heteroaryl optionally having one or three substituents. In some embodiments, L is alkylene, alkyleneoxyalkylene, alkyleneethioalkylene, alkylene-SO-alkylene, alkylene-SO<sub>2</sub>-alkylene. In some embodiments, a PAI-1 inhibitor is selected from a group consisting of: 5-Chloro-2-[(2-[[3-(furan-3-yl)phenyl]amino]-2-oxoethoxy)acetyl]amino benzoic acid, 5-Chloro-2-[[[3-(furan-3-yl)phenyl]amino](oxo)acetyl]amino benzoic acid, a benzopyran compound, a butadiene, spironolactone, imidapril, an angiotensin converting enzyme inhibitor (ACEI, captopril, or enalapril), an angiotensin II receptor antagonist (AIIIRA), a defibrotide (a polydeoxyribonucleotide), and any combination thereof. In some embodiments, a PAI-1 inhibitor is 5-Chloro-2-[(2-[[3-(furan-3-yl)phenyl]amino]-2-oxoethoxy)acetyl]amino benzoic acid.

[0027] In some embodiments, a PAI-1 inhibitor is delivered in an amount sufficient to reduce graying of one or more hairs.

[0028] In some embodiments, a PAI-1 inhibitor is delivered in an amount sufficient to treat a dermatological condition.

[0029] In some embodiments, a PAI-1 inhibitor is delivered in an amount sufficient to treat a non-dermatological condition. In some embodiments, a non-dermatological condition is lung fibrosis, lung cancer, chronic myeloid leukemia, metabolic syndrome, diabetes, thrombosis, obesity, kidney fibrosis, liver fibrosis, cardiac fibrosis, or atherosclerosis.

[0030] In some embodiments, a composition (e.g., an improved composition) is characterized in that, when administered to an animal comprising one or more gray hairs, achieves at least one of: (i) reduction in number of a plurality of gray hairs; (ii) restoration of color of one or more gray hairs; (iii) prevention of graying of one or more non-gray hairs; and (iv) a delayed onset of graying of one or more non-gray hairs. In some embodiments, a composition is characterized in that, when administered to an animal comprising a one or more hairs, achieves at least one of: (i) a reduction in hair loss; (ii) prevention of hair loss; (iii) a delayed onset of hair loss of one or more hairs; and (iv) an increase in number of hairs on a site.

[0031] Among other things, in some embodiments, provided herein are methods of treating or preventing hair graying.

[0032] Among other things, in some embodiments, provided herein are methods of treating or preventing hair loss.

[0033] Among other things, in some embodiments, provided herein are methods of treating or preventing a dermatological condition.

[0034] In some embodiments, methods described herein comprise (i) providing a composition (e.g., an improved composition) described herein and (ii) administering a composition to a site of a subject. In some embodiments, a site contains or did contain a plurality of hair follicles, each with a hair disposed therein, so that a PAI-1 inhibitor is delivered to a subject. In some embodiments, a hair is gray. In some embodiments, a hair is not gray.

[0035] In some embodiments, provided compositions (e.g., improved compositions) are administered in combination with microneedle skin conditioning (MSC) of a site. In some embodiments, MSC of a site is performed before applying a composition described herein. In some embodiments, MSC of a site is performed after applying a composition described herein. In some embodiments, MSC of a site and administration of a composition described herein occur at substantially the same time. In some embodiments, administration further comprises administering a plurality of doses of a composition described herein according to a dosing regimen in which at least two successive doses are separated from one another by a time period of at least 12 hours.

[0036] In some embodiments, a dermatological condition is keloids or scleroderma. In some embodiments, methods described herein further comprise administering one or more other active agents, wherein one or more other active agents is selected from a group comprising of pressure therapy, silicone gel sheeting, intra-lesional triamcinolone acetonide (TAC), cryosurgery, radiation, laser therapy, IFN, 5-FU, high doses of oxygen using hyperbaric oxygen therapy (HBOT), cryotherapy, surgical excision, topical agents, and combinations thereof.

[0037] In some embodiments, a dermatological condition is scleroderma. In some embodiments, a dermatological condition is systemic scleroderma. In some embodiments, a dermatological condition is cutaneous scleroderma. In some embodiments, methods described herein further comprise administering one or more other active agents, wherein a

one or more other active agents is selected from the group comprising of Angiotensin II Receptor Antagonists, Angiotensin Converting Enzyme (ACE) Inhibitors, NSAIDs, COX-2 Inhibitors, Analgesics, Low-Dose Corticosteroids, Narcotics, Antacids, H2 Blockers, Proton Pump Inhibitors, Prokinetic Agents, Somatostatin Agonist, Antibiotics, Prostaglandin Derivatives, Treprostinil, Iloprost, Endothelin Receptor Antagonists, IP Receptor Agonist, Phosphodiesterase type 5 (PDE5) inhibitors, Anti-Fibrotic Agent, Tyrosine Kinase Inhibitor, Immunosuppressants, Alkylating agents, Pilocarpine, and combinations thereof.

[0038] In some embodiments, a dermatological condition is Raynaud's phenomenon. In some embodiments, methods described herein further comprise administering one or more other active agents, wherein a one or more other active agents is selected from a group comprising of calcium channel blockers, alpha blockers, nitroglycerin, angiotensin II receptor antagonists, selective serotonin reuptake inhibitors, glyceryl trinitrate, tadalafil, *Ginkgo biloba* extract, SLx-2101, St. John's Wort, fasudil, cilostazol, iloprost, relaxin, treprostinil diethanolamine, sildenafil, atorvastatin, imatinib mesylate, treprostinil diethanolamine, and combinations thereof.

[0039] In some embodiments, a dermatological condition is or comprises hair graying. In some embodiments, methods described herein further comprise administering one or more other active agents, wherein a one or more other active agents is selected from a group comprising of cinnamidopropyltrimonium chloride, solid lipid nanoparticles, l-cystine, l-methionine, melatonin, and combinations thereof.

[0040] In some embodiments, in methods described herein, administering comprises maintaining a composition (e.g., an improved composition) on a skin surface for a period of time. In some embodiments, methods described herein further comprise, after a period of time, removing remaining composition from a site. In some embodiments, a step of administering a composition comprises massaging a composition into a site. In some embodiments, a period of time is at least 1 minute. In some embodiments, a period of time is at least 1 hour. In some embodiments, a period of time is within a range of 1 to 10 minutes.

[0041] In some embodiments, a composition (e.g., an improved composition) is or comprises a suspension. In some embodiments, a composition is or comprises a foam. In some embodiments, a composition comprises an emulsion. In some embodiments, an emulsion is a nanoemulsion.

[0042] In some embodiments, methods described herein further comprise a step of administering a penetrating treatment. In some embodiments, a penetrating treatment is or comprises a non-irritating chemical agent. In some embodiments, a penetrating treatment is or comprises administration of an electric or magnetic field. In some embodiments, a penetrating treatment is or comprises microneedling. In some embodiments, a penetrating treatment is or comprises laser treatment.

[0043] In some embodiments, a PAI-1 inhibitor penetrates a site within about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 minutes of administration. In some embodiments, a PAI-1 inhibitor penetrates a site within about 5 to about 60 minutes, about 5 to about 12 minutes, about 5 to about 15 minutes, or about 15 to about 30 minutes of administration. In some embodiments, a PAI-1 inhibitor penetrates a site within about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or 24 hours of administration. In some embodiments, a PAI-1 inhibitor penetrates a site within about 1 to about 12 hours, about 8 to about 12 hours or 12 hours to about 24 hours of administration.

[0044] In some embodiments, methods described herein comprise more than one administration of a composition (e.g., an improved composition) over time. In some embodiments, each administration comprising a PAI-1 inhibitor is separated by a specified period of time.

[0045] Among other things, in some embodiments, the present disclosure provides compositions (e.g., improved compositions) for use in treating a dermatological condition.

[0046] Among other things, in some embodiments, the present disclosure provides compositions (e.g., improved compositions) for use in treating or preventing hair graying.

[0047] Among other things, in some embodiments, the present disclosure provides compositions (e.g., improved compositions) for use in treating or preventing hair loss. In some embodiments, hair loss is androgenetic alopecia, alopecia areata, frontal fibrosing alopecia, and senescent alopecia.

[0048] In some embodiments, provided compositions (e.g., improved compositions) are for use in the manufacture of a medicament for treatment of hair graying.

[0049] In some embodiments, provided compositions (e.g., improved compositions) are for use in the manufacture of a medicament for treatment of hair loss.

[0050] In some embodiments, provided compositions (e.g., improved compositions) are for use in the manufacture of a medicament for treatment of a dermatological condition.

In some embodiments, a dermatological condition is selected from scleroderma, keloids, Raynaud's phenomenon, or hair graying.

[0051] Among other things, in some embodiments, the present disclosure provides kits comprising a composition (e.g., an improved composition) described herein and instructions for administering a composition to a site. In some embodiments, a kit further comprises gloves. In some embodiments, provided kits further comprise a patch for use in covering a composition after administration to a site.

[0052] In some embodiments, provided kits further comprise a device for facilitating penetration of a composition (e.g., an improved composition) into a site on a subject, and instructions for administering a composition to a site. In some embodiments, a device comprises a plurality of needles. In some embodiments, a device is a patch, a roller, stamp, or pen.

[0053] In some embodiments, provided compositions (e.g., improved compositions) are formulated as a lotion, serum, suspension, cream, powder, ointment, liniment, gel, drops, ointment, emollient, balm, or paste.

[0054] These, and other aspects encompassed by the present disclosure, are described in more detail below and in the claims.

## DEFINITIONS

[0055] In this application, unless otherwise clear from context, (i) the term "a" may be understood to mean "at least one"; (ii) the term "or" may be understood to mean "and/or"; (iii) the terms "comprising" and "including" may be understood to encompass itemized components or steps whether presented by themselves or together with one or more additional components or steps; and (iv) the terms "about" and "approximately" may be understood to permit standard variation as would be understood by those of ordinary skill in the art; and (v) where ranges are provided, endpoints are included.

[0056] **About:** The term "about", when used herein in reference to a value, refers to a value that is similar, in context to the referenced value. In general, those skilled in the art, familiar with the context, will appreciate the relevant degree of variance encompassed by "about" in that context. For example, in some embodiments, the term "about" may

encompass a range of values that within 25%, 20%, 19%, 18%, 17%, 16%, 15%, 14%, 13%, 12%, 11%, 10%, 9%, 8%, 7%, 6%, 5%, 4%, 3%, 2%, 1%, or less of the referred value.

**[0057]**        *Administration:* As used herein, the term “administration” typically refers to the administration of a composition to a subject or system to achieve delivery of an agent that is, or is included in, a composition. Those of ordinary skill in the art will be aware of a variety of routes that may, in appropriate circumstances, be utilized for administration to a subject, for example a human. For example, in some embodiments, administration may be ocular, oral, parenteral, topical, etc.. In some particular embodiments, administration may be bronchial (e.g., by bronchial instillation), buccal, dermal (which may be or comprise, for example, one or more of topical to the dermis, intradermal, interdermal, transdermal, etc), enteral, intra-arterial, intradermal, intragastric, intramedullary, intramuscular, intranasal, intraperitoneal, intrathecal, intravenous, intraventricular, within a specific organ (e. g. intrahepatic), mucosal, nasal, oral, rectal, subcutaneous, sublingual, topical, tracheal (e.g., by intratracheal instillation), vaginal, vitreal, etc. In some embodiments, administration may involve only a single dose. In some embodiments, administration may involve application of a fixed number of doses. In some embodiments, administration may involve dosing that is intermittent (e.g., a plurality of doses separated in time) and/or periodic (e.g., individual doses separated by a common period of time) dosing. In some embodiments, administration may involve continuous dosing (e.g., perfusion) for at least a selected period of time.

**[0058]**        *Agent :* In general, the term “agent”, as used herein, may be used to refer to a compound or entity of any chemical class including, for example, a polypeptide, nucleic acid, saccharide, lipid, small molecule, metal, or combination or complex thereof. In appropriate circumstances, as will be clear from context to those skilled in the art, the term may be utilized to refer to an entity that is or comprises a cell or organism, or a fraction, extract, or component thereof. Alternatively or additionally, as context will make clear, the term may be used to refer to a natural product in that it is found in and/or is obtained from nature. In some instances, again as will be clear from context, the term may be used to refer to one or more entities that is man-made in that it is designed, engineered, and/or produced through action of the hand of man and/or is not found in nature. In some embodiments, an agent may be utilized in isolated or pure form; in some embodiments, an agent may be utilized in crude form. In some embodiments, potential agents may be provided as collections or libraries, for example that may be screened to identify or characterize active agents within them. In some cases, the term “agent” may refer to a compound or entity that

is or comprises a polymer; in some cases, the term may refer to a compound or entity that comprises one or more polymeric moieties. In some embodiments, the term “agent” may refer to a compound or entity that is not a polymer and/or is substantially free of any polymer and/or of one or more particular polymeric moieties. In some embodiments, the term may refer to a compound or entity that lacks or is substantially free of any polymeric moiety.

**[0059]** *Agonist:* Those skilled in the art will appreciate that the term “agonist” may be used to refer to an agent condition, or event whose presence, level, degree, type, or form correlates with increased level or activity of another agent (i.e., the agonized agent). In general, an agonist may be or include an agent of any chemical class including, for example, small molecules, polypeptides, nucleic acids, carbohydrates, lipids, metals, and/or any other entity that shows the relevant activating activity. In some embodiments, an agonist may be direct (in which case it exerts its influence directly upon its target); in some embodiments, an agonist may be indirect (in which case it exerts its influence by other than binding to its target; e.g., by interacting with a regulator of the target, so that level or activity of the target is altered).

**[0060]** *Antagonist:* Those skilled in the art will appreciate that the term “antagonist”, as used herein, may be used to refer to an agent condition, or event whose presence, level, degree, type, or form correlates with decreased level or activity of another agent (i.e., the inhibited agent, or target). In general, an antagonist may be or include an agent of any chemical class including, for example, small molecules, polypeptides, nucleic acids, carbohydrates, lipids, metals, and/or any other entity that shows the relevant inhibitory activity. In some embodiments, an antagonist may be direct (in which case it exerts its influence directly upon its target); in some embodiments, an antagonist may be indirect (in which case it exerts its influence by other than binding to its target; e.g., by interacting with a regulator of the target, so that level or activity of the target is altered).

**[0061]** *Animal:* As used herein refers to any member of the animal kingdom. In some embodiments, “animal” refers to humans, of either sex and at any stage of development. In some embodiments, “animal” refers to non-human animals, at any stage of development. In certain embodiments, the non-human animal is a mammal (e.g., a rodent, a mouse, a rat, a rabbit, a monkey, a dog, a cat, a sheep, cattle, a primate, and/or a pig). In some embodiments, animals include, but are not limited to, mammals, birds, reptiles,

amphibians, fish, insects, and/or worms. In some embodiments, an animal may be a transgenic animal, genetically engineered animal, and/or a clone.

**[0062]      *Biologically active agent:*** As used herein, the phrase “biologically active agent” refers to any substance that has activity in a biological system and/or organism. For instance, a substance that, when administered to an organism, has a biological effect on that organism is considered to be biologically active. In some embodiments, where a substance (*e.g.*, a polypeptide, nucleic acid, antibody, *etc.*) is biologically active, a portion of that substance that shares at least one biological activity of the whole substance is typically referred to as a “biologically active” portion.

**[0063]      *Carrier:*** as used herein, refers to a diluent, adjuvant, excipient, or vehicle with which a composition is administered. In some exemplary embodiments, carriers can include sterile liquids, such as, for example, water and oils, including oils of petroleum, animal, vegetable or synthetic origin, such as, for example, peanut oil, soybean oil, mineral oil, sesame oil and the like. In some embodiments, carriers are or include one or more solid components.

**[0064]      *Cosmetic formulation:*** The term “cosmetic formulation” is used herein to refer to a topically applied composition that contains one or more agents having cosmetic properties. To give but a few examples, a cosmetic formulation may be a skin softener, nutrition lotion type emulsion, cleansing lotion, cleansing cream, skin milk, emollient lotion, massage cream, emollient cream, make-up base, lipstick, facial pack or facial gel, cleaner formulation such as shampoos, rinses, body cleanser, hair-tonics, or soaps, and/or a dermatological composition such as a lotion, ointment, gel, cream, patch, emollient, balm, paste, deodorant, antiperspirant, and/or spray.

**[0065]      *Composition:*** Those skilled in the art will appreciate that the term “composition”, as used herein, may be used to refer to a discrete physical entity that comprises one or more specified components. In general, unless otherwise specified, a composition may be of any form – *e.g.*, gas, gel, liquid, solid, *etc.*

**[0066]      *Comprising:*** A composition or method described herein as “comprising” one or more named elements or steps is open-ended, meaning that the named elements or steps are essential, but other elements or steps may be added within the scope of the composition or method. To avoid prolixity, it is also understood that any composition or method described as “comprising” (or which “comprises”) one or more named elements or steps also

describes the corresponding, more limited composition or method "consisting essentially of" (or which "consists essentially of") the same named elements or steps, meaning that the composition or method includes the named essential elements or steps and may also include additional elements or steps that do not materially affect the basic and novel characteristic(s) of the composition or method. It is also understood that any composition or method described herein as "comprising" or "consisting essentially of" one or more named elements or steps also describes the corresponding, more limited, and closed-ended composition or method "consisting of" (or "consists of") the named elements or steps to the exclusion of any other unnamed element or step. In any composition or method disclosed herein, known or disclosed equivalents of any named essential element or step may be substituted for that element or step.

[0067] ***Cream:*** The term "cream" refers to a spreadable composition, typically formulated for application to skin. Creams typically contain an oil and/or fatty acid based-matrix. Creams formulated according to the present disclosure may contain nanoparticles and may be capable of substantially complete penetration (e.g., of such nanoparticles) through skin upon topical administration. Such a cream could also act as a carrier for incorporated materials (e.g., for example, for one or more known therapeutic agents and/or independently active biologically active agents).

[0068] ***Dispersion medium:*** The term "dispersion medium" as used herein, refers to a liquid medium in which particles (e.g., empty nanoparticles and/or nanoparticles containing one or more known therapeutic agents and/or independently active biologically active agents) are dispersed. In general, a dispersion is formed when at least two immiscible materials are combined. An "oil-in-water" dispersion is one in which oily particles are dispersed within an aqueous dispersion medium. A "water-in-oil" dispersion is one in which aqueous particles are dispersed within an oily dispersion medium. Those of ordinary skill in the art will appreciate that a dispersion can be formed from any two immiscible media and is not limited strictly to combinations of aqueous and oily media. The term "dispersion medium" therefore applies broadly to any dispersion medium notwithstanding that it is common to refer to "aqueous" and "oily" categories.

[0069] ***Dosage form or unit dosage form:*** Those skilled in the art will appreciate that the term "dosage form" may be used to refer to a physically discrete unit of an active agent (e.g., a therapeutic or diagnostic agent) for administration to a subject. Typically, each

such unit contains a predetermined quantity of active agent. In some embodiments, such quantity is a unit dosage amount (or a whole fraction thereof) appropriate for administration in accordance with a dosing regimen that has been determined to correlate with a desired or beneficial outcome when administered to a relevant population (i.e., with a therapeutic dosing regimen). Those of ordinary skill in the art appreciate that the total amount of a therapeutic composition or agent administered to a particular subject is determined by one or more attending physicians and may involve administration of multiple dosage forms.

[0070] ***Dosing regimen:*** Those skilled in the art will appreciate that the term “dosing regimen” may be used to refer to a set of unit doses (typically more than one) that are administered individually to a subject, typically separated by periods of time. In some embodiments, a given therapeutic agent has a recommended dosing regimen, which may involve one or more doses. In some embodiments, a dosing regimen comprises a plurality of doses each of which is separated in time from other doses. In some embodiments, individual doses are separated from one another by a time period of the same length; in some embodiments, a dosing regimen comprises a plurality of doses and at least two different time periods separating individual doses. In some embodiments, all doses within a dosing regimen are of the same unit dose amount. In some embodiments, different doses within a dosing regimen are of different amounts. In some embodiments, a dosing regimen comprises a first dose in a first dose amount, followed by one or more additional doses in a second dose amount different from the first dose amount. In some embodiments, a dosing regimen comprises a first dose in a first dose amount, followed by one or more additional doses in a second dose amount same as the first dose amount. In some embodiments, a dosing regimen is correlated with a desired or beneficial outcome when administered across a relevant population (i.e., is a therapeutic dosing regimen).

[0071] ***Excipient:*** as used herein, refers to a non-therapeutic agent that may be included in a pharmaceutical composition, for example to provide or contribute to a desired consistency or stabilizing effect. In some embodiments, suitable pharmaceutical excipients may include, for example, starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like.

[0072] ***In vitro***: The term “in vitro” as used herein refers to events that occur in an artificial environment, e.g., in a test tube or reaction vessel, in cell culture, etc., rather than within a multi-cellular organism.

[0073] ***In vivo***: as used herein refers to events that occur within a multi-cellular organism, such as a human and a non-human animal. In the context of cell-based systems, the term may be used to refer to events that occur within a living cell (as opposed to, for example, *in vitro* systems).

[0074] ***Macroemulsion***: The term “macroemulsion,” as used herein, refers to an emulsion in which at least some droplets have diameters in the several hundred nanometers to micrometers size range. As will be understood by those of ordinary skill in the art, a macroemulsion is characterized by droplets greater than 300 nm in diameter. In some embodiments, a macroemulsion composition utilized in accordance with the present disclosure includes one or more large agents or one or more biologically active agents. In some embodiments, a large agent included in a macroemulsion composition may be a biologically active agent. It will be appreciated by those of ordinary skill in the art that a macroemulsion composition for use in accordance with the present disclosure may be prepared according to any available means including, for example, chemical or mechanical means. In some embodiments, droplets in a macroemulsion have a size within a range of about 301 nm and about 1000  $\mu\text{m}$ . In some embodiments, a macroemulsion has droplets in a size distribution of between about 301 nm and about 1000  $\mu\text{m}$ . In some embodiments, droplets in a macroemulsion have a size within a range of about 500 nm and about 5000  $\mu\text{m}$ . In some embodiments, a macroemulsion has droplets in a size distribution of between about 500 nm and about 5000  $\mu\text{m}$ .

[0075] ***Nanoemulsion***: The term “nanoemulsion,” as used herein, refers to an emulsion in which at least some droplets have diameters in the nanometer size range. As will be understood by those of ordinary skill in the art, a nanoemulsion is characterized by droplets 300 nm or smaller in diameter. In some embodiments, a nanoemulsion composition utilized in accordance with the present disclosure includes one or more large agents or one or more biologically active agents. In some embodiments, a large agent included in a nanoemulsion composition may be a biologically active agent. It will be appreciated by those of ordinary skill in the art that a nanoemulsion composition for use in accordance with the present disclosure may be prepared according to any available means including, for

example, chemical or mechanical means. In some embodiments, droplets in a nanoemulsion have a size within a range of about 1 nm and about 300 nm. In some embodiments, a nanoemulsion has droplets in a size distribution of between about 1 nm and about 300 nm.

**[0076]**        *Nanoparticle:* As used herein, the term “nanoparticle” refers to a solid particle having a diameter of less than 300 nm, as defined by the National Science Foundation. In some embodiments, a nanoparticle has a diameter of less than 100 nm as defined by the National Institutes of Health.

**[0077]**        *Nanoparticle composition:* As used herein, the term “nanoparticle composition” refers to any substance that contains at least one nanoparticle. In some embodiments, a nanoparticle composition is a uniform collection of nanoparticles. In some embodiments, nanoparticle compositions are dispersions or emulsions. In general, a dispersion or emulsion is formed when at least two immiscible materials are combined. An “oil-in-water” dispersion is one in which oily particles (or hydrophobic or non-polar) are dispersed within an aqueous dispersion medium. A “water-in-oil” dispersion is one in which aqueous (or hydrophilic or polar) particles are dispersed within an oily dispersion medium. Those of ordinary skill in the art will appreciate that a dispersion can be formed from any two immiscible media and is not limited strictly to combinations of aqueous and oily media. The term “dispersion medium” therefore applies broadly to any dispersion medium notwithstanding that it is common to refer to “aqueous” and “oily” categories. In some embodiments, nanoparticle compositions are nanoemulsions. In some embodiments, nanoparticle compositions comprise micelles. In some embodiments, nanoparticle compositions are stable. In some embodiments, nanoparticle compositions include one or more biologically active agents to be delivered in conjunction with the nanoparticles. In some embodiments, nanoparticle compositions are empty nanoparticle compositions (e.g., they do not contain any known therapeutic agents and/or independently active biologically active agents).

**[0078]**        *Pharmaceutical composition:* As used herein, the term “pharmaceutical composition” refers to a composition in which an active agent is formulated together with one or more pharmaceutically acceptable carriers. In some embodiments, the active agent is present in unit dose amount appropriate for administration in a therapeutic regimen that shows a statistically significant probability of achieving a predetermined therapeutic effect when administered to a relevant population. In some embodiments, a pharmaceutical

composition may be specially formulated for administration in solid or liquid form, including those adapted for the following: oral administration, for example, drenches (aqueous or non-aqueous solutions or suspensions), tablets, e.g., those targeted for buccal, sublingual, and systemic absorption, boluses, powders, granules, pastes for application to the tongue; parenteral administration, for example, by subcutaneous, intramuscular, intravenous or epidural injection as, for example, a sterile solution or suspension, or sustained-release formulation; topical application, for example, as a cream, ointment, or a controlled-release patch or spray applied to the skin, lungs, or oral cavity; intravaginally or intrarectally, for example, as a pessary, cream, or foam; sublingually; ocularly; transdermally; or nasally, pulmonary, and to other mucosal surfaces.

**[0079] Penetration enhancing agent or Penetrating Treatment:** As used herein, the term “penetration enhancing agent” or “penetrating treatment” refers to an agent whose presence or level correlates with increased penetration of an agent of interest across skin, as compared with that observed in its absence. In some embodiments, a penetration enhancing agent is characterized in that it degrades and/or disrupts skin structure. In some embodiments, a penetration enhancing agent is or comprises a chemical agent (e.g., a chemical or enzyme, for example) For example, chemical agents that that may damage, disrupt, and/or degrade one or more stratum corneum components) may include, for example, alcohols, such as short chain alcohols, long chain alcohols, or polyalcohols; amines and amides, such as urea, amino acids or their esters, amides, AZONE®, derivatives of AZONE®, pyrrolidones, or derivatives of pyrrolidones; terpenes and derivatives of terpenes; fatty acids and their esters; macrocyclic compounds; tensides; or sulfoxides (e.g., dimethylsulfoxide (DMSO), decylmethylsulfoxide, etc.); surfactants, such as anionic, cationic, and nonionic surfactants; polyols; essential oils; and/or hyaluronidase. In some embodiments, a penetration enhancing agent may be an irritant in that an inflammatory and/or allergic reaction occurs when the agent is applied to skin. In some embodiments, a penetration enhancing agent is not an irritant. In some embodiments, a penetration enhancing agent may be or comprise a chemical agent that does not damage, disrupt, or degrade skin structure but whose presence or level nonetheless correlates with increased penetration of an agent of interest across skin, as compared with that observed in its absence. In some embodiments, co-peptides, carrier molecules, and carrier peptides may be penetration enhancing agents which do not damage, disrupt, and/or degrade skin structure(s). In some embodiments, co-peptides, carrier molecules, and carrier peptides may

be penetration enhancing agents which do not irritate the skin. The term “penetration enhancing agent” does not encompass mechanical devices (e.g., needles, scalpels, etc.), or equivalents thereof (e.g., other damaging treatments). Also, those skilled in the art will appreciate that a structure such as a nanoparticle or an emulsion is not a chemical agent and therefore not a chemical penetration enhancing agent even if its presence correlates with enhanced skin penetration of an agent of interest that may be associated with the structure.

**[0080]**        *Pharmaceutically acceptable carrier:* As used herein, the term “pharmaceutically acceptable carrier” means a pharmaceutically-acceptable material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, or solvent encapsulating material, involved in carrying or transporting the subject compound from one organ, or portion of the body, to another organ, or portion of the body. Each carrier must be “acceptable” in the sense of being compatible with the other ingredients of the formulation and not injurious to the patient. Some examples of materials which can serve as pharmaceutically-acceptable carriers include: sugars, such as lactose, glucose and sucrose; starches, such as corn starch and potato starch; cellulose, and its derivatives, such as sodium carboxymethyl cellulose, ethyl cellulose and cellulose acetate; powdered tragacanth; malt; gelatin; talc; excipients, such as cocoa butter and suppository waxes; oils, such as peanut oil, cottonseed oil, safflower oil, sesame oil, olive oil, corn oil and soybean oil; glycols, such as propylene glycol; polyols, such as glycerin, sorbitol, mannitol and polyethylene glycol; esters, such as ethyl oleate and ethyl laurate; agar; buffering agents, such as magnesium hydroxide and aluminum hydroxide; alginic acid; pyrogen-free water; isotonic saline; Ringer’s solution; ethyl alcohol; pH buffered solutions; polyesters, polycarbonates and/or polyanhydrides; and other non-toxic compatible substances employed in pharmaceutical formulations.

**[0081]**        *Prevent or prevention:* As used herein when used in connection with the occurrence of a disease, disorder, and/or condition, refers to reducing the risk of developing the disease, disorder and/or condition and/or to delaying onset of one or more characteristics or symptoms of the disease, disorder or condition. Prevention may be considered complete when onset of a disease, disorder or condition has been delayed for a predefined period of time.

**[0082]**        *Self-administration:* The term “self-administration,” as used herein, refers to the situation where a subject has the ability to administer a composition to him or herself

without requiring medical supervision. In some embodiments of the invention, self-administration may be performed outside of a clinical setting. To give but one example, in some embodiments of the invention, a facial cosmetic cream may be administered by a subject in one's own home.

**[0083]**        *Serum:* Those skilled in the art will appreciate that the term “serum”, as used herein, may be used refer to a liquid composition. In some embodiments, a serum may comprise a concentrated amount of an active agent. In some embodiments, a serum may be used to topically deliver an active agent. In some embodiments, a serum may refer to a spreadable composition.

**[0084]**        *Small molecule:* As used herein, the term “small molecule” means a low molecular weight organic and/or inorganic compound. In general, a “small molecule” is a molecule that is less than about 5 kilodaltons (kD) in size. In some embodiments, a small molecule is less than about 4 kD, 3 kD, about 2 kD, or about 1 kD. In some embodiments, the small molecule is less than about 800 daltons (D), about 600 D, about 500 D, about 400 D, about 300 D, about 200 D, or about 100 D. In some embodiments, a small molecule is less than about 2000 g/mol, less than about 1500 g/mol, less than about 1000 g/mol, less than about 800 g/mol, or less than about 500 g/mol. In some embodiments, a small molecule is not a polymer. In some embodiments, a small molecule does not include a polymeric moiety. In some embodiments, a small molecule is not and/or does not comprise a protein or polypeptide (e.g., is not an oligopeptide or peptide). In some embodiments, a small molecule is not and/or does not comprise a polynucleotide (e.g., is not an oligonucleotide). In some embodiments, a small molecule is not and/or does not comprise a polysaccharide; for example, in some embodiments, a small molecule is not a glycoprotein, proteoglycan, glycolipid, *etc.*). In some embodiments, a small molecule is not a lipid. In some embodiments, a small molecule is a modulating agent (e.g., is an inhibiting agent or an activating agent). In some embodiments, a small molecule is biologically active. In some embodiments, a small molecule is detectable (e.g., comprises at least one detectable moiety). In some embodiments, a small molecule is a therapeutic agent. Those of ordinary skill in the art, reading the present disclosure, will appreciate that certain small molecule compounds described herein may be provided and/or utilized in any of a variety of forms such as, for example, crystal forms, salt forms, protected forms, pro-drug forms, ester forms, isomeric forms (e.g., optical and/or structural isomers), isotopic forms, etc. Those of skill in the art will appreciate that certain small molecule compounds have structures that can exist

in one or more stereoisomeric forms. In some embodiments, such a small molecule may be utilized in accordance with the present disclosure in the form of an individual enantiomer, diastereomer or geometric isomer, or may be in the form of a mixture of stereoisomers; in some embodiments, such a small molecule may be utilized in accordance with the present disclosure in a racemic mixture form. Those of skill in the art will appreciate that certain small molecule compounds have structures that can exist in one or more tautomeric forms. In some embodiments, such a small molecule may be utilized in accordance with the present disclosure in the form of an individual tautomer, or in a form that interconverts between tautomeric forms. Those of skill in the art will appreciate that certain small molecule compounds have structures that permit isotopic substitution (e.g.,  $^2\text{H}$  or  $^3\text{H}$  for  $\text{H}$ ;  $^{11}\text{C}$ ,  $^{13}\text{C}$  or  $^{14}\text{C}$  for  $^{12}\text{C}$ ;  $^{13}\text{N}$  or  $^{15}\text{N}$  for  $^{14}\text{N}$ ;  $^{17}\text{O}$  or  $^{18}\text{O}$  for  $^{16}\text{O}$ ;  $^{36}\text{Cl}$  for  $\text{XXC}$ ;  $^{18}\text{F}$  for  $\text{XXF}$ ;  $^{131}\text{I}$  for  $\text{XXXI}$ ; etc). In some embodiments, such a small molecule may be utilized in accordance with the present disclosure in one or more isotopically modified forms, or mixtures thereof. In some embodiments, reference to a particular small molecule compound may relate to a specific form of that compound. In some embodiments, a particular small molecule compound may be provided and/or utilized in a salt form (e.g., in an acid-addition or base-addition salt form, depending on the compound); in some such embodiments, the salt form may be a pharmaceutically acceptable salt form. In some embodiments, where a small molecule compound is one that exists or is found in nature, that compound may be provided and/or utilized in accordance in the present disclosure in a form different from that in which it exists or is found in nature. Those of ordinary skill in the art will appreciate that, in some embodiments, a preparation of a particular small molecule compound that contains an absolute or relative amount of the compound, or of a particular form thereof, that is different from the absolute or relative (with respect to another component of the preparation including, for example, another form of the compound) amount of the compound or form that is present in a reference preparation of interest (e.g., in a primary sample from a source of interest such as a biological or environmental source) is distinct from the compound as it exists in the reference preparation or source. Thus, in some embodiments, for example, a preparation of a single stereoisomer of a small molecule compound may be considered to be a different form of the compound than a racemic mixture of the compound; a particular salt of a small molecule compound may be considered to be a different form from another salt form of the compound; a preparation that contains only a form of the compound that contains one conformational isomer ((Z) or (E)) of a double bond may be considered to be a

different form of the compound from one that contains the other conformational isomer ((E) or (Z)) of the double bond; a preparation in which one or more atoms is a different isotope than is present in a reference preparation may be considered to be a different form; etc.

**[0085]        *Subject:*** As used herein, the term “subject” refers an organism, typically a mammal (e.g., a human, in some embodiments including prenatal human forms). In some embodiments, a subject is suffering from a relevant disease, disorder or condition. In some embodiments, a subject is susceptible to a disease, disorder, or condition. In some embodiments, a subject displays one or more symptoms or characteristics of a disease, disorder or condition. In some embodiments, a subject does not display any symptom or characteristic of a disease, disorder, or condition. In some embodiments, a subject is someone with one or more features characteristic of susceptibility to or risk of a disease, disorder, or condition. In some embodiments, a subject is a patient. In some embodiments, a subject is an individual to whom diagnosis and/or therapy is and/or has been administered.

**[0086]        *Suspension:*** Those skilled in the art will appreciate that the term “suspension”, as used herein, may be used to refer to a heterogeneous mixture. In some embodiments, a suspension may comprise particles suspended in a liquid. In some embodiments, a suspension may be used to deliver an active agent. In some embodiments, a suspension may be used to topically deliver an active agent. In some embodiments, a suspension may refer to a spreadable composition.

**[0087]        *Symptoms are reduced:*** As used herein, the term “symptoms are reduced” refers to when one or more symptoms of a particular disease, disorder or condition is reduced in magnitude (e.g., intensity, severity, etc.) and/or frequency. For purposes of clarity, a delay in the onset of a particular symptom is considered one form of reducing the frequency of that symptom.

**[0088]        *Therapeutic agent:*** As used herein, the term “therapeutic agent” refers to any agent that has a therapeutic effect and/or elicits a desired biological and/or pharmacological effect, when administered to a subject. In some embodiments, a therapeutic agent is an active agent as described herein.

**[0089]        *Therapeutically effective amount:*** As used herein, is meant an amount that produces the desired effect for which it is administered. In some embodiments, the term refers to an amount that is sufficient, when administered to a population suffering from or susceptible to a disease, disorder, and/or condition in accordance with a therapeutic dosing

regimen, to treat the disease, disorder, and/or condition. In some embodiments, a therapeutically effective amount is one that reduces the incidence and/or severity of, and/or delays onset of, one or more symptoms of the disease, disorder, and/or condition. Those of ordinary skill in the art will appreciate that the term "*therapeutically effective amount*" does not in fact require successful treatment be achieved in a particular individual. Rather, a therapeutically effective amount may be that amount that provides a particular desired pharmacological response in a significant number of subjects when administered to patients in need of such treatment. In some embodiments, reference to a therapeutically effective amount may be a reference to an amount as measured in one or more specific tissues (e.g., a tissue affected by the disease, disorder or condition) or fluids (e.g., blood, saliva, serum, sweat, tears, urine, etc.). Those of ordinary skill in the art will appreciate that, in some embodiments, a therapeutically effective amount of a particular agent or therapy may be formulated and/or administered in a single dose. In some embodiments, a therapeutically effective agent may be formulated and/or administered in a plurality of doses, for example, as part of a dosing regimen.

[0090] **Treatment:** As used herein, the term "treatment" (also "treat" or "treating") refers to any administration of a therapy that partially or completely alleviates, ameliorates, relieves, inhibits, delays onset of, reduces severity of, and/or reduces incidence of one or more symptoms, features, and/or causes of a particular disease, disorder, and/or condition. In some embodiments, such treatment may be of a subject who does not exhibit signs of the relevant disease, disorder and/or condition and/or of a subject who exhibits only early signs of the disease, disorder, and/or condition. Alternatively or additionally, such treatment may be of a subject who exhibits one or more established signs of the relevant disease, disorder and/or condition. In some embodiments, treatment may be of a subject who has been diagnosed as suffering from the relevant disease, disorder, and/or condition. In some embodiments, treatment may be of a subject known to have one or more susceptibility factors that are statistically correlated with increased risk of development of the relevant disease, disorder, and/or condition.

## BRIEF DESCRIPTION OF THE DRAWINGS

[0091] FIG. 1 shows a bar graph depicting amount of skin penetration measured by cumulative amount ( $\mu\text{g/mL}$ ) of an original composition and an improved composition that comprises and/or delivers a plasminogen activator inhibitor-1 (PAI-1) inhibitor.

### DETAILED DESCRIPTION

[0092] The present disclosure provides, among other things, compositions, methods, and kits formulated for topical application that comprise an active agent. The present disclosure provides, among other things, compositions, methods, and kits formulated for topical application that deliver an active agent. In some embodiments, an active agent is a PAI-1 inhibitor, as described herein.

[0093] In some embodiments, provided compositions, methods, and kits may be or comprise emulsions. In some embodiments provided methods, kits and compositions may be or comprise macroemulsions. In some embodiments, provided methods, and kits may be or comprise nanoemulsions. In some embodiments provided compositions, methods, and kits comprise a combination therapy or treatment, wherein for example, in some embodiments, provided compositions may be administered in combination with one or more additional treatments. In some embodiments a one or more additional treatment is or comprises other active agents and/or therapeutic modalities (e.g., one or more PAI-inhibitors, or other agents), such as known therapeutic agents and/or independently active biologically active agents.

#### Active Agents

[0094] Among other things, as described herein, the present disclosure provides compositions that comprise an active agent. Among other things, as described herein, the present disclosure provides compositions that deliver an active agent. In some embodiments, compositions that comprise or deliver an active agent as described herein can be used to treat a disease, disorder, and/or a condition. In some embodiments, an active agent is a PAI-1 inhibitor.

#### PAI-1 Inhibitors

[0095] PAI-1 inhibitors can be used to treat or prevent medical conditions or diseases associated with over-expression of PAI-1. The present disclosure, in some embodiments, encompasses a recognition that PAI-1 inhibitors may be particularly useful in

the treatment and/or prevention of dermatological conditions, such as hair loss, hair graying, scleroderma, keloids, Raynaud's Phenomenon, etc. While there are some partially effective prevention or treatment for hair loss, there are no highly effective prevention or treatment for hair loss and there are currently no effective prevention or treatment techniques for hair graying. In some embodiments, provided methods and/or compositions provide targeted therapy. For example, in some embodiments, provided methods and compositions provide surprisingly effective therapies comprising one or more PAI-1 inhibitors. Without wishing to be bound by any particular theory, it is proposed that, in some embodiments, administration of a PAI-1 inhibitor as described herein may stimulate Hair Follicle Stem Cells (HFSC) and Melanocyte Stem Cells (MSC), and such stimulation may contribute to treatment or prevention of hair loss and hair graying.

[0096] PAI-1 inhibitors can be antibodies, peptides, polypeptides, proteins, nucleic acids, lipids, carbohydrates, small molecules, metals, polymers, therapeutic antibodies, or any combinations thereof. In some embodiments, a PAI-1 inhibitor is an siRNA. In some embodiments, a PAI-1 inhibitor is a benzopyran compound, a butadiene, spironolactone, imidapril, an angiotensin converting enzyme inhibitor (ACEI, captopril, or enalapril), an angiotensin II receptor antagonist (AIIIRA), a defibrotide (a polydeoxyribonucleotide) and any combination thereof. In some embodiments, a PAI-1 inhibitor is a benzopyran compound.

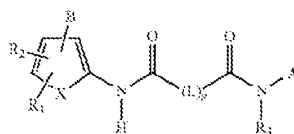
[0097] In some embodiments, a PAI-1 inhibitor is selected from a group consisting of polypeptides, nucleic acids, lipids, carbohydrates, small molecules, metals, polymers, therapeutic antibodies, fragments of therapeutic antibodies, and combinations thereof. In some embodiments, a PAI-1 inhibitor may be a small molecule.

[0098] In some embodiments, a composition comprises or delivers a compound as set forth herein or an active metabolite thereof.

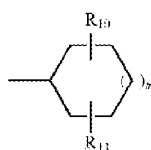
[0099] In some embodiments, a PAI-1 inhibitor is a 2-aminobenzoic acid analog.

[0100] In some embodiments, a PAI-1 inhibitor is a 5-chloro-2-aminobenzoic acid analog.

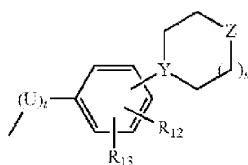
[0101] In some embodiments, a PAI-1 inhibitor is a compound of Formula (1):

**Formula (1)**

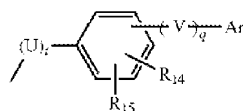
wherein, R<sub>1</sub> and R<sub>2</sub> are the same or different, and each represents hydrogen, halogen, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, cycloalkenyl, alkynyl, hydroxyl, alkoxy, cycloalkoxy, alkenyloxy, cycloalkenyloxy, aryloxy, aralkyl, aralkyloxy, heterocyclic-alkyl, heterocyclicalkyloxy, aryl optionally having one or two substituents, 5- to 6-membered ring heteroaryl optionally having one or two substituents, or benzo-fused heteroaryl optionally having one or two substituents, amino or carbonyl, each of which is optionally substituted with one or two substituents, or cyano, carboxy, or alkoxy-carbonyl; and R<sub>3</sub> and R<sub>2</sub> are optionally adjoined with each other to form a ring; R<sub>3</sub> is hydrogen, alkyl, cycloalkyl, or aryl optionally having one or two substituents; X is -C(R<sub>5</sub>)=C(R<sub>6</sub>)-, -C(R<sub>7</sub>)N-, or -N=C(R<sub>8</sub>)-, wherein R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub> and R<sub>8</sub> each represents hydrogen, halogen, alkyl optionally having one or two substituents, or alkoxy; L is alkylene (some carbon atoms in the alkylene optionally form a cycloalkyl ring), alkenylene, alkynylene, cycloalkylene, alkyleneoxyalkylene, alkyleneethioalkylene, alkylene-SO-alkylene, or alkylene-SO<sub>2</sub>-alkylene, each of which is optionally substituted with one or two substituents, or alkylene-N(R<sub>9</sub>)-alkylene optionally substituted with one or two substituents, wherein R<sub>9</sub> represents hydrogen, or alkyl optionally having one or two substituents; p represents an integer of 0 or 1; A is a group represented by any one of the following Formulae (2), (3), or (4):

**Formula (2)**

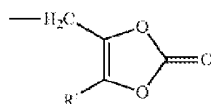
wherein, R<sub>10</sub> and R<sub>11</sub> are the same or different, and each represents hydrogen or straight- or branched-chain alkyl; and m represents an integer of 0 to 10,

**Formula (3)**

wherein,  $R_{12}$  and  $R_{13}$  are the same or different, and each represents hydrogen, halogen, or alkyl optionally having one or two substituents, cycloalkyl optionally having one or two substituents, or alkoxy optionally having one or two substituents; Y represents CH or nitrogen; Z represents  $\text{CH}_2$ , oxygen, or N-alkyl; n represents an integer of 0 to 3; U represents alkylene; and t represents an integer of 0 or 1,

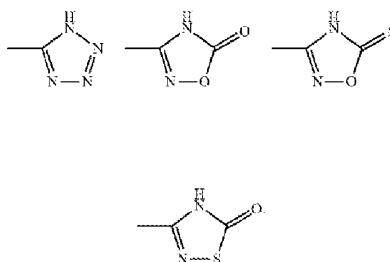
**Formula (4)**

wherein,  $R_{14}$  and  $R_{15}$  are the same or different, and each represents hydrogen, halogen, or alkyl optionally having one or two substituents, cycloalkyl optionally having one or two substituents, or alkoxy optionally having one or two substituents; V is alkylene, alkyleneoxyalkylene, oxyalkylene, alkyleneoxy, or oxygen; q represents an integer of 0 or 1; U and t are as defined above; and Ar represents aryl having one or two substituents (the one or two substituents optionally form a ring with a part of carbon atoms in the aryl group), 5- to 6-membered ring aryl group having one or two identical or different heteroatoms optionally having one or two substituents, or benzo-fused heteroaryl optionally having one to three substituents; and B represents  $\text{COOR}_{16}$ , wherein  $R_{16}$  represents hydrogen, alkyl, aryl or aralkyl, a group represented by  $\text{CH}(\text{R}_{17})\text{O}---\text{COR}_{18}$  or  $---\text{CH}(\text{R}_{17})---\text{O}---\text{CO}---\text{OR}_{18}$ , wherein  $R_{17}$  is hydrogen or alkyl, and  $R_{18}$  is alkyl or cycloalkyl, a (5-alkyl-2-oxo-1,3-dioxolen-4-yl)methyl group represented by the following Formula (5):

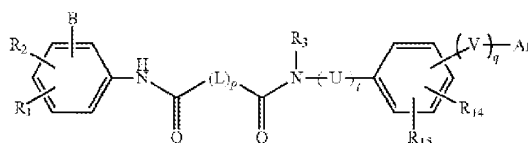


**Formula (5)**

wherein, R' represents alkyl, or a heterocyclic group: a 1H-tetrazol-5-yl group, a 4,5-dihydro-5-oxo-4H-1,2,4-oxadiazol-3-yl group, a 4,5-dihydro-5-thioxo-4H-1,2,4-oxadiazol-3-yl group, or a 4,5-dihydro-5-oxo-1,2,4-thiadiazol-3-yl group, represented by the following Formulae (6), (7), (8) (sequentially from the left), (9) (below):

**Formula (6), (7), (8) (sequentially from the left), (9) (bottom)**

**[0102]** In some embodiments, a PAI-1 inhibitor is a compound of Formula (10)

**Formula (10)**

wherein, R<sub>1</sub> and R<sub>2</sub> are the same or different, and each represents hydrogen, halogen, alkyl, or aryl optionally having one or two substituents; R<sub>3</sub> is hydrogen or alkyl; R<sub>14</sub> and R<sub>15</sub> are the same or different, and each represents hydrogen, alkyl, or halogen; V is alkylene, oxyalkylene, or oxygen; Ar is aryl optionally having one or two substituents, aryl group having one or two identical or different heteroatoms optionally having one or two substituents, or benzofused heteroaryl optionally having one or three substituents; L is alkylene, alkyleneoxyalkylene, alkyleneethioalkylene, alkylene-SO-alkylene, alkylene-SO<sub>2</sub>-alkylene; and q, U, t, p, and B are as defined above.

**[0103]** In some embodiments, a PAI-1 inhibitor is selected from a group consisting of: 5-Chloro-2-[(2-{[3-(furan-3-yl)phenyl]amino}-2-oxoethoxy)acetyl]amino benzoic acid, 5-Chloro-2-[[[3-(furan-3-yl)phenyl]amino](oxo)acetyl]amino benzoic acid, a benzopyran compound, a butadiene, spironolactone, imidapril, an angiotensin converting enzyme

inhibitor (ACEI, captopril, or enalapril), an angiotensin II receptor antagonist (AIIRA), a defibrotide (a polydeoxyribonucleotide), and any combination thereof

[0104] In some embodiments, a PAI-1 inhibitor is 5-Chloro-2-[(2-{[3-(furan-3-yl)phenyl]amino}-2-oxoethoxy)acetyl]amino benzoic acid. In some embodiments, a PAI-1 inhibitor is 5-Chloro-2-[[{[3-(furan-3-yl)phenyl]amino}(oxo)acetyl]amino} benzoic acid.

[0105] Table 1 below lists exemplary PAI-1 inhibitors.

Table 1 Exemplary PAI-1 inhibitors

| Chemical Name                                                                      | Molecular Formula                                               | Molecular Weight |
|------------------------------------------------------------------------------------|-----------------------------------------------------------------|------------------|
| 5-Chloro-2-[(2-{[3-(furan-3-yl)phenyl]amino}-2-oxoethoxy)acetyl]amino benzoic acid | C <sub>21</sub> H <sub>17</sub> ClN <sub>2</sub> O <sub>6</sub> | 428.82           |
| 5-Chloro-2-[[{[3-(furan-3-yl)phenyl]amino}(oxo)acetyl]amino} benzoic acid          | C <sub>19</sub> H <sub>13</sub> ClN <sub>2</sub> O <sub>5</sub> | 384.77           |

Compositions and Formulations

[0106] As described herein, the present disclosure provides compositions that comprise an active agent, for example a PAI-1 inhibitor. As described herein, the present disclosure provides compositions that deliver an active agent, for example a PAI-1 inhibitor. In some embodiments, a composition that comprises and/or delivers an active agent is formulated for topical administration. In some embodiments, a composition that comprises and/or delivers an active agent is formulated for topical application to a site of a subject. In some embodiments, a composition that comprises and/or delivers an active agent is an improved composition, as described herein. In some embodiments, a composition that comprises and/or delivers an active agent is formulated for parenteral administration (e.g., via injection or infusion).

[0107] In some embodiments, a composition that comprises and/or delivers an active agent comprises one more components as described herein. In some embodiments, components of a composition that comprises and/or delivers an active agent have a function as described herein. Among other things, it is an insight of the present disclosure that components of a composition that comprises and/or delivers an active agent can have more than one function in a composition.

[0108] In some embodiments, a composition as described herein is substantially free of one or more components as described herein.

[0109] In some embodiments, a composition as described herein is substantially free of ETOH.

[0110] In some embodiments, a composition as described herein is substantially free of sorbitol.

[0111] In some embodiments, a composition as described herein comprises a penetration enhancer. In some embodiments, a penetration enhancer is one or more of glycerin, isopropyl myristate and/or propylene glycol. In some embodiments, provided compositions comprise a penetration enhancer in an amount that is not more than 35% of a composition by weight.

[0112] In some embodiments, a composition as described herein comprises isopropyl myristate. In some embodiments, a composition as described herein comprises isopropyl myristate in an amount that is less than 15% by weight of a composition. In some embodiments, a composition as described herein comprises isopropyl myristate in an amount that is greater than 0.1% by weight of a composition. In some embodiments, a composition as described herein comprises isopropyl myristate in an amount that is at least 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, or 20% by weight of a composition. In some embodiments, a composition as described herein comprises isopropyl myristate in an amount that is at most 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, or 20% by weight of a composition. In some embodiments, a composition as described herein comprises isopropyl myristate in an amount greater than 1% but no more than 15% by weight of a composition. In some embodiments, a composition as described herein comprises isopropyl myristate in an amount greater than 5% but no more than 15% by weight of a composition. In some embodiments, a composition as described herein

comprises isopropyl myristate in an amount greater than 9% but no more than 12% by weight of a composition. In some embodiments, a composition as described herein comprises isopropyl myristate in an amount greater than 9% but no more than 11% by weight of a composition. In some embodiments, a composition as described herein comprises isopropyl myristate in an amount that is 10% by weight of a composition.

**[0113]** In some embodiments, provided compositions comprise a solvent. In some embodiments, a solvent is glycerin. In some embodiments, a composition as described herein comprises glycerin. In some embodiments, a composition as described herein comprises glycerin in an amount that is less than 15% by weight of a composition. In some embodiments, a composition as described herein comprises glycerin in an amount that is greater than 0.1% by weight of a composition. In some embodiments, a composition as described herein comprises glycerin in an amount that is at least 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, or 20% by weight of a composition. In some embodiments, a composition as described herein comprises glycerin in an amount that is at most 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, or 20% by weight of a composition. In some embodiments, a composition as described herein comprises glycerin in an amount that is greater than 1% but no more than 15% by weight of a composition. In some embodiments, a composition as described herein comprises glycerin in an amount that is greater than 5% but no more than 15% by weight of a composition. In some embodiments, a composition as described herein comprises glycerin in an amount that is greater than 9% but no more than 11% by weight of a composition. In some embodiments, a composition as described herein comprises glycerin in an amount that is no more than 10% by weight of a composition. In some embodiments, a composition as described herein comprises glycerin in an amount that is 10% by weight of a composition.

**[0114]** In some embodiments, a composition as described herein comprises propylene glycol. In some embodiments, a composition as described herein comprises propylene glycol in an amount that is less than 20% by weight of a composition. In some embodiments, a composition as described herein comprises propylene glycol in an amount that is greater than 0.1% by weight of a composition. In some embodiments, a composition as described herein comprises propylene glycol in an amount that is at least 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, or 20% by weight of a composition. In some embodiments, a composition as described herein

comprises propylene glycol in an amount that is at most 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, 10%, 11%, 12%, 13%, 14%, 15%, 16%, 17%, 18%, 19%, or 20% by weight of a composition. In some embodiments, a composition as described herein comprises propylene glycol in an amount that is greater than 5% but no more than 20% by weight of a composition. In some embodiments, a composition as described herein comprises propylene glycol in an amount that is greater than 14% but no more than 16% by weight of a composition. In some embodiments, a composition as described herein comprises propylene glycol in an amount that is 15% by weight of a composition.

[0115] In some embodiments, a composition as described herein comprises an emollient. In some embodiments, an emollient is isopropyl myristate.

[0116] In some embodiments, provided compositions comprise a solvent or carrier. In some embodiments, a solvent or carrier is water. In some embodiments, a composition as described herein comprises water in an amount that is less than 70% by weight of a composition. In some embodiments, a composition as described herein comprises water in an amount that is greater than 0.1% by weight of a composition. In some embodiments, a composition as described herein comprises water in an amount that is at least 1%, 10%, 20%, 30%, 40%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 58%, or 60%, by weight of a composition. In some embodiments, a composition as described herein comprises propylene glycol in an amount that is at most 1%, 10%, 20%, 30%, 40%, 50%, 51%, 52%, 53%, 54%, 55%, 56%, 57%, 58%, 58%, or 60% by weight of a composition. In some embodiments provided compositions comprise water in an amount that is greater than 15% but no more than 70% by weight of a composition. In some embodiments, provided compositions comprise water in an amount that is greater than 20% by weight of a composition. In some embodiments, provided compositions comprise water in an amount that is greater than 30% by weight of a composition. In some embodiments, provided compositions comprise water in an amount that is greater than 40% by weight of a composition. In some embodiments, provided compositions comprise water in an amount that is greater than 50% by weight of a composition. In some embodiments, provided compositions comprise water in an amount that is greater than 51% by weight of a composition. In some embodiments, provided compositions comprise water in an amount that is greater than 52% by weight of a composition. In some embodiments, provided compositions comprise water in an amount that is greater than 53% by weight of a composition. In some embodiments, provided compositions comprise water in an amount

that is greater than 53.5% by weight of a composition. In some embodiments, provided compositions comprise water in an amount that is greater than 53.6% by weight of a composition. In some embodiments, provided compositions comprise water in an amount that is greater than 53.7% by weight of a composition. In some embodiments, provided compositions comprise water in an amount that is greater than 53.8% by weight of a composition. In some embodiments, provided compositions comprise water in an amount that is greater than 53.84% by weight of a composition. In some embodiments, provided compositions comprise water in an amount that is no more than 54% by weight of a composition.

[0117] In some embodiments, a composition as described herein comprises a suspending agent. In some embodiments, a suspending agent is xanthan gum. In some embodiments, a composition as described herein comprises xanthan gum. In some embodiments, a composition as described herein comprises xanthan gum in an amount that is less than 0.5% by weight of a composition. In some embodiments, a composition as described herein comprises xanthan gum in an amount that is greater than 0.1% by weight of a composition. In some embodiments, a composition as described herein comprises xanthan gum in an amount that is at least 0.1%, 0.2%, 0.3%, 0.4%, or 0.5% by weight of a composition. In some embodiments, a composition as described herein comprises xanthan gum in an amount that is at most 0.1%, 0.2%, 0.3%, 0.4%, or 0.5% by weight of a composition. In some embodiments, a composition as described herein comprises xanthan gum in an amount that is greater than 0.1% but no more than 0.3% by weight of a composition. In some embodiments, a composition as described herein comprises xanthan gum in an amount that is 0.2% by weight of a composition.

[0118] In some embodiments, a composition as described herein comprises an emulsifier or solubilizer. In some embodiments, an emulsifier or solubilizer is Steareth 20. In some embodiments, an emulsifier or solubilizer is Tween 80. In some embodiments, an emulsifier or solubilizer is Steareth 20 and Tween 80.

[0119] In some embodiments, a composition as described herein comprises Steareth 20 in an amount that is less than 3% by weight of a composition. In some embodiments, a composition as described herein comprises Steareth 20 in an amount that is greater than 0.1% by weight of a composition. In some embodiments, a composition as described herein comprises Steareth 20 in an amount that is at least 1%, 1.5%, 2%, 2.5% or 3% by weight of

a composition. In some embodiments, a composition as described herein comprises Steareth 20 in an amount that is at most 1%, 1.5%, 2%, 2.5%, or 3% by weight of a composition. In some embodiments, a composition as described herein comprises Steareth 20 in amount that is greater than 1% but no more than 3% by weight of a composition. In some embodiments, a composition as described herein comprises Steareth 20 in amount that is greater than 1.5% but no more than 3.0% by weight of a composition. In some embodiments, a composition as described herein comprises Steareth 20 in amount that is 2.0% by weight of a composition.

[0120] In some embodiments, a composition as described herein comprises Tween 80 in an amount that is less than 6% by weight of a composition. In some embodiments, a composition as described herein comprises Tween 80 in an amount that is greater than 0.1% by weight of a composition. In some embodiments, a composition as described herein comprises Tween 80 in an amount that is at least 1%, 2%, 3%, 3.5%, 3.6%, 4%, 5%, or 6% by weight of a composition. In some embodiments, a composition as described herein comprises Tween 80 in an amount that is at most 1%, 2%, 3%, 3.5%, 3.6%, 4%, 5%, or 6% by weight of a composition. In some embodiments, a composition as described herein comprises Tween 80 in amount that is greater than 1% but no more than 6% by weight of a composition. In some embodiments, a composition as described herein comprises Tween 80 in amount that is greater than 3.0% but no more than 6% by weight of a composition. In some embodiments, a composition as described herein comprises Tween 80 in amount that is 3.5% by weight of a composition.

[0121] In some embodiments, a composition as described herein comprises methyl paraben in an amount that is less than 0.5% by weight of a composition. In some embodiments, a composition as described herein comprises methyl paraben in an amount that is greater than 0.1% by weight of a composition. In some embodiments, a composition as described herein comprises methyl paraben in an amount that is at least 0.1%, 0.15%, 0.2%, 0.25%, 0.3%, 0.4%, or 0.5% by weight of a composition. In some embodiments, a composition as described herein comprises methyl paraben in an amount that is at most 0.1%, 0.15%, 0.2%, 0.25%, 0.3%, 0.4%, or 0.5% by weight of a composition. In some embodiments, a composition as described herein comprises a preservative. In some embodiments, a preservative is methyl paraben. In some embodiments, a composition as described herein comprises methyl paraben in an amount that is greater than 0.1% but no more than 0.3% by weight of a composition. In some embodiments, a composition as

described herein comprises methyl paraben in an amount that is 0.2% by weight of a composition.

[0122] In some embodiments, a preservative is edetate disodium. In some embodiments, a composition as described herein comprises edetate disodium in an amount that is less than 1% by weight of a composition. In some embodiments, a composition as described herein comprises edetate disodium in an amount that is greater than 0.01% by weight of a composition. In some embodiments, a composition as described herein comprises edetate disodium in an amount that is at least 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09% or 0.1% by weight of a composition. In some embodiments, a composition as described herein comprises edetate disodium in an amount that is at most 0.01%, 0.02%, 0.03%, 0.04%, 0.05%, 0.06%, 0.07%, 0.08%, 0.09% or 0.1% by weight of a composition. In some embodiments, a composition as described herein comprises edetate disodium in an amount that is greater than 0.02% but no more than 0.06% by weight of a composition. In some embodiments, a composition as described herein comprises edetate disodium in an amount that is greater than 0.04% but no more than 1% by weight of a composition. In some embodiments, a composition as described herein comprises edetate disodium in an amount that is 0.05% by weight of a composition.

[0123] In some embodiments, a composition as described herein comprises propyl paraben in an amount that is less than 0.15% by weight of a composition. In some embodiments, a composition as described herein comprises propyl paraben in an amount that is greater than 0.05% by weight of a composition. In some embodiments, a composition as described herein comprises propyl paraben in an amount that is at least 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.1% or 0.15% by weight of a composition. In some embodiments, a composition as described herein comprises propyl paraben in an amount that is at most 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.1% or 0.15% by weight of a composition. In some embodiments, a preservative is propyl paraben. In some embodiments, a composition as described herein comprises propyl paraben in an amount that is greater than 0.05% but no more than 0.15% by weight of a composition. In some embodiments, a composition as described herein comprises propyl paraben in an amount that is 0.10% by weight of a composition.

[0124] In some embodiments, a composition as described herein comprises an oil-soluble antioxidant. In some embodiments, an oil-soluble antioxidant is butylated hydroxyl

toluene. In some embodiments, a composition as described herein comprises butylated hydroxyl toluene in an amount that is less than 0.15% by weight of a composition. In some embodiments, a composition as described herein comprises butylated hydroxyl toluene in an amount that is greater than 0.05% by weight of a composition. In some embodiments, a composition as described herein comprises butylated hydroxyl toluene in an amount that is at least 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.1% or 0.15% by weight of a composition. In some embodiments, a composition as described herein comprises butylated hydroxyl toluene in an amount that is at most 0.05%, 0.06%, 0.07%, 0.08%, 0.09%, 0.1% or 0.15% by weight of a composition. In some embodiments, a composition as described herein comprises butylated hydroxyl toluene in an amount that is greater than 0.05% but no more than 0.15% by weight of a composition. In some embodiments, a composition as described herein comprises butylated hydroxyl toluene in an amount that is 0.10% by weight of a composition.

**[0125]** In some embodiments, a composition as described herein comprises an active agent. In some embodiments, an active agent is an active agent, as described herein. In some embodiments, a composition as described herein comprises an active agent in an amount that is less than 10% by weight of a composition. In some embodiments, a composition as described herein comprises an active agent in an amount that is greater than 0.1% by weight of a composition. In some embodiments, a composition as described herein comprises an active agent in an amount that is at least 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, or 10% by weight of a composition. In some embodiments, a composition as described herein comprises an active agent in an amount that is at most 1%, 2%, 3%, 4%, 5%, 6%, 7%, 8%, 9%, or 10% by weight of a composition. In some embodiments, a composition as described herein comprises an active agent in an amount that is 5% by weight of a composition.

**[0126]** In some embodiments, provided compositions may be formulated for topical and/or transdermal delivery (e.g., as serums, suspensions, lotions, creams, liniments, ointments, powders, gels, drops, etc.). In some embodiments, provided compositions may be or include a nanoemulsion. In some embodiments, provided compositions may be or include a macroemulsion. In some embodiments administration is in combination with microneedle skin conditioning (MSC). In some embodiments, administration is via injection. In some embodiments, administration is in combination with laser treatment of the skin. In some embodiments, administration is in combination with light treatment of the

skin. In some embodiments, light treatment comprises treatment with one or more wavelengths or colors of light. In some embodiments, light treatment comprises treatment with a specific range of wavelengths or colors of light. In some embodiments, light treatment comprises treatment with wavelengths of light between 650 and 850 nm. In some embodiments, light treatment comprises treatment with wavelengths of light between 785 and 850 nm.

#### *Emulsions*

[0127] In some embodiments, provided herein are surprisingly effective technologies for administration and delivery of active agents. In some embodiments, the present disclosure teaches topical formulations and compositions of such active agents for various diseases, disorders, and/or conditions as described herein. In some embodiments, the present disclosure teaches methods of treating and/or preventing one or more diseases, disorders and/or conditions through the administration of active agent formulations and/or compositions to a subject in need thereof. In some embodiments, a formulation and/or composition comprises emulsions.

[0128] Moreover, the present disclosure appreciates that certain liquid nanoemulsion technologies have been demonstrated to provide remarkable transdermal delivery attributes, even for very large molecules, such as botulinum and/or antibody agents. See, e.g., U.S. Patent Publication No. 2012/0328701, U.S. Patent Publication No. 2012/0328702, 8,318,181, and U.S. Patent No. 8,658,391, the disclosures of which are herein incorporated by reference in their entireties.

#### Macroemulsions

[0129] In some embodiments, the present disclosure utilizes macroemulsion compositions comprising an active agent that are particularly effective and/or useful in a therapeutic, e.g., treatment of a disease, disorder and/or a condition as described herein. In some embodiments, particular macroemulsion compositions are particularly effective and/or useful for topical administration of an active agent as described herein to a subject in need thereof. In some embodiments macroemulsion compositions may comprise of one or more active agents.

[0130] In some embodiments, a macroemulsion may be formulated into a composition suitable for topical administration on skin. In some embodiments, a

composition suitable for topical administration may be a lotion, cream, powder, ointment, liniment, gel, drops, emollient, balm, or paste.

[0131] In some embodiments, macroemulsion formulations comprise water, medium chain triglyceride, span 65, polysorbate 80, methylparaben, and propylparaben. In some embodiments, macroemulsion formulations comprise water, medium chain triglyceride, span 65, and polysorbate 80.

[0132] In some embodiments, provided compositions comprise a mixture of a provided macroemulsion composition and one or more pharmaceutically acceptable excipients. In some embodiments, cream and/or lotion formulations comprise a mixture of a provided macroemulsion composition and/or a saline solution.

[0133] In some embodiments, provided compositions comprise macroemulsion compositions comprising one or more active agents. In some embodiments, provided compositions are cream and/or lotion formulations. In some embodiments, provided compositions comprise macroemulsion compositions. In some embodiments, compositions comprise provided macroemulsion compositions but are not cream and/or lotion formulations. In some embodiments, suitable compositions are formulated into creams and/or lotions but do not comprise a macroemulsion composition.

[0134] In some embodiments, provided compositions comprise a mixture of a provided macroemulsion composition and one or more pharmaceutically acceptable excipients, e.g., for topical and/or transdermal (e.g., by serums, suspensions, lotions, creams, powders, ointments, liniments, gels, drops, etc.) administration.

[0135] In some embodiments, a macroemulsion may be formulated into a composition suitable for topical administration. In some embodiments, a composition suitable for topical administration may be a lotion, cream, serum, suspension, powder, ointment, liniment, gel, drops, emollient, balm, or paste. In some embodiments, a macroemulsion may be formulated into an injectable composition. In some embodiments, an injectable composition may be sterile.

[0136] Macroemulsion formulations may act to stabilize an active agent and/or therapeutic agent. Macroemulsion formulations would not necessarily be expected in and of themselves to achieve transdermal delivery of active agents, nonetheless, the present disclosure encompasses that stabilization improvement that may be provided by

incorporation into a macroemulsion composition might, when combined with microneedling technologies as described herein, achieve synergistic enhancement of transdermal delivery.

#### Nanoemulsions

[0137] In some embodiments, the present disclosure utilizes nanoemulsion compositions comprising an active agent that are particularly effective and/or useful in a therapeutic, e.g., treatment of a disease, disorder and/or a condition as described herein. In some embodiments, particular nanoemulsion compositions are particularly effective and/or useful for topical administration of an active agent as described herein to a subject in need thereof. In some embodiments nanoemulsion compositions may comprise of one or more active agents.

[0138] In some embodiments, provided nanoemulsion compositions comprise oil and surfactant at a ratio ranging between about 0.1:1 to about 2:1. In some embodiments, provided nanoemulsion compositions comprise oil and surfactant at a ratio of about 0.1:1 to about 1:1. In some embodiments, provided nanoemulsion compositions comprise oil and surfactant at a ratio of about 0.5:1 to about 1:1. In some embodiments, provided nanoemulsion compositions comprise oil and surfactant at a ratio of about 0.5:1 to about 1:1.5. In some embodiments, provided nanoemulsion compositions comprise oil and surfactant at a ratio of about 0.1:1, about 0.15:1, about 0.2:1, about 0.25:1, about 0.3:1, about 0.35:1, about 0.4:1, about 0.45:1, about 0.5:1, about 0.5:1, about 0.55:1, about 0.6:1, about 0.65:1, about 0.7:1, about 0.75:1, about 0.8:1, about 0.85:1, about 0.9:1, about 0.95:1, or about 1:1. In some embodiments, provided nanoemulsion compositions comprise oil and surfactant at a ratio of about 0.67:1.

[0139] In some embodiments, an aqueous dispersion medium (e.g., water, buffer, salt solution, etc.) and surfactant are utilized at a ratio ranging between 0.01 and 20. In some embodiments, an aqueous dispersion medium (e.g., water, buffer, salt solution, etc.) and surfactant are utilized at a ratio ranging between 0.1 and 20. In some embodiments, an aqueous dispersion medium (e.g., water, buffer, salt solution, etc.) and surfactant are utilized at a ratio ranging between 0.5 and 10. In some embodiments, an aqueous dispersion medium (e.g., water, buffer, salt solution, etc.) and surfactant are utilized at a ratio ranging between 0.5 and 1. In some embodiments, a ratio of aqueous dispersion medium (e.g., water, buffer, salt solution, etc.) to surfactant is approximately 0.01:1, approximately 0.02:1, approximately 0.03:1, approximately 0.04:1, approximately 0.05:1, approximately 0.06:1,

approximately 0.07:1, approximately 0.08:1, approximately 0.0:1, approximately 0.1:1, approximately 0.2:1, approximately 0.3:1, approximately 0.4:1, approximately 0.5:1, approximately 1:1, approximately 2:1, approximately 3:1, approximately 4:1, approximately 5:1, approximately 6:1, approximately 7:1, approximately 8:1, approximately 9:1 or approximately 10:1. In some embodiments, the ratio of surfactant to water is approximately 0.5:1, approximately 1:1, approximately 2:1, approximately 3:1, approximately 4:1, approximately 5:1, approximately 6:1, approximately 7:1, approximately 8:1, approximately 9:1, approximately 10:1, approximately 11:1, approximately 12:1, approximately 13:1, approximately 14:1, approximately 15:1, approximately 16:1, approximately 17:1, approximately 18:1, approximately 19:1, or approximately 20:1. In some embodiments, aqueous dispersion medium (e.g., water, buffer, salt solution, etc.) and surfactant are utilized at a ratio ranging between 0.5 and 2. In some embodiments, a ratio of aqueous dispersion medium (e.g., water, buffer, salt solution, etc.) to surfactant is approximately 0.5:1, approximately 1:1, or approximately 2:1. In some embodiments, a ratio of surfactant to aqueous dispersion medium (e.g., water, buffer, salt solution, etc.) is approximately 0.5:1, approximately 1:1, or approximately 2:1. In some embodiments, a ratio of aqueous dispersion medium (e.g., water, buffer, salt solution, etc.) to surfactant is approximately 1:1. In some embodiments, compositions utilizing such ratios of aqueous dispersion medium (e.g., water, buffer, salt solution, etc.) to surfactant comprise water-in-oil emulsions.

**[0140]** In some embodiments, droplets within nanoemulsion compositions have diameters (e.g., average and/or median diameters) within a range of about 10 nm to about 300 nm, about 10 nm to about 200 nm, about 10 nm to about 150 nm, about 10 nm to about 130 nm, about 10 nm to about 120 nm, about 10 nm to about 115 nm, about 10 nm to about 110 nm, about 10 nm to about 100 nm, or about 10 nm to about 90 nm. In some embodiments, droplets within nanoemulsion compositions have diameters (e.g., average and/or median diameters) within a range of 1 nm to 300 nm, 1 nm to 200 nm, 1 nm to 150 nm, 1 nm to 120 nm, 1 nm to 100 nm, 1 nm to 75 nm, 1 nm to 50 nm, or 1 nm to 25 nm. In some embodiments, droplets within nanoemulsion compositions have diameters (e.g., average and/or median diameters) of 1 nm to 15 nm, 15 nm to 200 nm, 25 nm to 200 nm, 50 nm to 200 nm, or 75 nm to 200 nm.

**[0141]** In some embodiments, a total droplet distribution is encompassed within a specified range of droplet diameter size. In some embodiments, less than 50%, 25%, 10%, 5%, or 1% of a total droplet distribution is outside of a specified range of droplet diameter

sizes. In some embodiments, less than 1% of a total droplet distribution is outside of a specified range of droplet diameter sizes. In some embodiments, a nanoemulsion composition is substantially free of droplets having a diameter larger than 300 nm, 250 nm, 200 nm, 150 nm, 120 nm, 100 nm, 75 nm, 50 nm, or 25 nm. In some embodiments, less than 50%, 25%, 10%, 5%, or 1% of a total droplet distribution have diameters larger than 300 nm, 250 nm, 200 nm, 150 nm, 120 nm, 100 nm, 75 nm, 50 nm, or 25 nm.

**[0142]** In some embodiments, droplets within nanoemulsion compositions have an average droplet size that is under about 300 nm, about 250 nm, about 200 nm, about 150 nm, about 130 nm, about 120 nm, about 115 nm, about 110 nm, about 100 nm, about 90 nm, or about 50 nm. In some embodiments, average droplet size is within a range of about 10 nm and about 300 nm, about 50 nm and about 250, about 60 nm and about 200 nm, about 65 nm and about 150 nm, or about 70 nm and about 130 nm. In some embodiments, average droplet size is about 80 nm and about 110 nm. In some embodiments, average droplet size is about 90 nm and about 100 nm.

**[0143]** [0159] In some embodiments, nanoemulsion droplets have a zeta potential ranging between  $-80$  mV and  $+80$  mV. In some embodiments, nanoemulsion droplets have a zeta potential ranging between  $-50$  mV and  $+50$  mV. In some embodiments, nanoemulsion droplets have a zeta potential ranging between  $-25$  mV and  $+25$  mV. In some embodiments, nanoemulsion droplets have a zeta potential ranging between  $-10$  mV and  $+10$  mV. In some embodiments, nanoemulsion droplets have a zeta potential of about  $-80$  mV, about  $-70$  mV, about  $-60$  mV, about  $-50$  mV, about  $-40$  mV, about  $-30$  mV, about  $-25$  mV, about  $-20$  mV, about  $-15$  mV, about  $-10$  mV, about  $-5$  mV, or about  $-1$  mV. In some embodiments, nanoemulsion droplets have a zeta potential of about  $+50$  mV, about  $+40$  mV, about  $+30$  mV, about  $+25$  mV, about  $+20$  mV, about  $+15$  mV, about  $+10$  mV, or about  $+5$  mV. In some embodiments, nanoemulsion droplets have a zeta potential that is about  $0$  mV.

**[0144]** In some embodiments, aqueous dispersion media and surfactant are utilized at a ratio ranging between about 8:1 and about 9:1. In some embodiments, aqueous dispersion media and surfactant are utilized at a ratio of about 8:1, about 8.1:1, about 8.2:1, about 8.3:1, about 8.4:1, about 8.5:1, about 8.6:1, about 8.7:1, about 8.8:1, about 8.9:1, about 9:1, etc. In some embodiments, aqueous dispersion media and surfactant are utilized at a ratio of about 8.7:1. In some embodiments, aqueous dispersion media and surfactant are utilized at a ratio of about 8.8:1.

[0145] In some embodiments, aqueous dispersion media and oil are utilized at a ratio ranging between about 12:1 and about 14:1. In some embodiments, aqueous dispersion media and surfactant are utilized at a ratio of about 12:1, about 12.1:1, about 12.2:1, about 12.3:1, about 12.4:1, about 12.5:1, about 12.6:1, about 12.7:1, about 12.8:1, about 12.9:1, about 13:1, about 13.1:1, about 13.2:1, about 13.3:1, about 13.4:1, about 13.5:1, about 13.6:1, about 13.7:1, about 13.8:1, about 13.9:1, about 14:1, etc. In some embodiments, aqueous dispersion media and surfactant are utilized at a ratio of about 13.1:1.

[0146] In some embodiments, a percent of oil in a nanoemulsion ranges between 0% and 50%. In some embodiments, a percent of oil in a nanoemulsion ranges between 0% and 40%. In some embodiments, a percent of oil in a nanoemulsion ranges between 0% and 30%. In some embodiments, a percent of oil in a nanoemulsion ranges between 0% and 20%. In some embodiments, a percent of oil in a nanoemulsion ranges between 0% and 10%. In some embodiments, a percent of oil in a nanoemulsion ranges between 0% and 5%. In some embodiments, a percent of oil in a nanoemulsion ranges between 5% and 10%, between 10% and 15%, between 15% and 20%, between 20% and 25%, between 25% and 30%, between 35% and 40%, or between 45% and 50%. In some embodiments, a percent of oil in a nanoemulsion ranges between 10% and 20%, between 10% and 30%, between 10% and 40%, or between 10% and 50%. In some embodiments, a percent of oil in a nanoemulsion ranges between 20% and 30%, between 20% and 40%, between 20% and 50%. In some embodiments, a percent of oil in the nanoemulsion ranges between 30% and 40% or between 30% and 50%. In some embodiments, a percent of oil in a nanoemulsion ranges between 40% and 50%.

[0147] In some embodiments a percent of oil is approximately 1%, approximately 2%, approximately 3%, approximately 4%, approximately 5%, approximately 6%, approximately 7%, approximately 9%, approximately 10%, approximately 11%, approximately 12%, approximately 13%, approximately 14%, approximately 15%, approximately 16%, approximately 17%, approximately 18%, approximately 19%, approximately 20%, approximately 21%, approximately 22%, approximately 23%, approximately 24%, approximately 25%, approximately 26%, approximately 27%, approximately 28%, approximately 29%, approximately 30%, approximately 31%, approximately 32%, approximately 33%, approximately 34%, approximately 35%, approximately 36%, approximately 37%, approximately 38%, approximately 39%, approximately 40%, approximately 41%, approximately 42%, approximately 43%,

approximately 44%, approximately 45%, approximately 46%, approximately 47%, approximately 48%, approximately 49%, or approximately 50%. In some embodiments a percent of oil is approximately 10%. In some embodiments a percent of oil is approximately 9%. In some embodiments a percent of oil is approximately 8%. In some embodiments a percent of oil is approximately 7%. In some embodiments the percent of oil is approximately 6%. In some embodiments a percent of oil is approximately 5%. In some embodiments a percent of oil is approximately 4%. In some embodiments a percent of oil is approximately 3%. In some embodiments a percent of oil is approximately 2%. In some embodiments a percent of oil is approximately 1%.

**[0148]** In some embodiments, nanoemulsion formulations comprise water, medium chain triglyceride, polysorbate 80, methylparaben, and propylparaben. In some embodiments, nanoemulsion formulations comprise water, medium chain triglyceride, and polysorbate 80.

**[0149]** In some embodiments, a nanoemulsion may be formulated into a composition suitable for topical administration. In some embodiments, a composition suitable for topical administration may be a lotion, cream, powder, ointment, liniment, gel, drops, emollient, balm, or paste. In some embodiments, a nanoemulsion may be formulated into an injectable composition. In some embodiments, an injectable composition may be sterile.

**[0150]** These compositions are particularly useful in that they can be used for delivery of agents to a subject in need thereof via topical and/or transdermal (e.g., by lotions, creams, powders, ointments, liniments, gels, drops, etc.) administration. In some embodiments, provided compositions may be administered to a subject in need thereof via topical and/or transdermal (e.g., by serums, suspensions, lotions, creams, powders, ointments, liniments, gels, drops, etc.) administration. In some embodiments, provided nanoemulsion compositions may be formulated into cream and/or lotion formulations. In some embodiments, provided compositions comprising nanoemulsion compositions may be useful and/or effective for topical administration to a subject. In some embodiments, provided nanoemulsion compositions may be admixed with one or more cream components in a cream formulation and/or a saline solution for preparation of a pharmaceutical composition.

**[0151]** The present disclosure encompasses a recognition that emulsion compositions (e.g., macroemulsion compositions and nanoemulsion compositions) may be

formulated into cream and/or lotion formulations for administration to a subject. The present disclosure encompasses a recognition that provided compositions can be particularly useful for formulating emulsions, such as those described herein, for administration to a subject.

*Topical Formulations*

**[0152]** Compositions as described herein are particularly useful in that they can be used for delivery of an active agent as described herein to a subject in need thereof via topical and/or transdermal (e.g., by serums, suspensions, lotions, creams, powders, ointments, liniments, gels, drops, etc.) administration. In some embodiments, provided compositions comprising an active agent, as described herein, are administered to a subject in need thereof via topical (e.g., by serums, suspensions, lotions, creams, powders, ointments, liniments, gels, drops, etc.) administration. In some embodiments, compositions formulated for topical administration comprise macroemulsions, as described herein. In some embodiments, compositions formulated for topical administration comprise nanoemulsions, as described herein.

**[0153]** In some embodiments, cream and/or lotion formulations comprise purified water, methylparaben, mineral oil, isopropyl myristate, white petrolatum, emulsifying wax, and propylparaben. In some embodiments, cream and/or lotion formulations comprise purified water, mineral oil, isopropyl myristate, white petrolatum, and emulsifying wax.

**[0154]** In some embodiments, the present disclosure describes that provided compositions may be formulated into cream and/or lotion formulations as described herein. In some embodiments, provided compositions are formulated with water. In some embodiments, provided compositions are formulated with methylparaben. In some embodiments, provided compositions are formulated with mineral oil. In some embodiments, provided compositions are formulated with isopropyl myristate. In some embodiments, provided compositions are formulated with white petrolatum. In some embodiments, provided compositions are formulated with emulsifying wax. In some embodiments, provided compositions are formulated with propylparaben. In some embodiments, provided compositions are not formulated with any parabens. In some embodiments, provided compositions are not formulated with methylparaben. In some embodiments, provided compositions are not formulated with propylparaben.

[0155] In some embodiments, cream and/or lotion formulations may be useful for topical and/or transdermal administration. The present disclosure encompasses a recognition that, in some embodiments, provided compositions can be particularly useful for delivery of an active agent, for example, to a hair follicle located in a site of administration. In some embodiments, sites treated include those which used to have hair or hair follicles but no longer have hair or hair follicles. In some embodiments, provided compositions are formulated for topical delivery to a subject in need thereof. In some embodiments, provided compositions are administered to a subject in need thereof via topical delivery.

[0156] In some embodiments, provided compositions are formulated with cosmetically acceptable components. For example, in some embodiments, provided compositions are formulated with water and also any cosmetically acceptable solvent, in particular, monoalcohols, such as alkanols having 1 to 8 carbon atoms (like ethanol, isopropanol, benzyl alcohol and phenylethyl alcohol), polyalcohols, such as alkylene glycols (like glycerine, ethylene glycol and propylene glycol), and glycol ethers, such as mono-, di-, and tri-ethylene glycol monoalkyl ethers, for example, ethylene glycol monomethyl ether and diethylene glycol monomethyl ether, used singly or in a mixture. Such components can be present, for example, in proportions of up to as much as 60%, 70%, 80%, or 90% by weight, relative to the weight of the total composition.

[0157] In some embodiments, provided compositions for topical administration include one or more cosmetically acceptable components that impart appearance attributes desirable or appropriate for a subject to which a composition is to be administered (e.g., a matte appearance, which may be particularly desirable or appropriate for administration to subjects having greasy skin).

[0158] In some embodiments, provided compositions are formulated with at least one cosmetically acceptable filler material, for example, in order to obtain a matte product, which may be especially desired for individuals with greasy skin.

[0159] In some embodiments, one or more active agents are formulated into compositions suitable for topical administration. Exemplary active agents include those described herein. In some embodiments, provided compositions may be formulated and delivered in combination with microneedle skin conditioning (MSC) so that systemic delivery is achieved; in some embodiments, provided compositions may be formulated and/or delivered so that local, but not systemic, delivery is achieved.

**[0160]** In some embodiments, compositions suitable for topical formulation comprise a penetration enhancing agent. In some embodiments, a penetration enhancing agent degrades, disrupts and/or damages skin structure(s) and/or skin. In some embodiments, a penetration enhancing agent does not degrade, disrupt and/or damage skin structure(s) and/or skin. In some embodiments, a penetration enhancing agent is an irritant. In some embodiments, a penetration enhancing agent is not an irritant.

**[0161]** In some embodiments, provided compositions may be incorporated into a device such as, for example, a patch. A variety of transdermal patch structures are known in the art; those of ordinary skill will appreciate that provided compositions may readily be incorporated into any of a variety of such structures. In some embodiments, a transdermal patch may comprise a plurality of needles extending from one side of a patch that is administered to skin. In some embodiments, a transdermal patch may comprise a plurality of needles extending from one side of the patch that is administered to skin, wherein needles extend from a patch to project through a stratum corneum of skin. In some embodiments, needles do not rupture a blood vessel. In some embodiments, needles do not penetrate deeply enough to reach nerves in a dermis of skin.

**[0162]** In some embodiments, a transdermal patch includes an adhesive. Some examples of adhesive patches are well known (for example, see U.S. Design Patent 296,006; and U.S. Patents 6,010,715; 5,591,767; 5,008,110; 5,683,712; 5,948,433; and 5,965,154; all of which are incorporated herein by reference). Adhesive patches are generally characterized as having an adhesive layer, which will be administered to a patient's skin, a depot or reservoir for holding a provided composition, and an exterior surface that prevents leakage of the provided composition from the depot. The exterior surface of a patch may be non-adhesive.

**[0163]** In accordance with the present disclosure, a provided composition is incorporated into a patch so that it remains stable for extended periods of time. For example, in some embodiments, a provided composition may be incorporated into a polymeric matrix that stabilizes an active agent, and permits the agent to diffuse from the matrix and the patch. A provided composition may also be incorporated into an adhesive layer of a patch so that once the patch is administered to the skin, the provided composition may diffuse through skin. In some embodiments, an adhesive layer may be heat-activated where temperatures of about 37 °C cause the adhesive to slowly liquefy so that the agent

diffuses through skin. AN adhesive may remain tacky when stored at less than 37°C, and once administered to skin, an adhesive loses its tackiness as it liquefies.

[0164] In some embodiments, a provided composition can be provided in a depot in a patch so that pressure applied to the patch causes the provided composition to be directed out of the patch through microneedles and through the stratum corneum. Exemplary embodiments of microneedles are described above. Suitable devices for use in administering provided compositions intradermally include devices such as those described in U.S. Patent Nos. 4,886,499; 5,190,521; 5,328,483; 5,527,288; 4,270,537; 5,015,235; 5,141,496; and 5,417,662. Intradermal compositions may be administered by devices which limit the effective penetration length of a needle into skin, such as those described in PCT publication WO 99/34850 and functional equivalents thereof.

[0165] In some embodiments, for example in order to prolong effect of a provided composition, it may be desirable to slow absorption of a provided composition into skin. In some embodiments, this may be accomplished by use of a liquid suspension of crystalline or amorphous material with poor water solubility. A rate of absorption of a provided composition then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. In some embodiments, depending upon a ratio of provided composition to polymer and the nature of the particular polymer employed, a rate of provided composition release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides).

#### *Injectable Formulations*

[0166] In some embodiments, a composition may be formulated into a formulation suitable for injectable administration. In some embodiments, provided compositions may be formulated into an injectable formulation. In some embodiments, an injectable formulation may be sterile. In some embodiments, an injectable formulation may comprise one or more excipients. In some embodiments, an injectable formulation may comprise a nanoemulsion. In some embodiments, an injectable formulation may comprise a macroemulsion. In some embodiments, an injectable formulation comprises water. In some embodiments, an injectable composition comprises water which may be said composition's largest component (e.g., by percentage weight).

### Administration

[0167] The present disclosure provides technologies (e.g., compositions, methods, kits, etc.) for treating a disease, disorder and/or a condition. In some embodiments, the present disclosure provides technologies for treating dermatological conditions or disorders, using any provided composition (e.g., provided emulsion compositions; cream and/or lotion formulations; combination of provided emulsion compositions and cream and/or lotion formulation; etc.) as described herein.

[0168] As described herein, the present disclosure provides methods of administering provided compositions to a subject for various applications including, for example, cosmetic and/or medical applications. In some embodiments, the present disclosure provides methods of treating and/or preventing diseases, disorders, and/or conditions associated with activity of epidermal and/or dermal structures (e.g., sweat glands, sebaceous glands, hair follicles, etc.) by administering provided compositions to a subject in need thereof.

[0169] In some embodiments, provided methods involve topical administration of a composition, as described herein, comprising an active agent. In some embodiments, provided methods involve topical administration of an emulsion composition comprising an active agent. In some embodiments, an emulsion composition is a macroemulsion. In some embodiments, an emulsion composition is a nanoemulsion. In some embodiments, administration is topical via or in conjunction with MSC.

### *Transdermal Administration*

[0170] In some embodiments, the present disclosure describes a composition achieves transdermal delivery with provided compositions without use of abrasive or other disrupting agents (whether chemical, mechanical, electrical, magnetic, light-based, etc.). In some embodiments, the present disclosure achieves transdermal delivery of provided compositions without affirmative steps to permeabilize or disrupt a stratum corneum.

[0171] In some embodiments, the present disclosure contemplates transdermal delivery of provided compositions to achieve systemic delivery and/or effects. In some embodiments, the present disclosure contemplates transdermal delivery of provided compositions to achieve local delivery and/or effects, for example without achieving systemic delivery and/or effects.

[0172] In some embodiments, a provided composition is applied directly to skin. In some embodiments, an applied composition is absorbed through epidermal layers. In some embodiments, a provided composition can penetrate a top layer of skin, including a stratum corneum, dermal pores, and/or dermal glands, without the use of chemical or mechanical skin penetration enhancers or other agents that cause abrasion.

[0173] In some embodiments, the present disclosure provides methods and compositions for specific delivery of provided compositions to epidermal and/or dermal structures. In some embodiments, provided compositions are specifically delivered to epidermal and/or dermal structures without significant delivery to subdermal structures. In some embodiments, greater than about 50%, greater than about 60%, greater than about 70%, greater than about 80%, greater than about 85%, greater than about 90%, greater than about 95%, greater than about 96%, greater than about 97%, greater than about 98%, greater than about 99%, greater than about 99.5%, or about 100% of a provided composition administered to the skin of a subject is delivered specifically to the epidermis and/or dermis. In some embodiments, less than about 50%, less than about 40%, less than about 30%, less than about 20%, less than about 10%, less than about 5%, less than about 4%, less than about 3%, less than about 2%, less than about 1%, less than about 0.5%, or less than about 0.1% of a provided composition administered to the skin of a subject is delivered to subdermal structures.

[0174] In some embodiments, specific delivery to epidermal and/or dermal structures is achieved through application of a dose of provided composition that is lower than a dose per area used to achieve delivery to subdermal structures. For example, in some embodiments, a volume of provided composition is applied to a larger surface area; in some embodiments, a provided composition containing a reduced amount of provided composition per unit volume of composition is utilized than would be utilized to achieve delivery to subdermal structures; in some embodiments, penetration of provided composition into the skin is reduced (e.g., through combination with penetration inhibitors and/or adjustment of provided composition characteristics such as component ratios, component identity, etc., and combinations thereof). In some embodiments, such a lower dose is at least about 2-fold, about 3-fold, about 4-fold, about 5-fold, about 10-fold, about 20-fold, about 30-fold, about 40-fold, about 50-fold, about 100-fold, or greater than about 100-fold lower than a dose per area used to achieve delivery to subdermal structures.

*Site*

[0175] According to the present disclosure, an active agent can be administered to a site of interest for treatment and/or prevention of a disease, disorder and/or a condition at a site.

[0176] Technologies of the present disclosure are suitable for both human and veterinary use. In some embodiments, subjects suffering from any disease, disorder, and/or condition as described herein, which would benefit from topical administration of an active agent may be treated with the disclosed technologies.

[0177] In some embodiments, an administration site may be skin. In some embodiments, an administration site may be or comprise a site comprising a hair follicle. In some embodiments, an administration site is the skin overlying a muscle or muscle group of a subject. In some embodiments, a site is hairless. In some embodiments, a site is on a torso. In some embodiment a site is on a back. In some embodiments a site is on a chest. In some embodiments, a site is on a buttock. In some embodiments, a site is on a crotch. In some embodiments, a site is on a groin. In some embodiments, a site is on a head. In some embodiments a site is on a scalp. In some embodiments, a site is on a face. In some embodiments a site is on a neck. In some embodiments a site is on a décolleté. In some embodiments, a site is in an armpit. In some embodiments, a site is on an axillae. In some embodiments a site is on a hand. In some embodiments a site is a foot. In some embodiments a site is on an arm. In some embodiments a site is on a leg. In some embodiments, a site used to have hair or hair follicles but no longer have hair or hair follicles. In some embodiments, any site suitable site for MSC is a suitable administration site.

[0178] In some embodiments, a site of interest contains or did contain a plurality of hair follicles. In some embodiments, each hair follicle optionally comprises a hair disposed therein. In some embodiments, a hair follicle has normal structure and/or density. In some embodiments, a hair follicle does not comprise hairs. In some embodiments, a hair follicle comprises hairs. In some embodiments, percentage of hair follicles with hair is about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, about 49%, about 50%, about 51%, about 52%, about 53%, about 54%, about 55%, about 56%, about 57%, about 58%, about 59%, about 60%, about 61%,

about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 71%, about 72%, about 73%, about 74%, about 75%, about 76%, about 77%, about 78%, about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, or more.

**[0179]** In some embodiments, a hair in a hair follicle is not gray in color. In some embodiments, a hair in a hair follicle is gray in color. In some embodiments, percentage gray is about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, about 49%, about 50%, about 51%, about 52%, about 53%, about 54%, about 55%, about 56%, about 57%, about 58%, about 59%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 71%, about 72%, about 73%, about 74%, about 75%, about 76%, about 77%, about 78%, about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, or more.

**[0180]** In some embodiments, a site is affected by a dermatologic condition.

**[0181]** In some embodiments, the present disclosure provides methods of administration of provided compositions via topical and/or transdermal (e.g., by serums, suspensions, lotions, creams, liniments, ointments, powders, gels, drops, etc.) administration.

**[0182]** In some embodiments, provided methods involve topical, transdermal, or intradermal administration of provided compositions to a skin of a subject. In some embodiments, such routes achieve local delivery.

**[0183]** In some embodiments, an active agent (e.g., a PAI-1 inhibitor) penetrates skin within about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 minutes of administration. In some embodiments, an active agent penetrates skin within about 5 to about 60 minutes of administration. In some embodiments, an active agent penetrates skin within about 5 to about 12 minutes of administration. In some embodiments, an active agent penetrates skin within about 5 to about 15 minutes of administration. In some embodiments, an active agent penetrates skin within about 15 to about 30 minutes of administration. In some embodiments, an active agent penetrates skin within about 1 hour of administration. In some embodiments, an active agent penetrates skin within about 2 hours of administration.

In some embodiments, an active agent penetrates skin within about 3 hours of administration. In some embodiments, an active agent penetrates skin within about 4 hours of administration. In some embodiments, an active agent penetrates skin within about 5 hours of administration. In some embodiments, an active agent penetrates skin within about 6 hours of administration. In some embodiments, an active agent penetrates skin within about 7 hours of administration. In some embodiments, an active agent penetrates skin within about 8 hours of administration. In some embodiments, an active agent penetrates skin within about 12 hours of administration. In some embodiments, an active agent penetrates skin within about 24 hours of administration.

**[0184]** In some embodiments, an active agent (e.g., a PAI-1 inhibitor) penetrates a layer of skin within about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 minutes of administration. In some embodiments, an active agent penetrates a layer of skin within about 5 to about 60 minutes of administration. In some embodiments, an active agent penetrates a layer of skin within about 5 to about 12 minutes of administration. In some embodiments, an active agent penetrates a layer of skin within about 5 to about 15 minutes of administration. In some embodiments, an active agent penetrates a layer of skin within about 15 to about 30 minutes of administration. In some embodiments, an active agent penetrates a layer of skin within about 1 hour of administration. In some embodiments, an active agent penetrates a layer of skin within about 2 hours of administration. In some embodiments, an active agent penetrates a layer of skin within about 3 hours of administration. In some embodiments, an active agent penetrates a layer of skin within about 4 hours of administration. In some embodiments, an active agent penetrates a layer of skin within about 5 hours of administration. In some embodiments, an active agent penetrates a layer of skin within about 6 hours of administration. In some embodiments, an active agent penetrates a layer of skin within about 7 hours of administration. In some embodiments, an active agent penetrates a layer of skin within about 8 hours of administration. In some embodiments, an active agent penetrates a layer of skin within about 12 hours of administration. In some embodiments, an active agent penetrates a layer of skin within about 24 hours of administration.

**[0185]** In some embodiments, an active agent penetrates a top layer of skin within about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 minutes of administration. In some embodiments, an active agent penetrates a top layer of skin within about 5 to about 60 minutes of administration. In some embodiments, an active agent penetrates a top layer of skin within

about 5 to about 12 minutes of administration. In some embodiments, an active agent penetrates a top layer of skin within about 5 to about 15 minutes of administration. In some embodiments, an active agent penetrates a top layer of skin within about 15 to about 30 minutes of administration. In some embodiments, an active agent penetrates a top layer of skin within about 1 hour of administration. In some embodiments, an active agent penetrates a top layer of skin within about 2 hours of administration. In some embodiments, an active agent penetrates a top layer of skin within about 3 hours of administration. In some embodiments, an active agent penetrates a top layer of skin within about 4 hours of administration. In some embodiments, an active agent penetrates a top layer of skin within about 5 hours of administration. In some embodiments, an active agent penetrates a top layer of skin within about 6 hours of administration. In some embodiments, an active agent penetrates a top layer of skin within about 7 hours of administration. In some embodiments, an active agent penetrates a top layer of skin within about 8 hours of administration. In some embodiments, an active agent penetrates a top layer of skin within about 12 hours of administration. In some embodiments, an active agent penetrates a top layer of skin within about 24 hours of administration.

[0186] In some embodiments, an active agent penetrates a top layer of skin, including the stratum corneum, dermal pores, hair follicles, and/or dermal glands within about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 minutes of administration. In some embodiments, an active agent penetrates a top layer of skin, including the stratum corneum, dermal pores, hair follicles, and/or dermal glands within about 5 to about 60 minutes of administration. In some embodiments, an active agent penetrates a top layer of skin, including the stratum corneum, dermal pores, hair follicles, and/or dermal glands within about 5 to about 12 minutes of administration. In some embodiments, an active agent penetrates a top layer of skin, including the stratum corneum, dermal pores, hair follicles, and/or dermal glands within about 5 to about 15 minutes of administration. In some embodiments, an active agent penetrates a top layer of skin, including the stratum corneum, dermal pores, hair follicles, and/or dermal glands within about 15 to about 30 minutes of administration. In some embodiments, an active agent penetrates a top layer of skin, including the stratum corneum, dermal pores, hair follicles, and/or dermal glands within about 1 hour of administration. In some embodiments, an active agent penetrates a top layer of skin, including the stratum corneum, dermal pores, hair follicles, and/or dermal glands within about 2 hours of administration. In some embodiments, an active agent penetrates a top layer of skin,

including the stratum corneum, dermal pores, hair follicles, and/or dermal glands within about 3 hours of administration. In some embodiments, an active agent penetrates a top layer of skin, including the stratum corneum, dermal pores, hair follicles, and/or dermal glands within about 4 hours of administration. In some embodiments, an active agent penetrates a top layer of skin, including the stratum corneum, dermal pores, hair follicles, and/or dermal glands within about 5 hours of administration. In some embodiments, an active agent penetrates a top layer of skin, including the stratum corneum, dermal pores, hair follicles, and/or dermal glands within about 6 hours of administration. In some embodiments, an active agent penetrates a top layer of skin, including the stratum corneum, dermal pores, hair follicles, and/or dermal glands within about 7 hours of administration. In some embodiments, an active agent penetrates a top layer of skin, including the stratum corneum, dermal pores, hair follicles, and/or dermal glands within about 8 hours of administration. In some embodiments, an active agent penetrates a top layer of skin, including the stratum corneum, dermal pores, hair follicles, and/or dermal glands within about 12 hours of administration. In some embodiments, an active agent penetrates a top layer of skin, including the stratum corneum, dermal pores, hair follicles, and/or dermal glands within about 24 hours of administration.

#### *Subject*

[0187] In general a subject is an organism, typically a mammal (e.g., a human, in some embodiments including prenatal human forms). In some embodiments, a subject is male. In some embodiments, a subject is female. In some embodiments, a subject is human. In a particular embodiment, a human subject is at least 10 years old. In some embodiments, a subject has no hair. In some embodiments, a subject has hair. In some embodiments a subject has low follicular density. In some embodiments, a subject has a high follicular density. In some embodiments, a subject has colored hair. In some embodiments, a subject is suffering from a relevant disease, disorder or condition. In some embodiments, a subject is susceptible to a disease, disorder, or condition. In some embodiments, a subject displays one or more symptoms or characteristics of a disease, disorder or condition. In some embodiments, a subject does not display any symptom or characteristic of a disease, disorder, or condition. In some embodiments, a subject is someone with one or more features characteristic of susceptibility to or risk of a disease, disorder, or condition. In some embodiments, a subject is a patient. In some embodiments, a subject is an individual to whom diagnosis and/or therapy is and/or has been administered.

[0188] Technologies of the present disclosure are suitable for both human and veterinary use. In some embodiments, subjects suffering from any disease, disorder, and/or condition as described herein, which would benefit from topical administration of an active agent (e.g., a PAI-1 inhibitor) may be treated with disclosed technologies.

*Regimen*

[0189] In general, regimen is selected to achieve delivery of a therapeutically effective amount to a relevant site of action. In some embodiments, compositions and formulations described herein may be administered to a subject in need thereof at a relevant site of action in a single dose. In some embodiments, compositions and formulations described herein may be administered to a subject in need thereof a relevant site of action in multiple doses. For example, compositions and formulations described herein, can be administered through any one of the multiple routes of administration described herein (e.g., topical, via injection) sufficient to achieve delivery of effective amount of an active agent (e.g., a PAI-1 inhibitor).

[0190] In some embodiments, a dosing regimen for a particular active agent (e.g., a PAI-1 inhibitor) may involve intermittent or continuous (e.g., by perfusion or other slow release system) administration, for example to achieve a particular desired pharmacokinetic profile or other pattern of exposure in one or more tissues or fluids of interest in a subject receiving therapy.

[0191] In some embodiments, administration further comprises administering a plurality of doses of a composition described herein according to a dosing regimen in which at least two successive doses are separated from one another by a time period of at least 12 hours.

[0192] In some embodiments, different agents administered in combination may be administered via different routes of delivery and/or according to different schedules. Alternatively or additionally, in some embodiments, one or more doses of a first active agent is administered substantially simultaneously with, and in some embodiments via a common route and/or as part of a single composition with, one or more other active agents.

[0193] Factors to be considered when optimizing routes and/or dosing schedule for a given therapeutic regimen may include, for example, a particular indication being treated, a clinical condition of a subject (e.g., age, overall health, prior therapy received and/or response thereto) a site of delivery of an agent, the nature of an agent (e.g., an antibody or

other polypeptide-based compound), a mode and/or route of administration of an agent, presence or absence of combination therapy, and other factors known to medical practitioners. For example, in treatment of cancer, relevant features of an indication being treated may include, for example, one or more of cancer type, stage, location.

**[0194]** In some embodiments, one or more features of a particular pharmaceutical composition and/or of a utilized dosing regimen may be modified over time (*e.g.*, increasing or decreasing an amount of active agent in any individual dose, increasing or decreasing time intervals between doses), for example in order to optimize a desired therapeutic effect or response (*e.g.*, inhibition of a PAI-1 gene or gene product).

**[0195]** In general, type, amount, and frequency of dosing of active agents in accordance with the present disclosure are governed by safety and efficacy requirements that apply when one or more relevant agent(s) is/are administered to a mammal, preferably a human. In general, such features of dosing are selected to provide a particular, and typically detectable, therapeutic response as compared to what is observed absent therapy.

**[0196]** In the context of the present disclosure, an exemplary desirable therapeutic response may involve, but is not limited to, inhibition of a gene encoding an active agent and/or gene product, inhibition and/or a reduction in the degree and/or prevalence of a relevant disease, disorder and/or condition. Such criteria can be readily assessed by any of a variety of immunological, cytological, and other methods that are disclosed in the literature.

**[0197]** In some embodiments, an effective dose (and/or a unit dose) of an active agent, may be at least about 0.01 ng/kg body weight, at least about 0.01 µg/kg body weight, at least about 0.05 µg/kg body weight; at least about 0.1 µg/kg body weight, at least about 1 µg/kg body weight, at least about 2.5 µg/kg body weight, at least about 5 µg/kg body weight, at least about 10 µg /kg body weight, at least about 100 µg /kg body weight, at least about 1 mg /kg body weight, at least about 10 mg /kg body weight, at least about 100 mg /kg body weight, at least about 200 mg /kg body weight, at least about 300 mg /kg body weight, at least about 400 mg /kg body weight, and not more than about 500 mg/kg body weight. It will be understood by one of skill in the art that in some embodiments such guidelines may be adjusted for molecular weight of an active agent. The dosage may also be varied for route of administration, a cycle of treatment, or consequently to dose escalation protocol that can be used to determine a maximum tolerated dose and dose limiting toxicity (if any) in connection an additional therapeutic agent (*e.g.*, a PAI-1 antagonist) at increasing doses.

Consequently, relative amounts of each agent within a pharmaceutical composition may also vary, for example, each composition may comprise between 0.001 % and 100% (w/w) of a corresponding agent. Accordingly, in some embodiments, an effective dose (and/or a unit dose) of an active agent, may be at least about 0.001% w/w, at least about 0.005% w/w, at least about 0.01% w/w, at least about 0.05% w/w, at least about 0.1% w/w, at least about 0.5% w/w, at least about 1% w/w, at least about 1.5% w/w, at least about 2% w/w, at least about 2.5% w/w, at least about 5% w/w, at least about 10% w/w, at least about 15% w/w, at least about 20% w/w, at least about 25% w/w, at least about 30% w/w, at least about 35% w/w, at least about 40% w/w, at least about 45% w/w, at least about 50% w/w, at least about 55% w/w, at least about 60% w/w, at least about 65% w/w, at least about 70% w/w, at least about 75% w/w, at least about 80% w/w, at least about 85% w/w, at least about 90% w/w, at least about 95% w/w, and not more than about 100% w/w.

[0198] In some embodiments, toxicity and/or therapeutic efficacy of an active agent can be determined by standard pharmaceutical procedures in cell cultures or experimental animals, *e.g.*, for determining the maximum tolerated dose (MTD) and the ED<sub>50</sub> (effective dose for 50% maximal response). Typically, a dose ratio between toxic and therapeutic effects is the therapeutic index; in some embodiments, this ratio can be expressed as the ratio between MTD and ED<sub>50</sub>. Data obtained from such cell culture assays and animal studies can be used in formulating a range of dosage for use in humans.

[0199] In some embodiments, dosage may be guided by monitoring an active agent's effect on one or more pharmacodynamic markers of inhibition in diseased or surrogate tissue. For example, cell culture or animal experiments can be used to determine a relationship between doses required for changes in pharmacodynamic markers and doses required for therapeutic efficacy can be determined in cell culture or animal experiments or early stage clinical trials. In some embodiments, dosage of an active agent lies preferably within a range of circulating concentrations that include the ED<sub>50</sub> with little or no toxicity. In some embodiments, dosage may vary within such a range, for example depending upon the dosage form employed and/or the route of administration utilized. An exact formulation, route of administration and dosage can be chosen by an individual physician in view of a patient's condition. In treatment of crises or severe conditions, administration of a dosage approaching the MTD may be required to obtain a rapid response.

[0200] In some embodiments, dosage amount and/or interval may be adjusted individually, for example to provide plasma levels of an active moiety which are sufficient to maintain, for example a desired effect, or a minimal effective concentration (MEC) for a period of time required to achieve therapeutic efficacy. In some embodiments, MEC can be estimated, for example, from *in vitro* data and/or animal experiments. Dosages necessary to achieve the MEC will depend on individual characteristics and route of administration. In some embodiments, high pressure liquid chromatography (HPLC) assays or bioassays can be used to determine plasma concentrations.

[0201] In some embodiments, dosage intervals can be determined using an MEC value. In certain embodiments, active agents should be administered using a regimen which maintains plasma levels above a MEC for 10-90% of the time, preferably between 30-90% and most preferably between 50-90% until the desired amelioration of a symptom is achieved. In other embodiments, different MEC plasma levels will be maintained for differing amounts of time. In cases of local administration or selective uptake, the effective local concentration of the drug may not be related to plasma concentration.

[0202] One of skill in the art can select from a variety of administration regimens and will understand that an effective amount of an active agent may be dependent on the subject being treated, on the subject's weight, the severity of the affliction, the manner of administration and/or the judgment of the prescribing physician.

[0203] In some embodiments, the present disclosure involves administration of at least one provided composition, administered according to a dosing regimen sufficient to achieve a reduction in the degree and/or prevalence of a relevant dermatologic condition of at least about 20%; in some embodiments according to a dosing regimen sufficient to achieve a of at least about 25%; in some embodiments according to a dosing regimen sufficient to achieve a reduction of at least about 30%; in some embodiments according to a dosing regimen sufficient to achieve a reduction of at least about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, about 49%, about 50%, about 51%, about 52%, about 53%, about 54%, about 55%, about 56%, about 57%, about 58%, about 59%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 71%, about 72%, about 73%, about 74%, about 75%, about 76%, about 77%, about

78%, about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, or more.

[0204] In some embodiments, the present disclosure involves administration of at least one provided composition, administered in combination with MSC, according to a dosing regimen sufficient to achieve a reduction in the degree and/or prevalence of a relevant dermatologic condition of at least about 20%; in some embodiments according to a dosing regimen sufficient to achieve a of at least about 25%; in some embodiments according to a dosing regimen sufficient to achieve a reduction of at least about 30%; in some embodiments according to a dosing regimen sufficient to achieve a reduction of at least about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, about 49%, about 50%, about 51%, about 52%, about 53%, about 54%, about 55%, about 56%, about 57%, about 58%, about 59%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 71%, about 72%, about 73%, about 74%, about 75%, about 76%, about 77%, about 78%, about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90%, or more.

[0205] In some embodiments, the present disclosure involves administration of at least one provided composition, administered optionally in combination with MSC, according to a dosing regimen sufficient to achieve a reduction in the degree and/or prevalence of a relevant dermatologic condition of at least about 20% in a specified percentage of a population of patients to which a composition was administered; in some embodiments according to a dosing regimen sufficient to achieve a of at least about 25% in a specified percentage of a population of patients to which a composition was administered; in some embodiments according to a dosing regimen sufficient to achieve a reduction of at least about 30% in a specified percentage of a population of patients to which a composition was administered; in some embodiments according to a dosing regimen sufficient to achieve a reduction of at least about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, about 49%, about 50%, about 51%, about 52%, about 53%, about 54%, about 55%, about 56%, about 57%, about 58%, about 59%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about

66%, about 67%, about 68%, about 69%, about 70%, about 71%, about 72%, about 73%, about 74%, about 75%, about 76%, about 77%, about 78%, about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90% or more in a specified percentage of a population of patients to which a composition was administered. In some embodiments, the specified percentage of population of patients to which a composition was administered is at least about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, or about 100%. To give but a few illustrative examples, in some embodiments, the present disclosure involves administration of at least one provided composition according to a dosing regimen sufficient to achieve a reduction in the degree and/or prevalence of a relevant dermatologic condition of at least about 20% in at least about 50% of the population of patients to which a composition was administered. In some embodiments, the present disclosure involves administration of at least one provided composition according to a dosing regimen sufficient to achieve a reduction in the degree and/or prevalence of a relevant dermatologic condition of at least about 30% in at least about 50% of the population of patients to which a composition was administered.

[0206] The present disclosure provides technologies for treating conditions or disorders by administering to a patient a provided composition as described herein (e.g., a provided emulsion composition; serums and/or suspension formulation; cream and/or lotion formulation; combination of provided emulsion composition and cream and/or lotion formulation; etc.), optionally in combination with MSC. In some embodiments, the present disclosure provides technologies for treating conditions or disorders by topically administering to a patient a composition containing a provided emulsion composition, optionally in combination with MSC as described herein.

#### *Penetration Enhancing Treatment*

[0207] Among other things, in some embodiments, provided compositions may be administered in combination with one or more penetrating enhancing treatments (e.g., chemical agents, laser treatment, microneedling, physical massage etc.), such as known penetration enhancing agents and/or penetration enhancing treatment modalities, to for example, facilitating penetration of an active agent across biological barrier (e.g., skin). In some embodiments, provided compositions include one or more such other penetration

enhancing agents; in some embodiments, such other penetration enhancing agents are provided as part of distinct compositions. In some embodiments, penetration enhancing treatment involves simultaneous administration of two or more different penetration enhancing agents and/or penetration enhancing treatment modalities; in some embodiments, penetration enhancing treatment involves simultaneous exposure to two or more different penetration enhancing treatment agents and/or penetration enhancing treatment modalities, for example through simultaneous laser treatment and composition administration.

[0208] In some embodiments, penetration enhancing agents is or comprises chemical agents. For example, chemical agents that that may damage, disrupt, and/or degrade one or more stratum corneum components) may include, for example, alcohols, such as short chain alcohols, long chain alcohols, or polyalcohols; amines and amides, such as urea, amino acids or their esters, amides, AZONE®, derivatives of AZONE®, pyrrolidones, or derivatives of pyrrolidones; terpenes and derivatives of terpenes; fatty acids and their esters; macrocyclic compounds; tensides; or sulfoxides (e.g., dimethylsulfoxide (DMSO), decylmethylsulfoxide, etc.); surfactants, such as anionic, cationic, and nonionic surfactants; polyols; essential oils; and/or hyaluronidase. In some embodiments, a penetration enhancing agent may be an irritant in that an inflammatory and/or allergic reaction occurs when the agent is administered to skin. In some embodiments, a penetration enhancing agent is not an irritant. In some embodiments, a penetration enhancing agent may be or comprise a chemical agent that does not damage, disrupt, or degrade skin structure but whose presence or level nonetheless correlates with increased penetration of an agent of interest across skin, as compared with that observed in its absence. In some embodiments, co-peptides, carrier molecules, and carrier peptides may be penetration enhancing agents which do not damage, disrupt, and/or degrade skin structure(s). In some embodiments, co-peptides, carrier molecules, and carrier peptides may be penetration enhancing agents which do not irritate the skin. The term “penetration enhancing agent” does not encompass mechanical devices (e.g., needles, scalpels, etc.), or equivalents thereof (e.g., other damaging treatments). Also, those skilled in the art will appreciate that a structure such as a nanoparticle or an emulsion is not a chemical agent and therefore not a chemical penetration enhancing agent even if its presence correlates with enhanced skin penetration of an agent of interest that may be associated with the structure. In some embodiments, a penetration enhancing agents is or comprises alcohol.

[0209] In some embodiments, penetration enhancing treatment modalities is or comprises microneedling. In some embodiments, penetration enhancing treatment modalities is or comprises laser treatment. In some embodiments, penetration enhancing treatment modalities is or comprises physical massage. For example, in some embodiments, a composition may be administered before or after a performing laser treatment of a site. In some embodiments, penetration enhancing treatment modalities is or comprises administration of an electric or magnetic field.

Microneedling

[0210] In some embodiments, microneedle (MN) arrays for use in accordance with the present disclosure are or share features with minimally invasive systems, developed to overcome some of the disadvantages commonly associated with the use of hypodermic and subcutaneous needles, as well as improve patient comfort and compliance. Such disadvantages include, for example, potential for needle tip misplacement with a hypodermic needle because a health professional cannot visualize where exactly the needle is going; such needle misplacement can result in adverse reactions when injected incorrectly. MN would be less prone to such a problem. Other advantages of MN are that they may not cause bleeding, minimize introduction of pathogens through MN produced holes, and eliminate transdermal dosing variability. Other advantages are the possibility of self-administration, reduce risk of accidental needle stick injuries, reduce risk of transmitting infection, and ease of disposal. In some embodiments, MN are multiple microscopic projections assembled on one side of a support, such as a patch or a device (e.g., stamp, roller, array, applicator, pen).

[0211] In some embodiments, MN for use in accordance with the present disclosure may be designed and/or constructed in arrays in order to improve skin contact and facilitate penetration into the skin. In some embodiments, utilized MN are of suitable length, width, and shape to minimize contact with nerves when inserted into the skin, while still creating efficient pathways for drug delivery. Alkilani, A. Z., et al., "Transdermal drug delivery: Innovative pharmaceutical developments based on disruption of the barrier properties of the stratum corneum" *Pharmaceutics*. 7:438-470 (2015).

[0212] In some embodiments, a suitable MN may be solid, coated, porous, dissolvable, hollow, or hydrogel MN. Solid MN create microholes in the skin, thereby increasing transport of a drug formulation (e.g., "poke and patch" methods). Coated MN

allow for rapid dissolution of a coated drug into the skin (e.g., “coat and poke” methods). Dissolvable MN allow for rapid and/or controlled release of a drug incorporated within the microneedles. Hollow MN may be used to puncture the skin and enable release of a composition following active infusion or diffusion of a formulation through a microneedle’s bores (e.g., “poke and flow” methods”). In the case of dissolvable MN, MN can act as a drug depot, holding a drug composition until released by dissolution in the case of dissolvable MN or swelling in the case of hydrogel MN (e.g., “poke and release” methods). However, as already described herein, in many embodiments, the active agent is not delivered by injection via one or more microneedles. That is, in many embodiments, any microneedle utilized in accordance with such embodiments is not coated, loaded, or fabricated with the biologically active agent in any way that would achieve delivery of the biologically active agent. Alternatively, in some embodiments, as described herein, a MN, utilized in accordance with the present disclosure (whether in MSC or otherwise), may comprise and/or deliver a biologically active agent, if the biologically active agent is formulated in a macro- or nano- emulsion composition as described herein. Thus, as will be appreciated by those skilled in the art reading the specification described herein, treatment of skin with microneedle(s) that deliver the biologically active agent (e.g., by injection through a microneedle, by the release of a microneedle coating or by the release from a dissolving microneedle) is not microneedle skin conditioning.

**[0213]** In some embodiments, a microneedle has a diameter which is consistent throughout the microneedle’s length. In some embodiments, the diameter of a microneedle is greatest at the microneedle’s base end. In some embodiments, a microneedle tapers to a point at the end distal to the microneedle’s base. In some embodiments, a microneedle may be solid. In some embodiments, a microneedle may be hollow. In some embodiments a microneedle may be tubular. In some embodiments, a microneedle may be sealed on one end. In some embodiments, a microneedle is part of an array of microneedles. In some embodiments, a microneedle may have a length of between about 1  $\mu\text{m}$  to about 4,000  $\mu\text{m}$ . In some embodiments, a microneedle may have a length of between about 1  $\mu\text{m}$  to about 2,000  $\mu\text{m}$ . In some embodiments, a microneedle may have a length of between about 50  $\mu\text{m}$  to about 400  $\mu\text{m}$ . In some embodiments, a microneedle may have a length of between about 800  $\mu\text{m}$  to about 1500  $\mu\text{m}$ .

**[0214]** In some embodiments, MN for use in accordance with the present disclosure may be fabricated from different materials, using technologies including, but not limited to

micro-molding processes or lasers. In some embodiments, MN may be manufactured using various types of biocompatible materials including polymers, metal, ceramics, semiconductors, organics, composites, or silicon. Unless they are designed to break off into the skin and dissolve, in some embodiments, microneedles have the mechanical strength to remain intact and to deliver drugs, or collect biological fluid, while being inserted into the skin and/or removed from the skin after insertion. In some embodiments MN are capable of remaining in place for up to a number of days before intact removal. In some embodiments, microneedles may be sterilizable using standard technologies. In some embodiments, MN are biodegradable. In some embodiments, MN comprise a polymeric material. In some embodiments the polymeric material comprises poly-L-lactic acid, poly-glycolic acid, polycarbonate, poly-lactic-co-glycolic acid (PLGA), polydimethylsiloxane, polyvinylpyrrolidone (PVP), a copolymer of methyl vinyl ether and maleic anhydride, sodium hyaluronate, carboxymethyl cellulose, maltose, dextrin, galactose, starch, gelatin, or a combination thereof.

[0215] Suitable MN arrays and MSC devices for use in combination with compositions comprising biologically active agents for transdermal delivery of biologically active agents include devices such as those described in e.g., U.S. Patents 6,334,856; 6,503,231; 6,908,453; 8,257,324; and 9,144,671.

*Combination Therapy or Treatment*

[0216] According to the present disclosure, provided compositions may be administered in combination with one or more additional treatments. In some embodiments a one or more additional treatment is or comprises other active agents and/or therapeutic modalities (e.g., one or more PAI-inhibitors, or other agents), such as known therapeutic agents and/or independently active biologically active agents. In some embodiments, for example, provided compositions include one or more such other active agents; in some embodiments, such other active agents are provided as part of distinct compositions. In some embodiments, combination therapy involves simultaneous administration of one or more doses or units of two or more other active agents and/or therapeutic modalities; in some embodiments, combination therapy involves simultaneous exposure to two or more other active agents and/or therapeutic modalities, for example through overlapping dosing regimens.

[0217] In some embodiments, provided compositions include or are administered in combination with one or more other active agents useful for the treatment of a relevant dermatologic or other disease, disorder and/or condition, for example as discussed herein in context of the relevant disease, disorder, and/or condition.

#### Kits

[0218] In some embodiments, the present disclosure provides pharmaceutical packs or kits including one or more emulsion compositions comprising one or more active agents and/or one or more microneedle devices according to the present disclosure. In some embodiments, pharmaceutical packs or kits include preparations or pharmaceutical compositions containing provided compositions in one or more containers filled with optionally one or more additional ingredients of pharmaceutical compositions. In some embodiments, a pharmaceutical pack or kit includes an additional approved therapeutic agent for use in combination therapies. In some embodiments, optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceutical products, which notice reflects approval by the agency of manufacture, use, or sale for human administration.

[0219] Kits are provided that include therapeutic reagents and/or active agents (e.g., a PAI-1 inhibitor). As but one non-limiting example, provided compositions can be provided as topical formulations and administered as therapy. Pharmaceutical doses or instructions therefor may be provided in a kit for administration to an individual suffering from or at risk for conditions or disorders, e.g., those associated with a dermal level of skin.

[0220] In some embodiments, a kit may comprise a provided composition and instructions for administering a composition to a site.

[0221] In some embodiments, a kit may comprise (i) a provided composition; and (ii) at least one pharmaceutically acceptable excipient; and optionally (iii) at least one syringe, spatula, gloves, swab for administration to skin; and (iv) instructions for use.

[0222] In some embodiments, a kit may comprise (i) a provided composition; and (ii) at least one pharmaceutically acceptable excipient; and optionally (iii) a device for injection (e.g., syringe and needle, microneedle array, hair brush, etc.); and (iv) instructions for use. In some embodiments, a device is a patch, a roller, stamp, or pen.

[0223] It will be appreciated by those of ordinary skill in the art that inventive compositions for topical administration may have a cosmetic formulation such as skin softener, nutrition lotion type emulsion, cleansing lotion, cleansing cream, skin milk, emollient lotion, massage cream, emollient cream, make-up base, facial pack or facial gel, cleaner formulation such as shampoos, rinses, body cleanser, hair-tonics, or soaps, or dermatological composition such as lotions, ointments, gels, creams, patches or sprays. In some embodiments, compositions for topical administration are not formulated for administration to mucous membranes (e.g., are inappropriate for administration to mucous membranes and/or are not formulated to deliver an appropriate amount of large agent to or across mucous membranes).

#### Diseases, Disorders, and Conditions

In some embodiments, provided compositions and methods described herein may be used for treatment and/or prevention of various diseases, conditions, and/or disorders. Among other things, in some embodiments, compositions and methods described herein may be used for treatment and/or prevention of various dermatological conditions. In some embodiments, compositions and methods described herein may be used for treating and/or preventing diseases, disorders or conditions associated with an epidermal and/or dermal level of skin. In some embodiments, compositions and methods described herein may be used for treatment and/or prevention of various non-dermatological conditions. In some embodiments, compositions and methods described herein may be used for treating and/or preventing lung fibrosis, lung cancer, chronic myeloid leukemia, metabolic syndrome, diabetes, thrombosis, obesity, kidney fibrosis, liver fibrosis, cardiac fibrosis, or atherosclerosis.

[0224] In some embodiments, a dermatological condition is hair graying. In some embodiments, a dermatological condition is keloids. In some embodiments, a dermatological condition is scleroderma. In some embodiments, a dermatological condition is systemic scleroderma. In some embodiments, a dermatological condition is cutaneous scleroderma. In some embodiments, a dermatological condition is Raynaud's Disease (or Raynaud's Phenomenon). In some embodiments, a dermatological condition is melanoma or cutaneous angio-sarcoma.

[0225] In some embodiments, compositions and methods described herein may be used for treating and/or preventing one or more of specific types of hair loss (or alopecia),

including androgenetic alopecia, alopecia areata, frontal fibrosing alopecia, and senescent alopecia and/ or combinations thereof. In some embodiments, alopecia is radiation-induced alopecia, chemotherapy-induced alopecia, and alopecia due to chronic discoid lupus erythematosus.

#### *Hair Loss*

[0226] In some embodiments, compositions and methods described herein are useful for treating and/or preventing hair loss. In some embodiments, a provided composition is characterized in that, when administered to an animal comprising a one or more hairs, achieves at least one of: (i) a reduction in hair loss; (ii) prevention of hair loss; (iii) a delayed onset of hair loss of the one or more hairs; and (iv) an increase in the number of hairs on the site.

[0227] Baldness involves the state of lacking hair where it often grows, especially on the head. The most common form of baldness is a progressive hair thinning condition called androgenic alopecia or “male pattern baldness” that occurs in adult male humans and other species. The amount and patterns of baldness can vary greatly; it ranges from male and female “pattern alopecia” (androgenic alopecia, also called androgenetic alopecia or alopecia androgenetica); “alopecia areata,” which involves the loss of some of the hair from the head; “alopecia totalis,” which involves the loss of all head hair; to the most extreme form, “alopecia universalis,” which involves the loss of all hair from the head and the body. Frontal fibrosing alopecia (FFA) is characterized primarily by slowly progressive hair loss and scarring on the scalp near the forehead. In some cases, the hair loss in this type of alopecia may involve the eyebrows, eye lashes, and/or other body parts. Senescent alopecia, also known as involutional alopecia, is hair loss caused by old age. Other types of alopecia include, but are not limited to, radiation-induced alopecia, chemotherapy-induced alopecia, alopecia due to chronic discoid lupus erythematosus, postpartum alopecia, and telogen effluvium.

[0228] Current therapies used in the treatment of hair loss include, but are not limited to, botulinum toxin, aza-steroids, such as finasteride (PROPECIA®; PROSCAR®; etc.) or dutasteride (AVODART®); topically administered minoxidil, a vasodilator (ROGAINE®); antiandrogens (e.g., ketoconazole, fluconazole, spironolactone, etc.); platelet-rich plasma, saw palmetto; caffeine; copper peptides; nitroxide spin labels TEMPO and TEMPOL; unsaturated fatty acids (e.g., gamma linolenic acid); hedgehog agonists;

azelaic acid and zinc in combination; Chinese knotweed; pumpkin seed; spironolactone; tretinoin; zinc; stinging nettle; and/or combinations thereof. Pharmaceutical compositions in accordance with the present disclosure may be administered alone and/or in combination with these therapies that are used to treat the symptoms and/or causes of hair loss, for the treatment of hair loss.

[0229] In some embodiments, provided compositions for treatment and/or prevention of hair loss are formulated into a suspension.

[0230] In some embodiments, provided compositions for treatment and/or prevention of hair loss are formulated into a suspension, a foam, a cream, a liniment, a lotion, a gel, a shampoo, a conditioner, an ointment, an emollient, a balm, a paste, etc.

[0231] In some embodiments, provided compositions for treatment and/or prevention of hair loss are administered locally to an affected site (e.g., scalp, hair follicle, face, neck, back, arms, chest, etc.).

#### *Hair Graying*

[0232] In some embodiments, compositions and methods described herein may be used for treating and/or preventing a dermatological condition. In some embodiments, compositions and methods described herein may be used for treating and/or preventing hair graying.

[0233] In some embodiments, a provided composition is characterized in that, when administered to an animal suffering from or susceptible to such hair graying, achieves at least one of: (i) a reduction in the number of gray hairs (e.g., present at and/or near a site of administration); (ii) restoration of color of the one or more gray hairs, (iii) prevention of graying of one or more non-gray hairs (e.g., present at and/or near a site of administration) and (iv) a delayed onset of graying of one or more non-gray hairs (e.g., present at and/or near a site of administration).

[0234] Current therapies for hair graying include, but is not limited to photoprotectors, such as cinnamidopropyltrimonium chloride and solid lipid nanoparticles as carriers for UV blockers, oral supplementation with l-cystine and l-methionine, and topical melatonin. The most commonly used treatment or solution to premature hair graying is the use of temporary hair colorants. Pharmaceutical compositions in accordance with the present

disclosure may be administered alone and/or in combination with these therapies that are used to treat the symptoms and/or causes of hair graying, for the treatment of hair graying.

[0235] In some embodiments, provided compositions for treatment and/or prevention of hair graying are formulated into a suspension.

[0236] In some embodiments, compositions disclosed herein for treatment and/or prevention of hair graying are formulated into a suspension, a serum, a foam, a cream, a liniment, a lotion, a gel, a shampoo, a conditioner, an ointment, an emollient, a balm, a paste, etc.

[0237] In some embodiments, compositions disclosed herein for treatment and/or prevention of hair graying are administered locally to an affected site (e.g., scalp, hair follicle, face, neck, back, arms, chest, etc.).

[0238] In some embodiments, administration achieves systemic delivery. In some embodiments, administration achieves local delivery.

[0239] In some embodiments, the present disclosure involves administration of at least one therapeutic agent (e.g., a PAI-1 inhibitor) in a suspension, in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of hair graying of at least about 25%; in some embodiments in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of hair graying of at least about 30%; in some embodiments in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of hair graying of at least about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, about 49%, about 50%, about 51%, about 52%, about 53%, about 54%, about 55%, about 56%, about 57%, about 58%, about 59%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 71%, about 72%, about 73%, about 74%, about 75%, about 76%, about 77%, about 78%, about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90% or more.

[0240] In some embodiments, the present disclosure involves administration of at least one therapeutic agent (e.g., a PAI-1 inhibitor) in a nanoparticle composition or a nanoemulsion composition or an emulsion composition or a foam formulation or a cream formulation or an oil or a lotion formulation or a gel or a shampoo or a conditioner, in an

amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of hair graying of at least about 25%; in some embodiments in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of hair graying of at least about 30%; in some embodiments in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of hair graying of at least about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, about 49%, about 50%, about 51%, about 52%, about 53%, about 54%, about 55%, about 56%, about 57%, about 58%, about 59%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 71%, about 72%, about 73%, about 74%, about 75%, about 76%, about 77%, about 78%, about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90% or more.

#### *Keloids*

[0241] In some embodiments, compositions and methods described herein are useful for treating and/or preventing keloids.

[0242] Keloids are proliferated scar tissue that forms on the site of a cutaneous injury. In a particular example, the site of a cutaneous injury is a surgical incision or a site of trauma. Unlike hypertrophic scars, which are raised scars, keloids grow beyond the boundaries of the original wound. Keloids result from an overgrowth of granulation tissue or collagen type 3 at the site of the cutaneous injury. Keloids may be firm, rubbery lesions. In some embodiments, keloids may be shiny, fibrous nodules. While these are benign growth and not contagious, keloids may sometimes be accompanied with pain, itchiness, and may affect movement of the skin. An estimated 15% of African Americans and Hispanics have keloids.

[0243] While there is no effective treatment, current therapies for keloids include pressure therapy, silicone gel sheeting, intra-lesional triamcinolone acetate (TAC), cryosurgery, radiation, laser therapy, IFN, 5-FU, high doses of oxygen using hyperbaric oxygen therapy (HBOT), cryotherapy, and surgical excision as well as a multitude of extracts and topical agents. The most common form of treatment is currently surgical excision. However, the best treatment is prevention in patients with known predisposition.

Pharmaceutical compositions in accordance with the present disclosure may be administered alone and/or in combination with these therapies that are used to treat the symptoms and/or causes of keloids, for the treatment of keloids.

[0244] In some embodiments, provided compositions for treatment and/or prevention of keloids are formulated into a suspension.

[0245] In some embodiments, provided compositions for treatment and/or prevention of keloids are formulated into a suspension, a foam, a cream, a liniment, a lotion, a gel, a shampoo, a conditioner, an ointment, an emollient, a balm, a paste, etc.

[0246] In some embodiments, provided compositions for treatment and/or prevention of keloids are administered locally to an affected site (e.g., scalp, hair follicle, face, neck, back, arms, chest, etc.).

[0247] In some embodiments, administration achieves systemic delivery. In some embodiments, administration achieves local delivery.

[0248] In some embodiments, the present disclosure involves administration of at least one therapeutic agent (e.g., a PAI-1 inhibitor) in a suspension, in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of keloids of at least about 25%; in some embodiments in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of keloids of at least about 30%; in some embodiments in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of keloids of at least about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, about 49%, about 50%, about 51%, about 52%, about 53%, about 54%, about 55%, about 56%, about 57%, about 58%, about 59%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 71%, about 72%, about 73%, about 74%, about 75%, about 76%, about 77%, about 78%, about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90% or more.

[0249] In some embodiments, the present disclosure involves administration of at least one therapeutic agent (e.g., a PAI-1 inhibitor) in a nanoparticle composition or a nanoemulsion composition or an emulsion composition or a foam formulation or a cream formulation or an oil or a lotion formulation or a gel or a shampoo or a conditioner, in an

amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of keloids of at least about 25%; in some embodiments in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of keloids of at least about 30%; in some embodiments in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of keloids of at least about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, about 49%, about 50%, about 51%, about 52%, about 53%, about 54%, about 55%, about 56%, about 57%, about 58%, about 59%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 71%, about 72%, about 73%, about 74%, about 75%, about 76%, about 77%, about 78%, about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90% or more.

#### *Scleroderma*

[0250] In some embodiments, compositions and methods described herein are useful for treating and/or preventing scleroderma. In some embodiments, compositions and methods described herein are useful for treating and/or preventing systemic scleroderma. In some embodiments, compositions and methods described herein are useful for treating and/or preventing cutaneous scleroderma.

[0251] Scleroderma, or systemic sclerosis, is generally considered a chronic systemic autoimmune disease characterized, among other things, fibrosis or hardening, vascular alterations, and autoantibodies.

[0252] In some embodiments, scleroderma is also considered a connective tissue disease generally characterized with an excessive accumulation of Extracellular Matrix proteins in the skin and internal organs, vascular injury, and immunological abnormalities.

[0253] Many of the clinical manifestations of the disease are thought to involve a misregulation of vascular remodeling. One of the earliest symptoms of scleroderma is microvascular injury. This microvascular injury is thought to cause increased endothelial cell activation. Activated endothelial cells are believed to express adhesion molecules resulting in altered capillary permeability allowing migration of inflammatory cells through the endothelium and entrapment in the vessel wall. The immune activation is thought to contribute to sustained endothelial activation, which results in the breakdown of endothelial

cells. This process is believed to contribute to the loss of elasticity and narrowing of the vessels commonly observed in scleroderma patients. Furthermore, it is thought that microvascular injury contributes to perivascular infiltrates of mononuclear cells in the dermis which is thought to contribute to the activation of fibroblasts and many of the associated hallmark symptoms of scleroderma. As fibrosis increases, permeability decreases. As a result, it becomes more difficult for antibodies to penetrate diseased tissues. Therefore, the affinity of anti-CCL2 antibodies becomes particularly important to keep antibodies localized.

[0254] Many of the clinical manifestations of the disease are generally thought to involve the misregulation of fibroblasts. The main function of fibroblasts is to maintain the structural integrity of connective tissues by continuously secreting precursors of the extracellular matrix. Fibroblasts provide a structural framework (stroma) for many tissues, play an important role in wound healing and are the most common cells of connective tissue in animals. Fibroblasts are morphologically heterogeneous with diverse appearances depending on their location and activity.

[0255] There are two major forms of scleroderma: limited systemic sclerosis/scleroderma and diffuse systemic sclerosis/scleroderma. In limited cutaneous scleroderma, the fibrosis of the skin is generally confined to the area. Patients with limited cutaneous scleroderma generally experience vascular impairment. Cutaneous and organ fibrosis generally progresses slowly in patients with limited scleroderma. Patients with diffuse scleroderma generally experience fibrosis of skin and organs that progresses more rapidly than in limited scleroderma and/or widespread inflammation and/or more severe internal organ involvement than is seen in limited scleroderma.

[0256] It is generally thought that interstitial lung disease, resulting in pulmonary fibrosis, is the leading cause of scleroderma related deaths (Ludwicka-Bradley, A., et al. Coagulation and autoimmunity in scleroderma interstitial lung disease. *Semin Arthritis Rheum*, 41(2), 212-22, 2011). Further complications resulting in scleroderma-related deaths include but are not limited to cancer, heart failure, pulmonary hypertension, kidney failure, and malabsorption, or any combination thereof.

[0257] Scleroderma is most commonly diagnosed by inspection of skin symptoms. Tests to diagnosis include but are not limited to visual and/or manual inspection of the skin, blood pressure testing, chest x-ray, lung CT, echocardiogram, urinalysis, skin biopsy, and

blood tests including antinuclear antibody testing, anti-topoisomerase antibody testing, anti-centromere antibody testing, anti-U3 antibody testing, anti-RNA antibody testing, other types of antibody testing, erythrocyte sedimentation rate, and rheumatoid factor. There is currently no known cure for scleroderma. Treatments administered are designed to treat the symptoms of the disease. Treatments include Angiotensin II Receptor Antagonists, Angiotensin Converting Enzyme (ACE) Inhibitors, NSAIDs, COX-2 Inhibitors, Analgesics, Low-Dose Corticosteroids, Narcotics, Antacids, H2 Blockers, Proton Pump Inhibitors, Prokinetic Agents, Somatostatin Agonist, Antibiotics, Prostaglandin Derivatives, Treprostinil, Iloprost, Endothelin Receptor Antagonists, IP Receptor Agonist, Phosphodiesterase type 5 (PDE5) inhibitors, Anti-Fibrotic Agent, Tyrosine Kinase Inhibitor, Immunosuppressants, Alkylating agents, Pilocarpine, and combinations thereof.

[0258] In some embodiments, provided compositions for treatment and/or prevention of scleroderma are formulated into a suspension.

[0259] In some embodiments, provided compositions for treatment and/or prevention of scleroderma are formulated into a suspension, a foam, a cream, a liniment, a lotion, a gel, a shampoo, a conditioner, an ointment, an emollient, a balm, a paste, etc.

[0260] In some embodiments, provided compositions for treatment and/or prevention of scleroderma are administered locally to an affected site (e.g., scalp, hair follicle, face, neck, back, arms, chest, etc.).

[0261] In some embodiments, administration achieves systemic delivery. In some embodiments, administration achieves local delivery.

[0262] In some embodiments, the present disclosure involves administration of at least one therapeutic agent (e.g., a PAI-1 inhibitor) in a suspension, in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of scleroderma of at least about 25%; in some embodiments in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of scleroderma of at least about 30%; in some embodiments in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of scleroderma of at least about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, about 49%, about 50%, about 51%, about 52%, about 53%, about 54%, about 55%, about 56%, about 57%, about 58%, about 59%, about 60%, about 61%,

about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 71%, about 72%, about 73%, about 74%, about 75%, about 76%, about 77%, about 78%, about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90% or more.

**[0263]** In some embodiments, the present disclosure involves administration of at least one therapeutic agent (*e.g.*, a PAI-1 inhibitor) in a nanoparticle composition or a nanoemulsion composition or an emulsion composition or a foam formulation or a cream formulation or an oil or a lotion formulation or a gel or a shampoo or a conditioner, in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of scleroderma of at least about 25%; in some embodiments in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of scleroderma of at least about 30%; in some embodiments in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of scleroderma of at least about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, about 49%, about 50%, about 51%, about 52%, about 53%, about 54%, about 55%, about 56%, about 57%, about 58%, about 59%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 71%, about 72%, about 73%, about 74%, about 75%, about 76%, about 77%, about 78%, about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90% or more.

#### *Raynaud's Phenomenon*

**[0264]** In some embodiments, compositions and methods described herein are useful for treating and/or preventing Raynaud's Phenomenon.

**[0265]** Raynaud's phenomenon or Raynaud's disease is a vasospastic condition of the fingers and toes. Typically in response to cold or emotional stress, the skin of the fingers become discolored (white, blue, and/or red, often in this sequence) and painful. Severe Raynaud's can result in necrosis of the skin and ultimately the fingers and/or toes, resulting in "auto-amputation." Nails of Raynaud's patients may become brittle. This condition is frequently associated with connective tissue diseases such as scleroderma and/or rheumatoid arthritis.

[0266] Pharmaceutical compositions in accordance with the present disclosure may be administered alone and/or in combination with other agents that are used to treat the symptoms and/or causes of Raynaud's phenomenon, for the treatment of Raynaud's phenomenon. In some embodiments, such agents include calcium channel blockers (*e.g.*, nifedipine, *etc.*), alpha blockers (*e.g.*, hydralazine, *etc.*), nitroglycerin, angiotensin II receptor antagonists (*e.g.*, losartan, *etc.*), selective serotonin reuptake inhibitors (*e.g.*, fluoxetine, *etc.*), glyceryl trinitrate, tadalafil, *Ginkgo biloba* extract, SLx-2101, St. John's Wort, fasudil, cilostazol, iloprost, relaxin, treprostinil diethanolamine, sildenafil, atorvastatin, imatinib mesylate, treprostinil diethanolamine, and/or combinations thereof.

[0267] In some embodiments, provided compositions for treatment and/or prevention of Raynaud's disease are formulated into a suspension.

[0268] In some embodiments, compositions disclosed herein for treatment and/or prevention of Raynaud's disease are formulated into a suspension, a foam, a cream, a liniment, a lotion, a gel, a shampoo, a conditioner, an ointment, emollient, balm, a paste, *etc.*

[0269] In some embodiments, compositions disclosed herein for treatment and/or prevention of Raynaud's disease are administered locally to an affected site (*e.g.*, nose, lips, ears, nipples, fingers, toes, scalp, face, neck, back, arms, chest, *etc.*).

[0270] In some embodiments, administration achieves systemic delivery. In some embodiments, administration achieves local delivery.

[0271] In some embodiments, the present disclosure involves administration of at least one therapeutic agent (*e.g.*, a PAI-1 inhibitor) in a suspension, in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of Raynaud's phenomenon of at least about 25%; in some embodiments in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of Raynaud's phenomenon of at least about 30%; in some embodiments in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of Raynaud's phenomenon of at least about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, about 49%, about 50%, about 51%, about 52%, about 53%, about 54%, about 55%, about 56%, about 57%, about 58%, about 59%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 71%, about 72%,

about 73%, about 74%, about 75%, about 76%, about 77%, about 78%, about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90% or more.

[0272] In some embodiments, the present disclosure involves administration of at least one therapeutic agent (e.g., a PAI-1 inhibitor) in a nanoparticle composition or a nanoemulsion composition or an emulsion composition or a foam formulation or a cream formulation or an oil or a lotion formulation or a gel or a shampoo or a conditioner, in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of Raynaud's phenomenon of at least about 25%; in some embodiments in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of Raynaud's phenomenon of at least about 30%; in some embodiments in an amount sufficient to achieve a reduction in the degree and/or prevalence of one or more symptoms of Raynaud's phenomenon of at least about 31%, about 32%, about 33%, about 34%, about 35%, about 36%, about 37%, about 38%, about 39%, about 40%, about 41%, about 42%, about 43%, about 44%, about 45%, about 46%, about 47%, about 48%, about 49%, about 50%, about 51%, about 52%, about 53%, about 54%, about 55%, about 56%, about 57%, about 58%, about 59%, about 60%, about 61%, about 62%, about 63%, about 64%, about 65%, about 66%, about 67%, about 68%, about 69%, about 70%, about 71%, about 72%, about 73%, about 74%, about 75%, about 76%, about 77%, about 78%, about 79%, about 80%, about 81%, about 82%, about 83%, about 84%, about 85%, about 86%, about 87%, about 88%, about 89%, about 90% or more.

## EXEMPLIFICATION

### Example 1: Formulation of an improved composition comprising a PAI-1 inhibitor

[0273] The present Example describes formulation of a composition for topical application that comprises and/or delivers a PAI-1 inhibitor, according to an embodiment of the present disclosure. In some embodiments, a composition that comprises and/or delivers a PAI-1 inhibitor as described herein is an improved composition relative to an original composition that comprises and/or delivers a PAI-1 inhibitor.

[0274] An original composition that comprises and/or delivers a PAI-1 inhibitor was formulated as an ethanol-based composition. For example, an original composition comprising a PAI-1 inhibitor was formulated according to a formula in Table 2.

Table 2

| Component                 | Trade Name                | Formula (%) |
|---------------------------|---------------------------|-------------|
| Water                     | Water, purified USP       | 14.75       |
| Glycerin                  | Glycerin, 99.7% USP       | 10.00       |
| Sorbitol Solution         | Sorbitol Solution, USP/EP | 5.00        |
| Steareth 20               | SP Brij S20 MBAL-PA-(RB)  | 4.00        |
| Tween 80                  | SP Tween 80 MBAL-LQ-(MH)  | 5.00        |
| Methyl paraben            | Methyl paraben, NF        | 0.05        |
| Edetate disodium          | Dissolvane NA2-P          | 0.05        |
| Ethanol Dehydrated USP    | Ethanol Dehydrated USP    | 40.00       |
| Isopropyl myristate       | Dermol IPM, NF            | 1.00        |
| Propyl paraben            | Propyl paraben, NF        | 0.05        |
| Butylated Hydroxy Toluene | BHT, NF                   | 0.10        |
| Propylene glycol          | Puraguard PG, USP         | 15.00       |
| Active agent              | TM-5441 (jet-milled)      | 5.00        |
| Total                     |                           | 100.00      |

[0275] Among other things, it is an insight of the present disclosure that an active agent in an ethanol-based composition that comprises and/or delivers a PAI-1 inhibitor can settle to the bottom of a container over time. That is, the present disclosure identifies the source of a problem with such ethanol-based compositions. Among other things, the present disclosure provides PAI-1 inhibitor compositions with reduced ethanol, for example relative to an appropriate reference composition (e.g., an original composition, as described herein). Such a PAI-1 inhibitor composition with reduced ethanol was found to prevent settling of the PAI-1 inhibitor over time when compared to an appropriate reference composition (e.g., an original composition, as described herein), for example, an ethanol-based composition comprising the PAI-1 inhibitor.

[0276] A composition that comprises and/or delivers a PAI-1 inhibitor was reformulated to prevent settling of an active agent to a bottom of a container. An improved composition that comprises and/or delivers a PAI-1 inhibitor was formulated and comprises less ethanol relative to an appropriate reference composition (e.g., an original composition, as described

herein), that comprises and/or delivers the same PAI-1 inhibitor. In some embodiments, a provided composition is substantially free of ethanol.

[0277] Alternatively or additionally, in some embodiments, a provided composition comprises more water relative to such reference (e.g., original) composition that comprises and/or delivers the relevant PAI-1 inhibitor. In some embodiments, a provided composition comprises about 50% water, or more (e.g., between about 50% and about 60%, or about 50% and about 55%).

[0278] Again alternatively or additionally, in some embodiments, a provided composition that comprises and/or delivers a PAI-1 inhibitor as described herein (e.g., as presented for example in Table 3) is substantially free of sorbitol.

[0279] In some embodiments, a provided composition comprises about 50% water, or more (e.g., between about 50% and about 60%, or about 50% and about 55%) and is substantially free of ethanol.

[0280] In some embodiments, a provided composition comprises about 50% water, or more (e.g., between about 50% and about 60%, or about 50% and about 55%) and is substantially free of ethanol and sorbitol.

[0281] Table 3 exemplifies a particular improved composition that comprises and/or delivers a PAI-1 inhibitor in accordance with the present disclosure.

Table 3

| Component                 | Trade Name                | Formula (%) |
|---------------------------|---------------------------|-------------|
| Water                     | Water, purified USP       | 53.85       |
| Glycerin                  | Glycerin, 99.7% USP       | 10.00       |
| Xanthan Gum               | Vanzan, NF                | 0.20        |
| Sorbitol Solution         | Sorbitol Solution, USP/EP | ~           |
| Steareth 20               | SP Brij S20 MBAL-PA-(RB)  | 2.00        |
| Tween 80                  | SP Tween 80 MBAL-LQ-(MH)  | 3.50        |
| Methyl paraben            | Methyl paraben, NF        | 0.20        |
| Edetate disodium          | Dissolve NA2-P            | 0.05        |
| Ethanol Dehydrated USP    | Ethanol Dehydrated USP    | ~           |
| Isopropyl myristate       | Dermol IPM, NF            | 10.00       |
| Propyl paraben            | Propyl paraben, NF        | 0.10        |
| Butylated Hydroxy Toluene | BHT, NF                   | 0.10        |
| Propylene glycol          | Puraguard PG, USP         | 15.00       |
| Active agent              | TM-5441 (jet-milled)      | 5.0         |
| <b>Total</b>              |                           | 100         |

[0282] Accordingly, the present Example describes formulation of a composition that comprises and/or delivers a PAI-1 inhibitor formulated for topical application, which is substantially free of ethanol (ETOH).

**Example 2: Topical Formulation comprising a PAI-1 inhibitor shows improved skin penetration**

[0283] The present Example demonstrates a surprising result that an improved composition that comprises and/or delivers a PAI-1 inhibitor formulated for topical application which is substantially free of ethanol showed improved skin penetration relative to an ethanol-based composition that comprises and/or delivers a PAI-1 inhibitor formulated for topical application.

[0284] Topical penetration properties of an original composition and a new composition as described in the present disclosure were tested using a Franz cell diffusion chamber employing human skin according to standard protocols. In order to effectively compare the original and new compositions (as described, for example, in Example 1), each composition was newly manufactured at the same concentration of a PAI-1 inhibitor prior to

testing. Each composition was fully suspended when tested. At 24 hours after application to a skin surface, the new composition had surprisingly approximately 2.5 times ( $p = 0.0003$ ) more skin penetration than the original composition, as shown in FIG. 1. This result was achieved with newly manufactured, fully suspended compositions despite the change in formulation from the original to new composition consisting of removal and substitution of ethanol, a known skin penetration enhancer with water, which is not a skin penetration enhancer.

[0285] In some embodiments, less active ingredient may be used in a new composition relative to an original composition to achieve comparable therapeutic effects.

[0286] Accordingly, the present Example demonstrates that a composition that comprises and/or delivers a PAI-1 inhibitor and is formulated for topical application to a site of a subject, which composition is substantially free of ethanol achieved greater skin penetration relative to an ethanol-based composition that comprises and/or delivers a PAI-1 inhibitor.

### EQUIVALENTS

[0287] Those skilled in the art will recognize, or be able to ascertain using no more than routine experimentation, many equivalents to the specific embodiments of the invention described herein. The scope of the present disclosure is not intended to be limited to the above Description, but rather is as set forth in the following claims:

**CLAIMS**

We claim:

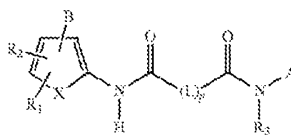
1. A composition that comprises or delivers a PAI-1 inhibitor and is formulated for topical application to a site of a subject, which composition is substantially free of ETOH.
2. The composition of claim 1, wherein the site is skin.
3. The composition of claim 2, wherein the site contains or did contain a plurality of hair follicles.
4. The composition of claim 3, wherein each hair follicle optionally comprises a hair disposed therein.
5. The composition of claim 1, wherein the composition is substantially free of all alcohols.
6. The composition of claim 1, wherein the composition is substantially free of sorbitol.
7. The composition of claim 1, wherein not more than 35% of the composition by weight is comprised of a penetration enhancer.
8. The composition of claim 7, wherein the penetration enhancer is one or more of glycerin, isopropyl myristate and/or propylene glycol.
9. The composition of claim 8, wherein the composition includes glycerin in an amount that is greater than 1% but no more than 15% by weight of the composition.

10. The composition of claim 9, wherein the composition includes glycerin in amount that is 10% by weight of the composition.
11. The composition of claim 8, wherein the composition includes propylene glycol in an amount that is greater than 1% but no more than 15% by weight of the composition.
12. The composition of claim 11, wherein the composition includes propylene glycol in an amount that is 10% by weight of the composition.
13. The composition of claim 8, wherein the composition includes isopropyl myristate in an amount that is less than 15% by weight of the composition.
14. The composition of claim 13, wherein the composition includes isopropyl myristate in an amount greater than 1% but no more than 15% by weight of the composition.
15. The composition of claim 14, wherein the composition includes isopropyl myristate in an amount that is 10% by weight of the composition.
16. The composition of claim 1, wherein the composition includes Steareth 20 in an amount that is greater than 1% but no more than 3% by weight of the composition.
17. The composition of claim 16, wherein the composition includes Steareth 20 in an amount that is 2% by weight of the composition.
18. The composition of claim 1, wherein the composition includes Tween 80 in an amount that is greater than 1% but no more than 6% by weight of the composition.

19. The composition of claim 18, wherein the composition includes Tween 80 in an amount that is 3.5% by weight of the composition.
20. The composition of claim 1, wherein the composition includes propyl paraben in an amount that is greater than 0.05% but no more than 0.15% by weight of a composition.
21. The composition of claim 20, wherein the composition includes propyl paraben in an amount that is 0.10% by weight of a composition.
22. The composition of claim 1, wherein the composition includes butylated hydroxyl toluene in an amount that is greater than 0.05% but no more than 0.15% by weight of a composition.
23. The composition of claim 22, wherein the composition includes butylated hydroxyl toluene in an amount that is 0.10% by weight of a composition.
24. The composition of claim 1, wherein the composition includes water in an amount that is greater than 15% but no more than 70% by weight of the composition.
25. The composition of claim 24, wherein the composition includes water in an amount that is no more than 54% by weight of the composition.
26. The composition of claim 1, wherein the composition comprises xanthan gum.
27. The composition of claim 26, wherein the composition includes xanthan gum in an amount that is greater than 0.1% but no more than 0.3% by weight of the composition.

28. The composition of claim 27, wherein the composition includes xanthan gum in an amount that is 0.2% by weight of the composition.
29. The composition of claim 1, wherein the composition includes methyl paraben in an amount that is greater than 0.1% but no more than 0.3% by weight of the composition.
30. The composition of claim 29, wherein the composition includes methyl paraben in an amount that is 0.2% by weight of the composition.
31. The composition of claim 1, wherein the composition includes edetate disodium.
32. The composition of claim 31, wherein the composition includes edetate disodium in an amount that is greater than 0.01% but no more than 0.1% by weight of the composition.
33. The composition of claim 32, wherein the composition includes edetate disodium in an amount that is 0.05% by weight of the composition.
34. The composition of claim 1, wherein the PAI-1 inhibitor is selected from the group consisting of: polypeptides, nucleic acids, lipids, carbohydrates, small molecules, metals, polymers, therapeutic antibodies, fragments of therapeutic antibodies, and combinations thereof.
35. The composition of claim 1, wherein the PAI-1 inhibitor is a 2-aminobenzoic acid analog.
36. The composition of claim 1, wherein the PAI-1 inhibitor is a 5-chloro-2-aminobenzoic acid analog.

37. The composition of claim 1, wherein the PAI-1 inhibitor is a compound of Formula (1)



Formula (1)

wherein,

$R_1$  and  $R_2$  are the same or different, and each represents hydrogen, halogen, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, cycloalkenyl, alkynyl, hydroxyl, alkoxy, cycloalkoxy, alkenyloxy, cycloalkenyloxy, aryloxy, aralkyl, aralkyloxy, heterocyclic-alkyl, heterocyclicalkyloxy, aryl optionally having one or two substituents, 5- to 6-membered ring heteroaryl optionally having one or two substituents, or benzo-fused heteroaryl optionally having one or two substituents, amino or carbonyl, each of which is optionally substituted with one or two substituents, or cyano, carboxy, or alkoxy-carbonyl; and  $R_1$  and  $R_2$  are optionally adjoined with each other to form a ring;

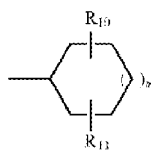
$R_3$  is hydrogen, alkyl, cycloalkyl, or aryl optionally having one or two substituents;

X is  $-C(R_5)=C(R_6)-$ ,  $-C(R_7)N-$ , or  $-N=C(R_8)-$ , wherein  $R_5$ ,  $R_6$ ,  $R_7$  and  $R_8$  each represents hydrogen, halogen, alkyl optionally having one or two substituents, or alkoxy;

L is alkylene (some carbon atoms in the alkylene optionally form a cycloalkyl ring), alkenylene, alkynylene, cycloalkylene, alkyleneoxyalkylene, alkyleneethioalkylene, alkylene-SO-alkylene, or alkylene-SO<sub>2</sub>-alkylene, each of which is optionally substituted with one or two substituents, or alkylene-N( $R_9$ )-alkylene optionally substituted with one or two substituents, wherein  $R_9$  represents hydrogen, or alkyl optionally having one or two substituents;

p represents an integer of 0 or 1;

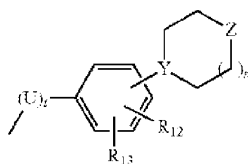
A is a group represented by any one of the following Formulae (2), (3) or (4):



Formula (2)

wherein,

$R_{10}$  and  $R_{11}$  are the same or different, and each represents hydrogen or straight- or branched-chain alkyl; and  $m$  represents an integer of 0 to 10,



Formula (3)

wherein,

$R_{12}$  and  $R_{13}$  are the same or different, and each represents hydrogen, halogen, or alkyl optionally having one or two substituents, cycloalkyl optionally having one or two substituents, or alkoxy optionally having one or two substituents;

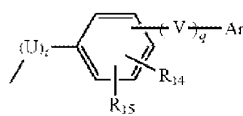
$Y$  represents CH or nitrogen;

$Z$  represents  $CH_2$ , oxygen, or N-alkyl;

$n$  represents an integer of 0 to 3;

$U$  represents alkylene; and

$t$  represents an integer of 0 or 1,



Formula (4)

wherein,

R<sub>14</sub> and R<sub>15</sub> are the same or different, and each represents hydrogen, halogen, or alkyl optionally having one or two substituents, cycloalkyl optionally having one or two substituents, or alkoxy optionally having one or two substituents;

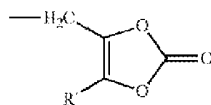
V is alkylene, alkyleneoxyalkylene, oxyalkylene, alkyleneoxy, or oxygen;

q represents an integer of 0 or 1;

U and t are as defined above; and

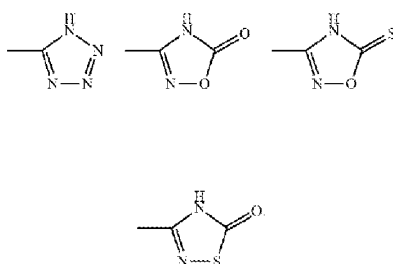
Ar represents aryl having one or two substituents (the one or two substituents optionally form a ring with a part of carbon atoms in the aryl group), 5- to 6-membered ring aryl group having one or two identical or different heteroatoms optionally having one or two substituents, or benzo-fused heteroaryl optionally having one to three substituents; and

B represents COOR<sub>16</sub>, wherein R<sub>16</sub> represents hydrogen, alkyl, aryl or aralkyl, a group represented by CH(R<sub>17</sub>)O---COR<sub>18</sub> or ---CH(R<sub>17</sub>)---O---CO---OR<sub>18</sub>, wherein R<sub>17</sub> is hydrogen or alkyl, and R<sub>18</sub> is alkyl or cycloalkyl; a (5-alkyl-2-oxo-1,3-dioxolen-4-yl)methyl group represented by the following Formula (5):



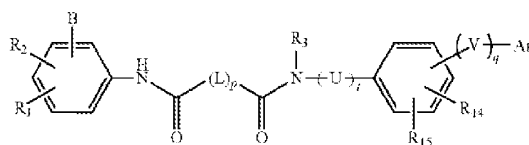
Formula (5)

wherein, R' represents alkyl, or a heterocyclic group: a 1H-tetrazol-5-yl group, a 4,5-dihydro-5-oxo-4H-1,2,4-oxadiazol-3-yl group, a 4,5-dihydro-5-thioxo-4H-1,2,4-oxadiazol-3-yl group, or a 4,5-dihydro-5-oxo-1,2,4-thiadiazol-3-yl group, represented by the following Formulae (6), (7), (8) (sequentially from the left), (9) (bottom):



Formulae (6), (7), (8) (sequentially from the left), (9) (bottom).

38. The composition of claim 1, wherein the PAI-1 inhibitor is a compound of Formula (10)



Formula (10)

wherein,

R<sub>1</sub> and R<sub>2</sub> are the same or different, and each represents hydrogen, halogen, alkyl, or aryl optionally having one or two substituents;

R<sub>3</sub> is hydrogen or alkyl;

R<sub>14</sub> and R<sub>15</sub> are the same or different, and each represents hydrogen, alkyl, or halogen;

V is alkylene, oxyalkylene, or oxygen;

Ar is aryl optionally having one or two substituents, aryl group having one or two identical or different heteroatoms optionally having one or two substituents, or benzofused heteroaryl optionally having one or three substituents;

L is alkylene, alkyleneoxyalkylene, alkylenethioalkylene, alkylene-SO-alkylene, alkylene-SO<sub>2</sub>-alkylene; and

q, U, t, p, and B are as defined in claim 37.

39. The composition of claim 1, wherein the PAI-1 inhibitor is selected from a group consisting of: 5-Chloro-2-[(2-[[3-(furan-3-yl)phenyl]amino]-2-oxoethoxy)acetyl]amino benzoic acid, 5-Chloro-2-[[[3-(furan-3-yl)phenyl]amino](oxo)acetyl]amino benzoic acid, a benzopyran compound, a butadiene, spironolactone, imidapril, an angiotensin converting enzyme inhibitor (ACEI, captopril, or enalapril), an angiotensin II receptor antagonist (AIIRA), a defibrotide (a polydeoxyribonucleotide), and any combination thereof.

40. The composition of claim 39, wherein the PAI-1 inhibitor is 5-Chloro-2-[(2-{[3-(furan-3-yl)phenyl]amino}-2-oxoethoxy)acetyl]amino benzoic acid.
41. The composition of claim 1, wherein the PAI-1 inhibitor is delivered in an amount sufficient to reduce graying of one or more hairs.
42. The composition of claim 1, wherein the PAI-1 inhibitor is delivered in an amount sufficient to treat a dermatological condition.
43. The composition of claim 1, wherein the PAI-1 inhibitor is delivered in an amount sufficient to treat a non-dermatological condition.
44. The composition of claim 43, wherein the non-dermatological condition is lung fibrosis, lung cancer, chronic myeloid leukemia, metabolic syndrome, diabetes, thrombosis, obesity, kidney fibrosis, liver fibrosis, cardiac fibrosis, or atherosclerosis.
45. The composition of claim 1, wherein the composition is characterized in that, when administered to an animal comprising a one or more gray hairs, achieves at least one of:
- (i) reduction in the number of the plurality of gray hairs;
  - (ii) restoration of color of the one or more gray hairs;
  - (iii) prevention of graying of one or more non-gray hairs; and
  - (iv) a delayed onset of graying of the one or more non-gray hairs.
46. The composition of claim 1, wherein the composition is characterized in that, when administered to an animal comprising a one or more hairs, achieves at least one of:
- (i) a reduction in hair loss;
  - (ii) prevention of hair loss;
  - (iii) a delayed onset of hair loss of the one or more hairs; and

(iv) an increase in the number of hairs on the site.

47. A method of treating or preventing hair graying, the method comprising:

providing the composition of claim 1;

administering the composition to a site of a subject, wherein the site contains or did contain a plurality of hair follicles, each with a hair disposed therein, so that the PAI-1 inhibitor is delivered to the subject.

48. A method of treating or preventing hair loss, the method comprising:

providing the composition if claim 1;

administering the composition to a subject, wherein a site of the subject contains or did contain a plurality of hair follicles, each with a hair disposed therein, so that the PAI-1 inhibitor is delivered to the subject.

49. A method of treating or preventing a dermatological condition, the method comprising:

providing the composition if claim 1;

administering the composition to a subject, wherein a site of the subject contains or did contain a plurality of hair follicles, each with a hair disposed therein, so that the PAI-1 inhibitor is delivered to the subject.

50. The method of claims 47-49, wherein the hair is gray.

51. The method of claims 47-49, wherein the hair is not gray.

52. The method of claims 47-51, wherein the composition is administered in combination with microneedle skin conditioning (MSC) of the site.

53. The method of claim 52, wherein the MSC of the site is performed before applying the composition.
54. The method of claim 52, wherein the MSC of the site is performed after applying the composition.
55. The method of claim 52, wherein the MSC of the site and administration of the composition occur at substantially the same time.
56. The method of claim 52, further comprising administering a plurality of doses of the composition according to a dosing regimen in which at least two successive doses are separated from one another by a time period of at least 12 hours.
57. The method of claim 49, wherein the dermatological condition is keloids or scleroderma.
58. The method of claim 57, further comprising administering one or more other active agents, wherein the one or more other active agents is selected from the group comprising of pressure therapy, silicone gel sheeting, intra-lesional triamcinolone acetonide (TAC), cryosurgery, radiation, laser therapy, IFN, 5-FU, high doses of oxygen using hyperbaric oxygen therapy (HBOT), cryotherapy, surgical excision, topical agents, and combinations thereof.
59. The method of claim 49, wherein the dermatological condition is scleroderma.
60. The method of claim 49, wherein the dermatological condition is systemic scleroderma.

61. The method of claim 49, wherein the dermatological condition is cutaneous scleroderma.
62. The method of claim 59, further comprising administering one or more other active agents, wherein the one or more other active agents is selected from the group comprising of Angiotensin II Receptor Antagonists, Angiotensin Converting Enzyme (ACE) Inhibitors, NSAIDs, COX-2 Inhibitors, Analgesics, Low-Dose Corticosteroids, Narcotics, Antacids, H2 Blockers, Proton Pump Inhibitors, Prokinetic Agents, Somatostatin Agonist, Antibiotics, Prostaglandin Derivatives, Treprostinil, Iloprost, Endothelin Receptor Antagonists, IP Receptor Agonist, Phosphodiesterase type 5 (PDE5) inhibitors, Anti-Fibrotic Agent, Tyrosine Kinase Inhibitor, Immunosuppressants, Alkylating agents, Pilocarpine, and combinations thereof.
63. The method of claim 49, wherein the dermatological condition is Raynaud's phenomenon.
64. The method of claim 63, further comprising administering one or more other active agents, wherein the one or more other active agents is selected from the group comprising of calcium channel blockers, alpha blockers, nitroglycerin, angiotensin II receptor antagonists, selective serotonin reuptake inhibitors, glyceryl trinitrate, tadalafil, *Ginkgo biloba* extract, SLx-2101, St. John's Wort, fasudil, cilostazol, iloprost, relaxin, treprostinil diethanolamine, sildenafil, atorvastatin, imatinib mesylate, treprostinil diethanolamine, and combinations thereof.
65. The method of claim 49, wherein the dermatological condition is or comprises hair graying.
66. The method of claim 65, further comprising administering one or more other active agents, wherein the one or more other active agents is selected from the group comprising of cinnamidopropyltrimonium chloride, solid lipid nanoparticles, l-cystine, l-methionine, melatonin, and combinations thereof.

67. The method of any of the preceding claims, wherein the administering comprises maintaining the composition on the skin surface for a period of time.
68. The method of claim 67 further comprising, after the period of time, removing remaining composition from the site.
69. The method of any of the preceding claims, wherein the step of administering the composition comprises massaging the composition into the site.
70. The method of claim 67, wherein the period of time is at least 1 minute.
71. The method of claim 67, wherein the period of time is at least 1 hour.
72. The method of claim 67, wherein the period of time is within a range of 1 to 10 minutes.
73. The method as claimed in any one of the preceding claims, wherein the composition is or comprises a suspension.
74. The method as claimed in any one of the preceding claims, wherein the composition is or comprises a foam.
75. The method as claimed in any one of the preceding claims, wherein the composition comprises an emulsion.
76. The method as claimed in any one of the preceding claims, wherein the emulsion is a nanoemulsion.

77. The method as claimed in any one of the preceding claims, further comprising a step of administering a penetrating treatment.

78. The method as claimed in claim 77, wherein the penetrating treatment is or comprises a non-irritating chemical agent.

79. The method as claimed in claim 77, wherein the penetrating treatment is or comprises administration of an electric or magnetic field.

80. The method as claimed in claim 77, wherein the penetrating treatment is or comprises microneedling.

81. The method as claimed in claim 77, wherein the penetrating treatment is or comprises laser treatment.

82. The method of any of the preceding claims, wherein the PAI-1 inhibitor penetrates the site within about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 minutes of administration.

83. The method of any of the preceding claims, wherein the PAI-1 inhibitor penetrates the site within about 5 to about 60 minutes, about 5 to about 12 minutes, about 5 to about 15 minutes, or about 15 to about 30 minutes of administration.

84. The method of any of the preceding claims, wherein the PAI-1 inhibitor penetrates the site within about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or 24 hours of administration.

85. The method of any of the preceding claims, wherein the PAI-1 inhibitor penetrates the site within about 1 to about 12 hours, about 8 to about 12 hours or 12 hours to about 24 hours of administration.

86. The method as claimed in any one of the preceding claims, comprising more than one administration of the composition over time.

87. The method as claimed in claim 86, wherein each administration comprising the PAI-1 inhibitor is separated by a specified period of time.

88. The composition of claim 1 for use in treating a dermatological condition.

89. The composition of claim 1 for use in treating or preventing hair graying.

90. The composition of claim 1 for use in treating or preventing hair loss.

91. The composition of claim 90, wherein the hair loss is androgenetic alopecia, alopecia areata, frontal fibrosing alopecia, and senescent alopecia.

92. Use of the composition of claim 1 in the manufacture of a medicament for the treatment of hair graying.

93. Use of the composition of claim 1 in the manufacture of a medicament for the treatment of hair loss.

94. Use of the composition of claim 1 in the manufacture of a medicament for the treatment of a dermatological condition.

95. The use of claim 94, wherein the dermatological condition is selected from scleroderma, keloids, Raynaud's phenomenon, or hair graying.
96. A kit comprising the composition of claim 1 and instructions for administering the composition to the site.
97. The kit of claim 96, wherein the kit further comprises gloves.
98. A kit comprising the composition of claim 1 and a patch for use in covering the composition after administration to the site.
99. A kit comprising the composition of claim 1, a device for facilitating penetration of the composition into a site on a subject, and instructions for administering the composition to the site.
100. The kit of claim 98, wherein the device comprises a plurality of needles.
101. The kit of claim 99, wherein the device is a patch, a roller, stamp, or pen.
102. The composition of claims 1-46 and 87-91, wherein the composition is formulated as a lotion, serum, suspension, cream, powder, ointment, liniment, gel, drops, emollient, balm, or paste.
103. The method of claims 47-87, wherein the composition is formulated as a lotion, serum, suspension, cream, powder, ointment, liniment, gel, drops, emollient, balm, or paste.
104. The use of claims 92-95, wherein the composition is formulated as a lotion, serum, suspension, cream, powder, ointment, liniment, gel, drops, emollient, balm, or paste.

105. The kit of claims 96-101, wherein the composition is formulated as a lotion, serum, suspension, cream, powder, ointment, liniment, gel, drops, emollient, balm, or paste.