PLASMINOGEN ACTIVATOR INHIBITOR 1 (PAI-1) INHIBITORS AND USES THEREFOR

Cross-Reference To Related Applications

[0001] This application claims priority to United States Provisional Application No. 62/731,074, filed September 13, 2018, the entirety of which is incorporated herein by reference.

Background

[0002] Graying hair and other dermatological conditions often promote significant anxiety; many people go to great lengths to hide their gray, particularly if it arrives prematurely. Previously available therapies have largely proven unsatisfactory, hence new treatment options are needed.

Summary

[0002a] In an aspect of the present disclosure, there is provided a ~~use of a plasminogen activator inhibitor-1 (PAI-1) inhibitor in the manufacture of a medicament for~~ non-therapeutic method of treating ~~a dermatological condition~~ hair graying, wherein the ~~treating~~ method comprises:
providing a composition that comprises or delivers ~~the~~ a plasminogen activator inhibitor-1 (PAI-1) inhibitor;
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.

[0002b] In another aspect of the present disclosure, there is provided a ~~use of a plasminogen activator inhibitor-1 (PAI-1) inhibitor in the manufacture of a medicament for~~ non-therapeutic method of treating ~~a dermatological condition~~ hair graying, wherein the ~~treating~~ method comprises:
providing a composition that comprises or delivers a plasminogen activator inhibitor-1 ~~the~~ (PAI-1) inhibitor;
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.

[0002c] In a further aspect of the present disclosure, there is provided a ~~use of a plasminogen activator inhibitor-1 (PAI-1) inhibitor in the manufacture of a medicament for~~ non-therapeutic method of preventing the occurrence or progression ~~a dermatological condition~~of hair graying, wherein the ~~preventing~~ method comprises:

providing a composition that comprises or delivers ~~the~~a plasminogen activator inhibitor-1 (PAI-1) inhibitor;

administering the composition topically to a site of the subject, wherein the site is a skin surface that contains or contained a plurality of hair follicles, each with a hair disposed therein; and

leaving the composition on the site for a period of time, so that the PAI-1 inhibitor is delivered to the subject.

[0002d] In another aspect of the present disclosure, there is provided a composition comprising ~~a therapeutically effective~~an amount of a PAI-1 inhibitor effective to treat hair graying and a pharmaceutically acceptable carrier formulated for topical administration to a site of a subject, wherein the site contains or did contain a plurality of hair follicles, each with a hair disposed therein.

[0002e] In a further aspect of the present disclosure, there is provided a kit comprising a composition ~~comprising a PAI-1 inhibitor~~ as disclosed herein and a patch for use in covering the composition comprising the PAI-1 inhibitor after administration to a site.

[0002f] In another aspect of the present disclosure, there is provided a kit comprising a composition ~~comprising a PAI-1 inhibitor~~as disclosed herein, a device for facilitating penetration of a composition comprising the PAI-1 inhibitor into a site on a subject, and instructions for administering the composition to the site.

[0002g] In a further aspect of the present disclosure, there is provided a composition comprising ~~a therapeutically effective~~an amount of a PAI-1 inhibitor effective to achieve, when~~,~~ ~~wherein~~ the composition is ~~characterized in that, when~~ topically administered to a site on an animal comprising ~~a~~ one or more gray hairs, ~~achieves~~ at least one of:

(i) a reduction in the number of the plurality of gray hairs at the site;

(ii) prevention of graying of one or more non-gray hairs at the site; and

(iii) a delayed onset of graying of the one or more non-gray hairs at the site.

[0003] The present disclosure provides, *inter alia*, new technologies (e.g., methods, kits, compositions, etc) for treatment and/or prevention of certain dermatological conditions, specifically including graying hair. Among other things, the present disclosure provides an insight that plasminogen activator inhibitor -1 (PAI-1) inhibitors may be useful in the treatment and/or prevention of certain dermatological conditions, for example, in treatment and/or prevention of graying hair.

Claims

We claim:

1. A non-therapeutic method of ~~Use of a plasminogen activator inhibitor-1 (PAI-1) inhibitor in the manufacture of a medicament for~~ treating ~~a dermatological condition~~hair graying, wherein the ~~treating~~ method comprises:

providing a composition that comprises or delivers a plasminogen activator inhibitor-1 ~~the~~ (PAI-1) inhibitor;

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.

2. The ~~use~~ method of claim 1, wherein the administering is by topically applying to a site on a skin surface.

3. The method ~~use~~ of claim 2, wherein the administering comprises maintaining the composition on the skin surface for a period of time.

4. The method ~~use~~ of claim 1, wherein the administering is by injection.

5. A non-therapeutic method of ~~Use of a plasminogen activator inhibitor-1 (PAI-1) inhibitor in the manufacture of a medicament for~~ treating ~~a dermatological condition~~hair graying, wherein the ~~treating~~ method comprises:

providing a composition that comprises or delivers ~~the~~ a plasminogen activator inhibitor-1 (PAI-1) inhibitor;

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.

6. The method ~~use~~ of claim 5, wherein the administering is by oral administration.

7. The method ~~use~~ of claim 3, wherein the method ~~treating~~ further comprises, after the period of time, removing remaining composition from the site.

8. The method ~~use~~ of any one of claims 3, 4, or 7, wherein the step of administering the composition comprises massaging the composition into the site.

9. The method ~~use~~ of claim 3, wherein the period of time is at least 1 minute.

10. The method ~~use~~ of claim 3, wherein the period of time is at least 1 hour.

11. The method ~~use~~ of claim 9, wherein the period of time is within a range of 1 to 10 minutes.

12. The method ~~use~~ of any of the preceding claims, wherein the PAI-1 inhibitor is selected from the group consisting of: polypeptides, nucleic acids, lipids, carbohydrates, small molecules, metals, polymers, therapeutic antibodies, and combinations thereof.

13. The method ~~use~~ of claim 12, wherein the nucleic acid is or comprises siRNA.

14. The method ~~use~~ of claim 12, 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.

15. The method ~~use~~ of claim~~s~~ 14, wherein the PAI-1 inhibitor is 5-Chloro-2-{[(2-{[3-(furan-3-yl)phenyl]amino}-2-oxoethoxy)acetyl]amino benzoic acid.

16. The method ~~use~~ of any one of the preceding claims, wherein the composition comprising the PAI-1 inhibitor is or comprises a suspension.

17. The method ~~use~~ of any one of the preceding claims, wherein the composition comprising the PAI-1 inhibitor is or comprises a foam.

18. The method ~~use~~ of any one of the preceding claims, wherein the composition comprising the PAI-1 inhibitor comprises an emulsion.

19. The method ~~use~~ of claim 18, wherein the emulsion is a nanoemulsion.

20. The method ~~use~~ of any one of the claims 1-3 or 7-19, wherein the method ~~treating~~ further comprises a step of administering a penetrating treatment.

21. The method ~~use~~ of claim 20, wherein the penetrating treatment is or comprises a non-irritating chemical agent.

22. The method ~~use~~ of claim 20, wherein the penetrating treatment is or comprises administration of an electric or magnetic field.

23. The method ~~use~~ of claim 20, wherein the penetrating treatment is or comprises microneedling.

24. The method ~~use~~ of claim 20, wherein the penetrating treatment is or comprises laser treatment.

~~25. The use of any one of the claims 1-3 or 7-24, wherein the PAI-1 inhibitor penetrates the site within about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 minutes of administration.~~

~~26. The use of any one of the claims 1-3 or 7-25, 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.~~

~~27. The use of any one of the claims 1-3 or 7-26, 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.~~

~~28. The use of any one of the claims 1-3 or 7-27, 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.~~

25~~29~~. The method ~~use~~ of any one of the preceding claims, wherein the treating comprises more than one administration of the composition~~-~~ over time.

26~~30~~. The method ~~use~~ of claim 25~~29~~, wherein each administration comprising the PAI-1 inhibitor is separated by a specified period of time.

~~31. The use of claim 30, wherein the specified period of time is longer as compared to the specified period of time for administering a reference treatment regimen.~~

~~32. The use of any one of the preceding claims, wherein the dermatological condition is or comprises hair graying.~~

27~~33~~. The method ~~use~~ of any one of the preceding claims, wherein the hair is gray.

~~34~~28. The method ~~use~~ of any one of the claims 1-3 or 7-27~~33~~, wherein the composition is formulated as a suspension, a foam, a lotion, a cream, a gel, an oil, a powder, a liniment, or drops.

29~~35~~. A non-therapeutic method of ~~Use of a plasminogen activator inhibitor-1 (PAI-1) inhibitor in the manufacture of a medicament for~~ preventing the occurrence or progression of hair graying~~a dermatological condition~~, wherein the ~~preventing~~ method comprises:

providing a composition that comprises or delivers ~~the~~ a plasminogen activator inhibitor-1 (PAI-1) inhibitor;

administering the composition topically to a site of the subject, wherein the site is a skin surface that contains or contained a plurality of hair follicles, each with a hair disposed therein; and

leaving the composition on the site for a period of time, so that the PAI-1 inhibitor is delivered to the subject.

30~~36~~. The method ~~use~~ of claim 29~~35~~, wherein the method ~~preventing~~ further comprises, after the period of time, removing remaining composition from the site.

37~~31~~. The method ~~use~~ of claim~~s~~ 1-3,~~25~~ or ~~claim 36~~7-30, wherein the step of administering the composition comprises massaging the composition into the site.

32~~38~~. The method ~~use~~ of any of claims 29~~35~~ to ~~37~~31, wherein the period of time is within a range of ~~about~~ 1 to ~~about~~ 10 minutes, ~~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, ~~about~~ 1 to ~~about~~ 12 hours, ~~about~~ 8 to ~~about~~ 12 hours or 12 hours to ~~about~~ 24 hours.

~~39~~33. The method ~~use~~ of any of claims 29~~35~~ to ~~37~~31, wherein the PAI-1 inhibitor is selected from the group consisting of: polypeptides, nucleic acids, lipids, carbohydrates, small molecules, metals, polymers, therapeutic antibodies, and combinations thereof.

~~40~~34. The method ~~use~~ of claim 33~~39~~, wherein the nucleic acid is or comprises siRNA.

~~41~~35. The method ~~use~~ of claim ~~39~~33, 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.

~~42~~36. The method ~~use~~ of claim~~s 41~~ 35, wherein the PAI-1 inhibitor is 5-Chloro-2-{[(2-{[3-(furan-3-yl)phenyl]amino}-2-oxoethoxy)acetyl]amino benzoic acid.

37~~43~~. The method ~~use~~ of any one of claims 29~~35~~ to 36~~42~~, wherein the composition comprising the PAI-1 inhibitor is or comprises a suspension.

38~~44~~. The method ~~use~~ of any one of claims 29~~35~~ to 36~~42~~, wherein the composition comprising the PAI-1 inhibitor is or comprises a foam.

39~~45~~. The method ~~use~~ of any one of claims 29~~35~~ to 36~~42~~, wherein the composition comprising the PAI-1 inhibitor comprises an emulsion.

40~~46~~. The method ~~use~~ of claim 39~~45~~, wherein the emulsion is a nanoemulsion.

~~47. The use of any one of claims 35 to 46, wherein the preventing further comprises a step of administering a penetrating treatment.~~

~~48. The use of claim 47, wherein the penetrating treatment is or comprises a non-irritating chemical agent.~~

~~49. The use of claim 47, wherein the penetrating treatment is or comprises administration of an electric or magnetic field.~~

~~50. The use of claim 47, wherein the penetrating treatment is or comprises microneedling.~~

~~51. The use of claim 47, wherein the penetrating treatment is or comprises laser treatment.~~

~~52. The use of any one of claims 35 to 51 wherein the PAI-1 inhibitor penetrates the site within about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 minutes of administration.~~

~~53. The use of any one of claims 35 to 52, 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.~~

~~54. The use of any one of claims 35 to 53, 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.~~

~~55. The use of any one of the claims 35 to 54, 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.~~

4156. The method ~~use~~ of any one of claims 2935 to 4055, comprising more than one administration of the composition comprising the PAI-1 inhibitor over time.

4257. The method ~~use~~ of claim 4156, wherein each administration comprising the PAI-1 inhibitor is separated by a specified period of time.

~~58. The use of claim 57, wherein the specified period of time is longer as compared to the specified period of time for administering a reference treatment regimen.~~

~~59. The use any one of claims 35 to 58, wherein the dermatological condition is or comprises hair graying.~~

4360. The method ~~use~~ of any one of claims 2935 to 4259, wherein the hair is not gray.

4461. The method ~~use~~ of any one of claims 2935 to 4360, wherein the composition is formulated as a suspension, a foam, a lotion, a cream, ~~-~~a gel, an oil, a powder, a liniment, or drops.

4562. A composition comprising ~~a therapeutically effective~~ an amount of a PAI-1 inhibitor effective to treat hair graying and a pharmaceutically acceptable carrier formulated for topical administration to a site of a subject, wherein the site contains or did contain a plurality of hair follicles, each with a hair disposed therein.

~~63. The composition of claim 62, wherein the composition is formulated for topical administration.~~

4664. The composition of claim 6345, wherein the ~~therapeutically effective~~ amount is ~~about~~ 0.1% w/w to ~~about~~ 5 % w/w, ~~about~~ 0.1 % to ~~about~~ 10% w/w, ~~about~~ 0.1% to ~~about~~ 15% w/w, ~~about~~ 0.1% w/w to ~~about~~ 20% w/w, or ~~about~~ 1% w/w to ~~about~~ 5% w/w.

~~65. The composition of claim 62, wherein the composition is formulated for oral administration.~~

~~66. The composition of claim 65, wherein the therapeutically effective amount is about 10 mg/day to about 100 mg/day, about 10 mg/day to about 200 mg/day, about 10 mg/day to about 300 mg/day, about 10 mg/day to about 400 mg/day, about 10 mg/day to about 500 mg/day, about 10 mg/day to about 600 mg/day, about 10 mg/day to about 700 mg/day, about 10 mg/day to about 800 mg/day, about 10 mg/day to about 900 mg/day, or about 10 mg/day to about 1000 mg/day.~~

4767. The composition of ~~any one of claims 62 to 66~~claim 45 or claim 46, wherein the PAI-1 inhibitor is selected from the group consisting of~~-~~: polypeptides, nucleic acids, lipids, carbohydrates, small molecules, metals, polymers, therapeutic antibodies, and combinations thereof.

4868. The composition of claim 6747, wherein the nucleic acid is or comprises siRNA.

4969. The composition of claim 6747, 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.

5070. The composition of claim 6949, wherein the PAI-1 inhibitor is 5-Chloro-2-{[(2-{[3-(furan-3-yl)phenyl]amino}-2-oxoethoxy)acetyl]amino benzoic acid.

5171. The composition of any one of claims 4562 to 5070, wherein the composition comprising the PAI-1 inhibitor is or comprises a suspension.

5272. The composition of any one of claims 4562 to 5070, wherein the composition comprising the PAI-1 inhibitor is or comprises a foam.

5373. The composition of any one of claims 4562 to 5070, wherein the composition comprising the PAI-1 inhibitor comprises an emulsion.

5474. The composition of claim 5373, wherein the emulsion is a nanoemulsion.

5575. The composition of any one of claims 4562 to 5474, wherein the composition comprising the PAI-1 inhibitor is formulated as a suspension, a foam, a lotion, a cream, a gel, an oil, a powder, a liniment, or drops.

5676. A kit comprising a composition ~~comprising a PAI-1 inhibitor~~of claim 45 and a patch for use in covering the composition comprising the PAI-1 inhibitor after administration to a site.

5777. The kit of claim 7656, wherein the composition comprising the PAI-1 inhibitor is incorporated into the patch.

5878. The kit of claim ~~76~~ 56 or claim ~~77~~57, wherein the patch comprises microneedles.

5979. The kit of any one of claims 5676 to 5878, wherein the composition comprising the PAI-1 inhibitor is or comprises a suspension.

6080. The kit of any one of claims 5676 to 5878, wherein the composition comprising the PAI-1 inhibitor is or comprises a foam.

6181. The kit of any one of claims 5676 to 5878, wherein the composition comprising the PAI-1 inhibitor comprises an emulsion.

6282. The kit of claim 8161, wherein the emulsion is a nanoemulsion.

6383. A kit comprising a composition ~~comprising a PAI-1 inhibitor~~of claim 45, a device for facilitating penetration of a composition comprising the PAI-1 inhibitor into a site on a subject, and instructions for administering the composition to the site.

6484. The kit of any one of claim 6383, wherein the composition comprising the PAI-1 inhibitor is or comprises a suspension.

6585. The kit of any one of claim 6383, wherein the composition comprising the PAI-1 inhibitor is or comprises a foam.

6686. The kit of claim 6383, wherein the composition comprising the PAI-1 inhibitor is or comprises an emulsion.

6787. The kit of claim 6686, wherein the emulsion is a nanoemulsion.

6888. The kit of any one of claims 6383 to 6787, wherein the device is a brush or a comb.

6989. The kit of any one of claims 6383 to 6688, wherein the device is a patch, a roller, or a pen.

7090. The kit of any one of claims 5676 to 6989, wherein the composition comprising the PAI-1 inhibitor is formulated as a suspension, a foam, a lotion, a cream, a powder, an ointment, a liniment, a gel, or drops.

7191. A composition comprising a therapeutically effectivean amount of a PAI-1 inhibitor effective to achieve, when, wherein the composition is characterized in that, whentopically administered to a site on an animal comprising a one or more gray hairs, achieves at least one of:

(i) a reduction in the number of the plurality of gray hairs at the site;

(ii) prevention of graying of one or more non-gray hairs at the site; and

(iii) a delayed onset of graying of the one or more non-gray hairs at the site.

92. The composition of claim 91, wherein the composition is formulated for topical administration.

7293. The composition of claim 7192, wherein the therapeutically effective amount is about 0.1% w/w to about 5 % w/w, about 0.1 % to about 10% w/w, about 0.1% to about 15% w/w, about 0.1% w/w to about 20% w/w, or about 1% w/w to about 5% w/w.

94. The composition of claim 91, wherein the composition is formulated for oral administration.

95. The composition of claim 94, wherein the therapeutically effective amount is about 10 mg/day to about 100 mg/day, about 10 mg/day to about 200 mg/day, about 10 mg/day to

~~about 300 mg/day, about 10 mg/day to about 400 mg/day, about 10 mg/day to about 500 mg/day, about 10 mg/day to about 600 mg/day, about 10 mg/day to about 700 mg/day, about 10 mg/day to about 800 mg/day, about 10 mg/day to about 900 mg/day, or about 10 mg/day to about 1000 mg/day.~~

73~~96~~. The composition of ~~any one of~~ claim~~s~~ 71~~91 to 95~~ or claim 72, wherein the PAI-1 inhibitor is selected from the group consisting of : polypeptides, nucleic acids, lipids, carbohydrates, small molecules, metals, polymers, therapeutic antibodies, and combinations thereof.

74~~97~~. The composition of claim 73~~96~~, wherein the nucleic acid is or comprises siRNA.

75~~98~~. The composition of claim 73~~96~~, 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.

76~~99~~. The composition of claim 75~~98~~, wherein the PAI-1 inhibitor is 5-Chloro-2-{[(2-{[3-(furan-3-yl)phenyl]amino}-2-oxoethoxy)acetyl]amino benzoic acid.

77~~100~~. The composition of any one of claims 71~~91~~ to 76~~99~~, wherein the composition comprising the PAI-1 inhibitor is or comprises a suspension.

78~~101~~. The composition of any one of claims 71~~91~~ to 76~~99~~, wherein the composition comprising the PAI-1 inhibitor is or comprises a foam.

79102. The composition of any one of claims 7191 to 7699, wherein the composition comprising the PAI-1 inhibitor comprises an emulsion.

80103. The composition of claim 79102, wherein the emulsion is a nanoemulsion.

81104. The composition of any one of claims 7191 to 80103, wherein the composition comprising the PAI-1 inhibitor is formulated as a suspension, a foam, a lotion, a cream, a gel, an oil, a powder, a liniment, or drops.

~~105. The use of any one of claims 1 to 61, wherein the dermatological condition is hair graying.~~

82106. The ~~use~~ method of any one of claims ~~105~~ 1 to 44, 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.

~~107. The use of any one of claims 1 to 61, wherein the dermatological condition is keloids.~~

~~108. The use of claim 107, 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.~~

~~109. The use of any one of claims 1 to 61, wherein the dermatological condition is scleroderma.~~

~~110. The use of claim 109, 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, Phosphosdiesterase type 5 (PDE5) inhibitors, Anti-Fibrotic Agent, Tyrosine Kinase Inhibitor, Immunosuppressants, Alkylating agents, Pilocarpine, and combinations thereof.~~

~~111. The use of any one of claims 1 to 61, wherein the dermatological condition is Raynaud's phenomenon.~~

~~112. The use of claim 111, 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.~~