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 non-therapeutic method of treating hair graying, wherein the method comprises:
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.

[0002b] In another aspect of the present disclosure, there is provided a non-therapeutic method of treating hair graying, wherein the method comprises:
providing a composition that comprises or delivers 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.

[0002c] In a further aspect of the present disclosure, there is provided a non-therapeutic method of preventing the occurrence or progression of hair graying, wherein the method comprises:

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.

[0002d] In another aspect of the present disclosure, there is provided a composition comprising 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 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 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 an amount of a PAI-1 inhibitor effective to achieve, when the composition is topically administered to a site on an animal comprising one or more gray hairs, 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 treating hair graying, wherein the method comprises:

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.

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

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

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

5. A non-therapeutic method of treating hair graying, wherein the method comprises:

providing a composition that comprises or delivers 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 of claim 5, wherein the administering is by oral administration.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

28. The method of any one of the claims 1-3 or 7-27, 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. A non-therapeutic method of preventing the occurrence or progression of hair graying, wherein the method comprises:

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.

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

31. The method of claims 1-3, or 7-30, wherein the step of administering the composition comprises massaging the composition into the site.

32. The method of any of claims 29 to 31, wherein the period of time is within a range of 1 to 10 minutes, 5 to 60 minutes, 5 to 12 minutes, 5 to 15 minutes, or 15 to 30 minutes, 1 to 12 hours, 8 to 12 hours or 12 hours to 24 hours.

33. The method of any of claims 29 to 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.

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

35. The method of claim 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.

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

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

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

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

40. The method of claim 39, wherein the emulsion is a nanoemulsion.

41. The method of any one of claims 29 to 40, comprising more than one administration of the composition comprising the PAI-1 inhibitor over time.

42. The method of claim 41, wherein each administration comprising the PAI-1 inhibitor is separated by a specified period of time.

43. The method of any one of claims 29 to 42, wherein the hair is not gray.

44. The method of any one of claims 29 to 43, wherein the composition is formulated as a suspension, a foam, a lotion, a cream, a gel, an oil, a powder, a liniment, or drops.

45. A composition comprising 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.

46. The composition of claim 45, wherein the amount is 0.1% w/w to 5 % w/w, 0.1 % to 10% w/w, 0.1% to 15% w/w, 0.1% w/w to 20% w/w, or 1% w/w to 5% w/w.

47. The composition of 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.

48. The composition of claim 47, wherein the nucleic acid is or comprises siRNA.

49. The composition of claim 47, 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.

50. The composition of claim 49, wherein the PAI-1 inhibitor is 5-Chloro-2-{[(2-{[3-(furan-3-yl)phenyl]amino}-2-oxoethoxy)acetyl]amino benzoic acid.

51. The composition of any one of claims 45 to 50, wherein the composition comprising the PAI-1 inhibitor is or comprises a suspension.

52. The composition of any one of claims 45 to 50, wherein the composition comprising the PAI-1 inhibitor is or comprises a foam.

53. The composition of any one of claims 45 to 50, wherein the composition comprising the PAI-1 inhibitor comprises an emulsion.

54. The composition of claim 53, wherein the emulsion is a nanoemulsion.

55. The composition of any one of claims 45 to 54, 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.

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

57. The kit of claim 56, wherein the composition comprising the PAI-1 inhibitor is incorporated into the patch.

58. The kit of claim 56 or claim 57, wherein the patch comprises microneedles.

59. The kit of any one of claims 56 to 58, wherein the composition comprising the PAI-1 inhibitor is or comprises a suspension.

60. The kit of any one of claims 56 to 58, wherein the composition comprising the PAI-1 inhibitor is or comprises a foam.

61. The kit of any one of claims 56 to 58, wherein the composition comprising the PAI-1 inhibitor comprises an emulsion.

62. The kit of claim 61, wherein the emulsion is a nanoemulsion.

63. A kit comprising a composition 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.

64. The kit of any one of claim 63, wherein the composition comprising the PAI-1 inhibitor is or comprises a suspension.

65. The kit of any one of claim 63, wherein the composition comprising the PAI-1 inhibitor is or comprises a foam.

66. The kit of claim 63, wherein the composition comprising the PAI-1 inhibitor is or comprises an emulsion.

67. The kit of claim 66, wherein the emulsion is a nanoemulsion.

68. The kit of any one of claims 63 to 67, wherein the device is a brush or a comb.

69. The kit of any one of claims 63 to 66, wherein the device is a patch, a roller, or a pen.

70. The kit of any one of claims 56 to 69, 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.

71. A composition comprising an amount of a PAI-1 inhibitor effective to achieve, when the composition is topically administered to a site on an animal comprising one or more gray hairs, 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.

72. The composition of claim 71, wherein the therapeutically effective amount is 0.1% w/w to 5 % w/w, 0.1 % to 10% w/w, 0.1% to 15% w/w, 0.1% w/w to 20% w/w, or 1% w/w to 5% w/w.

73. The composition of claim 71 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. The composition of claim 73, wherein the nucleic acid is or comprises siRNA.

75. The composition of claim 73, 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. The composition of claim 75, wherein the PAI-1 inhibitor is 5-Chloro-2-{[(2-{[3-(furan-3-yl)phenyl]amino}-2-oxoethoxy)acetyl]amino benzoic acid.

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

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

79. The composition of any one of claims 71 to 76, wherein the composition comprising the PAI-1 inhibitor comprises an emulsion.

80. The composition of claim 79, wherein the emulsion is a nanoemulsion.

81. The composition of any one of claims 71 to 80, 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.

82. The method of any one of claims 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.