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 cosmetic 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,
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.

[0002b] In another aspect of the present disclosure, there is provided a cosmetic 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;
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.

[0002c] In a further aspect of the present disclosure, there is provided a cosmetic 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; 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.

[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, wherein the composition is or comprises a suspension, a foam, or an emulsion, and wherein the PAI-1 inhibitor is selected from the 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.

[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 cosmetic method comprising topically applying 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,

wherein the composition is or comprises a suspension, a foam, or an emulsion, and 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.

[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 cosmetic 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,
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.

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 cosmetic 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;
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.

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 5-Chloro-2-{[(2-{[3-(furan-3-yl)phenyl]amino}-2-oxoethoxy)acetyl]amino} benzoic acid.

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

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

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

16. The method of claim 15, wherein the emulsion is a nanoemulsion.

17. The method of any one of the claims 1-3 or 7-16, wherein the method further comprises a step of administering a penetrating treatment.

18. The method of claim 17, wherein the penetrating treatment is or comprises a non-irritating chemical agent.

19. The method of claim 17, wherein the penetrating treatment is or comprises administration of an electric or magnetic field.

20. The method of claim 17, wherein the penetrating treatment is or comprises microneedling.

21. The method of claim 17, wherein the penetrating treatment is or comprises laser treatment.

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

23. The method of claim 22, wherein each administration comprising the PAI-1 inhibitor is separated by a specified period of time.

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

25. The method of any one of the claims 1-3 or 7-24, wherein the composition is formulated as a suspension, a foam, a lotion, a cream, a gel, an oil, a powder, a liniment, or drops.

26. A cosmetic 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;
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.

27. The method of claim 26, wherein the method further comprises, after the period of time, removing remaining composition from the site.

28. The method of claims 1-3, or 7-27, wherein the step of administering the composition comprises massaging the composition into the site.

29. The method of any of claims 26 to 28, 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.

30. The method of any of claims 26-28, wherein the PAI-1 inhibitor is 5-Chloro-2-{[(2-{[3-(furan-3-yl)phenyl]amino}-2-oxoethoxy)acetyl]amino} benzoic acid.

31. The method of any one of claims 26 to 30, wherein the composition comprising the PAI-1 inhibitor is or comprises a suspension.

32. The method of any one of claims 26 to 30, wherein the composition comprising the PAI-1 inhibitor is or comprises a foam.

33. The method of any one of claims 26 to 30, wherein the composition comprising the PAI-1 inhibitor comprises an emulsion.

34. The method of claim 33, wherein the emulsion is a nanoemulsion.

35. The method of any one of claims 26 to 34, comprising more than one administration of the composition comprising the PAI-1 inhibitor over time.

36. The method of claim 35, wherein each administration comprising the PAI-1 inhibitor is separated by a specified period of time.

37. The method of any one of claims 26 to 36, wherein the hair is not gray.

38. The method of any one of claims 26 to 37, wherein the composition is formulated as a suspension, a foam, a lotion, a cream, a gel, an oil, a powder, a liniment, or drops.

39. 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, wherein the composition is or comprises a suspension, a foam, or an emulsion, and wherein the PAI-1 inhibitor is selected from the 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.

40. The composition of claim 39, 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.

41. The composition of claim 39 or claim 40, wherein the PAI-1 inhibitor is 5-Chloro-2-{[(2-{[3-(furan-3-yl)phenyl]amino}-2-oxoethoxy)acetyl]amino} benzoic acid.

42. The composition of any one of claims 39 to 41, wherein the emulsion is a nanoemulsion.

43. The composition of any one of claims 39 to 42, 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.

44. A kit comprising a composition of any one of claims 39-43 and a patch for use in covering the composition comprising the PAI-1 inhibitor after administration to a site.

45. The kit of claim 44, wherein the composition comprising the PAI-1 inhibitor is incorporated into the patch.

46. The kit of claim 44 or claim 45, wherein the patch comprises microneedles.

47. The kit of any one of claims 44 to 46, wherein the composition comprising the PAI-1 inhibitor is or comprises a suspension.

48. The kit of any one of claims 44 to 46, wherein the composition comprising the PAI-1 inhibitor is or comprises a foam.

49. The kit of any one of claims 44 to 46, wherein the composition comprising the PAI-1 inhibitor comprises an emulsion.

50. The kit of claim 49, wherein the emulsion is a nanoemulsion.

51. A kit comprising a composition of any one of claims 39-43, 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.

52. The kit of claim 51, wherein the composition comprising the PAI-1 inhibitor is or comprises a suspension.

53. The kit of claim 51, wherein the composition comprising the PAI-1 inhibitor is or comprises a foam.

54. The kit of claim 51, wherein the composition comprising the PAI-1 inhibitor is or comprises an emulsion.

55. The kit of claim 54, wherein the emulsion is a nanoemulsion.

56. The kit of any one of claims 51 to 55, wherein the device is a brush or a comb.

57. The kit of any one of claims 51 to 54, wherein the device is a patch, a roller, or a pen.

58. The kit of any one of claims 44 to 57, 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.

59. A cosmetic method comprising topically applying a composition comprising an amount of a PAI-1 inhibitor effective to achieve, when the composition is 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,

wherein the composition is or comprises a suspension, a foam, or an emulsion, and 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.

60. The method of claim 59, wherein the amount of the PAI-1 inhibitor 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.

61. The method of claim 59 or claim 60, wherein the PAI-1 inhibitor is 5-Chloro-2-{[(2-{[3-(furan-3-yl)phenyl]amino}-2-oxoethoxy)acetyl]amino} benzoic acid.

62. The method of any one of claims 59-61, wherein the emulsion is a nanoemulsion.

63. The method of any one of claims 59 to 62, 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.

64. The method of any one of claims 1 to 38, 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.