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 treating a dermatological condition, wherein the treating comprises:
providing a composition that comprises or delivers 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.

[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 treating a dermatological condition, wherein the treating comprises:
providing a composition that comprises or delivers 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 preventing the occurrence or progression a dermatological condition, wherein the preventing comprises:

providing a composition that comprises or delivers the 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 amount of a PAI-1 inhibitor and a pharmaceutically acceptable carrier.

[0002e] In a further aspect of the present disclosure, there is provided a kit comprising a composition comprising a PAI-1 inhibitor 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, 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 amount of a PAI-1 inhibitor, 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) a reduction in the number of the plurality of gray hairs;
(ii) prevention of graying of one or more non-gray hairs; and
(iii) a delayed onset of graying of the one or more non-gray hairs.

[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.

[0004] Those skilled in the art are aware that over-expression of PAI-1 is associated with the prevention of the conversion of plasminogen to plasmin which is essential to fibrinolysis, which is the physiological breakdown of blood clots. The present disclosure provides an insight PAI-1 may also be associated with certain dermatological conditions. The present disclosure provides new technologies (e.g., methods, kits, compositions, etc) for treatment and/or prevention of certain dermatological conditions, including graying hair. Alternatively or additionally, in some examples, provided technologies may be utilized for treatment and/or prevention of dermatological conditions such as keloids, scleroderma, and Raynaud's phenomenon.

[0005] In some examples, the present disclosure provides methods of treating a dermatological condition comprising providing a composition that comprises or delivers 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. Additionally or alternatively, in some examples, the present disclosure provides methods of treating a dermatological condition comprising administering a provided composition to a subject, at 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.

[0006] In some examples, the present disclosure provides methods of preventing the occurrence or progression of a dermatological condition, comprising providing a composition that comprises or delivers 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.

[0007] In some examples, the present disclosure provides new technologies for treating and/or preventing the occurrence or progression of a dermatological condition. In some examples, a dermatological condition is or comprises hair graying. In some examples, a dermatological condition is or comprises keloids. In some examples, a dermatological condition is or comprises scleroderma. In some examples, a dermatological condition is or comprises Raynaud's disease.

[0008] In some examples, the present disclosure provides new compositions that comprise and/or deliver a therapeutically effective amount of a PAI-1 inhibitor. In certain examples, the present disclosure provides new compositions that comprise and/or deliver a therapeutically effective amount of a PAI-1 inhibitor and a pharmaceutically acceptable carrier. In some examples, a therapeutically effective amount in w/w is about 0.1% to about 5 %, about 0.1 % to about 10%, about 0.1% to about 15% , about 0.1% to about 20%, or about 1% to about 5% . In some examples, a 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.

[0009] In some examples, a provided new composition is characterized in that, when administered to an animal suffering from or susceptible to at least one dermatological condition, it achieves at least one of: (i) treatment of at least one dermatological condition in an animal; (ii) delay, retardation, or prevention of progression of at least one dermatological condition in an animal. In certain particular examples, for example when a dermatological condition is or comprises hair graying, a provided new composition may be 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) prevention of graying of one or more non-gray hairs (e.g., present at and/or near a site of administration) and (iii) a delayed onset of graying of one or more non-gray hairs (e.g., present at and/or near a site of administration).

[0010] In general, administration of a composition in accordance with the present disclosure may be by any of a variety of routes.. In some examples, administration is topical. In some examples, administration is by injection. In some examples, administration is oral.

[0011] In some examples, administration achieves systemic delivery. In some examples, administration achieves local delivery.

[0012] In some examples administration is or comprises maintaining a composition at or on a site for a period of time. In some examples administration is or comprises massaging a composition into a site.

[0013] In some examples, a composition is maintained at or on a site for a period of time that is at least 1 minute. In some examples, a period of time is at least 1 hour. In

some examples, a period of time is within a range of 1 to 10 minutes. In some examples, a 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.

[0014] In some examples, provided methods of treating a dermatological condition may include, removing administered composition (e.g., removing composition that may remain after a period of time) from its site of administration. In some examples, such removing is or comprises rinsing or wiping (e.g., using a wipe that, in some examples may be wet or, in some examples, may be dry).

[0015] In some examples, a site to which a composition is administered in accordance with the present disclosure may be on a skin surface. In some examples, a site is or comprises hair follicles. In some examples a site comprises hair. In some examples, a site is or comprises skin overlying a muscle or muscle group. In some examples, a site is hairless. In some examples, a site is on the torso. In some example a site is on the back. In some examples a site is on the chest. In some examples, a site is on the buttocks. In some examples, a site is on the crotch. In some examples, a site is on the groin. In some examples, a site is on the head. In some examples a site is on the scalp. In some examples, a site is on the face. In some examples a site is on the neck. In some examples a site is on the décolleté. In some examples, a site is in the armpit. In some examples, a site is on the axillae. In some examples a site is on the hands. In some examples a site is on the feet. In some examples a site is on the arms. In some examples a site is on the legs. In some examples, a site formerly had hair or hair follicles but no longer has hair or hair follicles. In some examples, a site has hair follicles. In some examples, hair follicles present at a site have normal structure and/or density. In some examples, a site has hair; in some examples, such hair is gray but in some examples,such hair is not gray.

[0016] In some examples, a PAI-1 inhibitor for use in accordance with the present disclosure, is or comprises a polypeptide, a nucleic acid, a lipid, a carbohydrate, a

small molecule, a metal, or a combination thereof. In some examples, a PAI-1 inhibitor is or comprises a polymer (e.g., a polypeptide or polynucleotide). In some examples, a PAI-1 inhibitor is or comprises an antibody (e.g., an anti-PAI-1 antibody). In some examples, a PAI-1 inhibitor is or comprises a nucleic acid (e.g., is an oligonucleotide, such as an antisense oligonucleotide, an siRNA, etc). In some examples, a PAI-1 inhibitor is or comprises a small molecule. In some examples, a PAI-1 inhibitors is or comprises 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, e.g., captopril, or enalapril), an angiotensin II receptor antagonist (AIIRA), a defibrotide (a polydeoxyribonucleotide) or any combination thereof. In some examples, a PAI-1 inhibitor is or comprises 5-Chloro-2-{[(2-{[3-(furan-3-yl)phenyl]amino}-2-oxoethoxy)acetyl]amino benzoic acid.

[0017] In some examples, the present disclosure provides and/or utilizes a composition that comprises and/or delivers a PAI-1 inhibitor. In some examples, such a composition is or comprises a suspension. In some examples, such a composition is or comprises a foam. In some examples, such a composition is or comprises an emulsion, e.g., a nanoemulsion. In some examples, such a composition is formulated as a suspension, a foam, a lotion, a cream, a gel, an oil, a powder, a liniment, or drops.

[0018] In some examples, provided methods of treating a dermatological condition comprises a step of administering a penetrating treatment. In some examples, a penetrating treatment is or comprises a non-irritating chemical agent. In some examples, a penetrating treatment is or comprises administration of an electric or magnetic field. In some examples, a penetrating treatment is or comprises microneedling. In some examples, a penetrating treatment is or comprises laser treatment.

[0019] In some examples, provided technologies aide in PAI-1 inhibitor penetration of site of administration. In some examples, a provided PAI-1 inhibitor (e.g., in or from a composition as described herein) penetrates its site of administration

within about 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 minutes of administration. In some examples, a provided PAI-1 inhibitor penetrates site of administration 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 examples, a provided PAI-1 inhibitor penetrates site of administration within about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 or 24 hours of administration. In some examples, a provided PAI-1 inhibitor penetrates site of administration within about 1 to about 12 hours, about 8 to about 12 hours or 12 hours to about 24 hours of administration.

[0020] In some examples, according to the present disclosure, methods of treatment and/or prevention of dermatological conditions comprises two or more administrations of a PAI-1 inhibitor composition over time. In some examples, administration of two or more administrations of a composition is separated by a specified period of time. In some examples, according to the present disclosure, a specified period of time for administering a composition may be longer than a specified period of time for administering a reference treatment regimen.

[0021] Disclosed herein, in certain examples, are kits comprising compositions that comprise or deliver a PAI-1 inhibitor.

[0022] In some examples, provided kits comprise a patch. In some examples, a patch is arrange, constructed, and/or utilized for administration to cover an administered composition. Alternatively or additionally, in some examples, a patch may contain or comprise a composition that comprises and/or delivers a PAI-1 inhibitor. In some examples, a patch comprises microneedles.

[0023] In some examples, provided kits comprise a device for facilitating penetration of a composition into a site on a subject. In some such examples, a provided device may be or comprises a brush, a comb, patch, a roller, a pen, etc.

[0024] In some examples, provided kits comprise instructions for administering a composition as described herein. In some examples, the present disclosure provides insight into administering combination therapy and/or treatment to treat or prevent the

occurrence of a dermatological condition. In some examples, the combination therapy or treatment, comprises administering a PAI-1 inhibitor as described herein in combination with one or more other active agents. In some examples, for example for hair graying, 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. In some examples, for example for keloids, 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. In some examples, for example for scleroderma, 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. In some examples, for example for Raynaud's disease or Raynaud's phenomenon, 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.

Definitions

[0025] 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

Claims

We claim:

1. Use of a plasminogen activator inhibitor-1 (PAI-1) inhibitor in the manufacture of a medicament for treating a dermatological condition, wherein the treating comprises:

providing a composition that comprises or delivers 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 of claim 1, wherein the administering is by topically applying to a site on a skin surface.

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

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

5. Use of a plasminogen activator inhibitor-1 (PAI-1) inhibitor in the manufacture of a medicament for treating a dermatological condition, wherein the treating comprises:

providing a composition that comprises or delivers 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.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

24. The 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.

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

30. The use of claim 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.

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

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

35. Use of a plasminogen activator inhibitor-1 (PAI-1) inhibitor in the manufacture of a medicament for preventing the occurrence or progression a dermatological condition, wherein the preventing comprises:

providing a composition that comprises or delivers the 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.

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

37. The use of claim 25 or claim 36, wherein the step of administering the composition comprises massaging the composition into the site.

38. The use of any of claims 35 to 37, 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. The use of any of claims 35 to 37, 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. The use of claim 39, wherein the nucleic acid is or comprises siRNA.

41. The use of claim 39, 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. The use of claims 41, wherein the PAI-1 inhibitor is 5-Chloro-2-{[(2-{[3-(furan-3-yl)phenyl]amino}-2-oxoethoxy)acetyl]amino benzoic acid.

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

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

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

46. The use of claim 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.

56. The use of any one of claims 35 to 55, comprising more than one administration of the composition comprising the PAI-1 inhibitor over time.

57. The use of claim 56, 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.

60. The use of any one of claims 35 to 59, wherein the hair is not gray.

61. The use of any one of claims 35 to 60, wherein the composition is formulated as a suspension, a foam, a lotion, a cream, a gel, an oil, a powder, a liniment, or drops.

62. A composition comprising a therapeutically effective amount of a PAI-1 inhibitor and a pharmaceutically acceptable carrier.

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

64. The composition of claim 63, 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.

67. The composition of any one of claims 62 to 66, 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.

68. The composition of claim 67, wherein the nucleic acid is or comprises siRNA.

69. The composition of claim 67, 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.

70. The composition of claim 69, wherein the PAI-1 inhibitor is 5-Chloro-2-{[(2-{[3-(furan-3-yl)phenyl]amino}-2-oxoethoxy)acetyl]amino benzoic acid.

71. The composition of any one of claims 62 to 70, wherein the composition comprising the PAI-1 inhibitor is or comprises a suspension.

72. The composition of any one of claims 62 to 70, wherein the composition comprising the PAI-1 inhibitor is or comprises a foam.

73. The composition of any one of claims 62 to 70, wherein the composition comprising the PAI-1 inhibitor comprises an emulsion.

74. The composition of claim 73, wherein the emulsion is a nanoemulsion.

75. The composition of any one of claims 62 to 74, 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.

76. A kit comprising a composition comprising a PAI-1 inhibitor and a patch for use in covering the composition comprising the PAI-1 inhibitor after administration to a site.

77. The kit of claim 76, wherein the composition comprising the PAI-1 inhibitor is incorporated into the patch.

78. The kit of claim 76 or claim 77, wherein the patch comprises microneedles.

79. The kit of any one of claims 76 to 78, wherein the composition comprising the PAI-1 inhibitor is or comprises a suspension.

80. The kit of any one of claims 76 to 78, wherein the composition comprising the PAI-1 inhibitor is or comprises a foam.

81. The kit of any one of claims 76 to 78, wherein the composition comprising the PAI-1 inhibitor comprises an emulsion.

82. The kit of claim 81, wherein the emulsion is a nanoemulsion.

83. A kit comprising a composition comprising a PAI-1 inhibitor, 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.

84. The kit of any one of claim 83, wherein the composition comprising the PAI-1 inhibitor is or comprises a suspension.

85. The kit of any one of claim 83, wherein the composition comprising the PAI-1 inhibitor is or comprises a foam.

86. The kit of claim 83, wherein the composition comprising the PAI-1 inhibitor is or comprises an emulsion.

87. The kit of claim 86, wherein the emulsion is a nanoemulsion.

88. The kit of any one of claims 83 to 87, wherein the device is a brush or a comb.

89. The kit of any one of claims 83 to 88, wherein the device is a patch, a roller, or a pen.

90. The kit of any one of claims 76 to 89, 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.

91. A composition comprising a therapeutically effective amount of a PAI-1 inhibitor, 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) a reduction in the number of the plurality of gray hairs;

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

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

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

93. The composition of claim 92, 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.

96. The composition of any one of claims 91 to 95, 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.

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

98. The composition of claim 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.

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

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

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

102. The composition of any one of claims 91 to 99, wherein the composition comprising the PAI-1 inhibitor comprises an emulsion.

103. The composition of claim 102, wherein the emulsion is a nanoemulsion.

104. The composition of any one of claims 91 to 103, 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.

106. The use of claim 105, 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.