[0009] Botulinum toxin is classified into eight neurotoxins that are serologically related, but distinct. Of these, seven can cause paralysis, namely botulinum neurotoxin serotypes A, B, C, D, E, F and G. Each of these is distinguished by neutralization with type-specific antibodies. Nonetheless, the molecular weight of the botulinum toxin protein molecule, for all seven of these active botulinum toxin serotypes, is about 150 kD. As released by the bacterium, the botulinum toxins are complexes comprising the 150 kD botulinum toxin protein molecule in question along with associated non-toxin proteins. The botulinum toxin type A complex can be produced by Clostridia bacterium as 900 kD, 500 kD and 300 kD forms. Botulinum toxin types B and C are apparently produced as only a 700 kD or 500 kD complex. Botulinum toxin type D is produced as both 300 kD and 500 kD complexes. Botulinum toxin types E and F are produced as only approximately 300 kD complexes. The complexes (i.e. molecular weight greater than about 150 kD) are believed to contain a non-toxin hemaglutinin protein and a non-toxin and non-toxic nonhemaglutinin protein. These two non-toxin proteins (which along with the botulinum toxin molecule comprise the relevant neurotoxin complex) may act to provide stability against denaturation to the botulinum toxin molecule and protection against digestive acids when toxin is ingested. Additionally, it is possible that the larger (greater than about 150 kD molecular weight) botulinum toxin complexes may result in a slower rate of diffusion of the botulinum toxin away from a site of intramuscular injection of a botulinum toxin complex.

[0010] The different serotypes of botulinum toxin vary in the animal species that they affect and in the severity and duration of the paralysis they evoke. For example, it has been determined that botulinum toxin type A is 500 times more potent, as measured by the rate of paralysis produced in the rat, than is botulinum toxin type B. Additionally, botulinum toxin type B has been determined to be non-toxic in primates at a dose of 480 U/kg, about 12 times the primate LD_{50} for type A. Due to the molecule size and molecular structure of botulinum toxin, it cannot cross stratum corneum and the multiple layers of the underlying skin architecture.

[0010a] Botulism, the characteristic symptom complex from systemic botulinum toxin exposure, has existed in Europe since antiquity. In 1895, Emile P. van Ermengem first isolated the anaerobic spore-forming bacillus from raw salted pork meat obtained from post-mortem tissue of victims who died of botulism in

[0011] Botulinum toxin type A is said to be the most lethal natural biological agent known to man. Spores of *C. botulinum* are found in soil and can grow in improperly sterilized and sealed food containers. Ingestion of the bacteria can cause botulism, which can be fatal. At the same time, the muscle-paralyzing effects of botulinum toxin have been used for therapeutic effects. Controlled administration of botulinum toxin has been used to provide muscle paralysis to treat conditions, for example, neuromuscular disorders characterized by hyperactive skeletal muscles. Conditions that have been treated with botulinum toxin include hemifacial spasm, adult onset spasmodic torticollis, anal fissure, blepharospasm, cerebral palsy, cervical dystonia, migraine headaches, strabismus, temperomandibular joint disorder, and various types of muscle cramping and spasms. More recently the muscle-paralyzing effects of botulinum toxin have been taken advantage of in therapeutic and cosmetic facial applications such as treatment of wrinkles, frown lines, and other results of spasms or contractions of facial muscles.

[0012] Topical application of botulinum toxin would provide for a safer and more desirable treatment alternative due to the painless nature of application, the larger treatment surface area that can be covered, the ability to formulate a pure toxin with higher specific activity, the reduced training necessary for applying the botulinum therapeutic, the smaller doses that would be necessary to produce the desired effect, and the lack of a requirement for large wells of toxin to reach a therapeutic clinical result. An effective means for transdermal delivery of botulinum toxin, as well as an effective means for administering botulinum toxin to treat or prevent a number of conditions that does not require injection is thus highly desirable.

SUMMARY ~~OF THE INVENTION~~

[0013] This ~~invention~~ disclosure relates to new compositions comprising a botulinum toxin, more specifically to such compositions that enable the transport or delivery of a botulinum toxin through the skin or epithelium (also referred to as "transdermal delivery"), and that therefore may be used as topical applications for providing a botulinum toxin to a subject, for various therapeutic, aesthetic and/or cosmetic purposes, as described herein.

[0014] ~~One aspect of this invention is to provide~~Disclosed is a composition containing a botulinum toxin and a carrier. The carrier has a polymeric backbone with attached

positively charged branching groups. The association between the carrier and the botulinum toxin is non-covalent.

[0015] ~~Another aspect of this invention is to provide~~Also disclosed is a kit for administration of a botulinum toxin to a subject. The kit includes a botulinum toxin present in an effective amount for transdermal delivery thereof, and a carrier that has a polymeric backbone with attached positively charged branching groups. The association between the carrier and the botulinum toxin is non-covalent.

[0016] ~~Yet another aspect of this invention is to provide~~Further disclosed is a kit for administration of a botulinum toxin to a subject. The kit includes a device for delivering the botulinum toxin to the skin and a composition containing a carrier having a polymeric backbone with attached positively charged branching groups selected from – $(gly)_{n1}$-$(arg)_{n2}$, HIV-TAT and fragments thereof, and Antennapedia PTD, in which the subscript n1 is an integer of from 0 to about 20, and the subscript n2 is independently an odd integer of from about 5 to about 25.

[0017] This ~~invention~~ disclosure also provides a method of administering a botulinum toxin to a subject involving topically applying to the skin or epithelium of the subject the botulinum toxin in conjunction with an effective amount of a carrier. The carrier has a polymeric backbone with attached positively charged branching groups, and associates non-covalently with the botulinum toxin.

[0018] In one ~~aspect~~embodiment, this ~~invention~~ disclosure relates to a composition comprising a botulinum toxin (as defined herein) and a carrier comprising a positively charged "backbone" having positively charged branching or "efficiency" groups, as described herein. Most preferably the positively charged carrier is a long-chain positively charged polypeptide or a positively charged nonpeptidyl polymer, for example, a polyalkyleneimine. The ~~invention~~ disclosure further relates to a method for producing a biologic effect such as muscle paralysis, reducing hypersecretion or sweating, treating neurologic pain or migraine headache, reducing muscle spasms, preventing or reducing acne, or reducing or enhancing an immune response, by topically applying an effective amount of such a composition, preferably to the skin, of a subject or patient in need of such treatment. The ~~invention~~ disclosure also relates to a method for producing an aesthetic or cosmetic effect, for example by topical application of botulinum toxin to the face instead of by injection into facial muscles.

[0018a] In one aspect, there is provided use of a composition comprising:

a botulinum toxin, and

a positively charged carrier comprising a positively charged polymeric backbone having attached positively charged efficiency groups,

wherein the botulinum toxin is not covalently modified and wherein the positively charged carrier and the botulinum toxin non-covalently and directly associate;

in the manufacture of a medicament for use in treatment of:

(a) symptoms associated with urological disorders;

(b) symptoms associated with subjective or clinical hyperhidrosis;

(c) symptoms associated with subjective or clinical dystonic contractions or dystonia;

(d) symptoms associated with muscle spasm;

(e) symptoms associated with migraine headache

(f) symptoms associated with acne;

(g) symptoms associated with mucous secretion;

(h) symptoms associated with obesity;

(i) symptoms associated with inflammation;

(j) symptoms associated with psoriasis;

(k) snoring;

(l) cutaneous symptoms associated with diabetes;

(m) wound healing;

(n) symptoms associated autonomic nerve dysfunction;

(o) symptoms associated with cerebral palsy;

(p) symptoms associated with Hashimoto's thyroiditis;

(q) symptoms associated with mammary gland disorders

(r) altering hair growth;

(s) symptoms associated with parathyroid disorders;

(t) symptoms associated with movement disorders;

(u) symptoms associated with parkinson's disease;

(v) symptoms associated with tremors;

(w) symptoms associated with epilepsy;

(x) symptoms associated with inner ear disorders;

(y) symptoms associated with cholinergic-controlled secretions;

(z) symptoms associated with neurophychiatric disorders;

(aa) symptoms associated with injured muscles;

(bb) symptoms associated with ear disorders;

(cc) symptoms associated with cancer;

(dd) symptoms associated with nerve entrapment disorders; or

(ee) symptoms associated with hypercalcemia.

[0018b] In one aspect, there is provided use of a composition comprising:

a botulinum toxin; and

a positively charged carrier comprising a positively charged polymeric backbone having attached positively charged efficiency groups;

wherein the botulinum toxin is not covalently modified, and wherein the positively charged carrier and the botulinum toxin non-covalently and directly associate;

in the manufacture of a medicament for treating, preventing, or reducing symptoms associated with subjective or clinical hyperhidrosis in a subject in need thereof, wherein the medicament is to be topically applied to the skin or epithelium of the subject.

[0018c] In one aspect, there is provided use of a composition comprising:

a botulinum toxin; and

a positively charged carrier comprising a positively charged polymeric backbone having attached positively charged efficiency groups;

wherein the botulinum toxin is not covalently modified, and wherein the positively charged carrier and the botulinum toxin non-covalently and directly associate;

in the manufacture of a medicament for treating, preventing, or reducing the severity of fine lines and/or wrinkles in a subject in need thereof, wherein the medicament is to be topically applied to the skin or epithelium of the subject.

[0018d] In one aspect, there is provided use of a composition comprising:

a botulinum toxin; and

a positively charged carrier comprising a positively charged polymeric backbone having attached positively charged efficiency groups;

wherein the botulinum toxin is not covalently modified, and wherein the positively charged carrier and the botulinum toxin non-covalently and directly associate;

in the manufacture of a medicament for treating urologic disorder in a subject in need thereof, wherein the medicament is to be topically applied to the skin or epithelium of the subject.

[0018e] In one aspect, there is provided use of a composition comprising:

a botulinum toxin; and

a positively charged carrier comprising a positively charged polymeric backbone having attached positively charged efficiency groups;

wherein the botulinum toxin is not covalently modified, and wherein the positively charged carrier and the botulinum toxin non-covalently and directly associate;

in the manufacture of a medicament for treating neurologic pain; migraine headache pain or other headache pain; or relieving muscle spasm-related pain in a subject in need thereof, wherein the medicament is to be topically applied to the skin or epithelium of the subject.

[0018f] In one aspect, there is provided use of a composition comprising:

a botulinum toxin; and

a positively charged carrier comprising a positively charged polymeric backbone having attached positively charged efficiency groups;

wherein the botulinum toxin is not covalently modified, and wherein the positively charged carrier and the botulinum toxin non-covalently and directly associate;

in the manufacture of a medicament for enhancing or reducing an immune response.

[0019] This ~~invention~~ disclosure also provides kits for preparing or formulating a composition that comprises the carrier and the botulinum toxin, as well as such additional items that are needed to produce a usable formulation, or a premix that may in turn be used to produce such a formulation. Alternatively the kit comprises means for separately but in conjunction administering the botulinum toxin and the carrier to a subject.

BRIEF DESCRIPTION OF THE DRAWINGS

[0020] **Figure 1** represents the results of an experiment demonstrating efficiency of transdermal delivery of botulinum toxin using a composition of the invention comprising a peptide backbone.

[0021] **Figure 2** is a photograph depicting the state of the hind limbs of a mouse in which the area of one limb was treated with a composition of the invention and the area of the other was treated with another botulinum toxin-containing composition that did not contain a carrier according to the invention.

[0022] **Figure 3** is a photograph depicting wrinkles on subject's forehead before and after treatment with "Essentia Botox lotion" topically.

[0023] **Figure 4** shows a Mikrosil cast of the forehead (A) after topical treatment of wrinkles with "Essentia Botox Lotion", and (b) before treatment. These Mikrosil casts, which are useful because they minimize artifacts that can result from photographing the actual subject, clearly show that the untreated side has deeper wrinkles.

[0024] **Figure 5** shows photographs depicting Minor's starch/iodine test performed on subject's forehead five days after application of "Essentia Botox Lotion" (A) and a control lotion (B). The control lotion contained a positively charged polylysine backbone with a molecular weight of about 21,000 and with TAT branching groups. These pictures were taken two minutes after application.

[0025] **Figure 6** is the same as Figure 5, but except that they were taken after four minutes had elapsed. .

[0026] **Figure 7** shows the dose area used in the axillary hyperhidrosis studies. Note that the dose area extends one centimeter beyond the area of the skin covered by axillary hair.

WHAT IS CLAIMED IS:

1. A composition comprising a botulinum toxin and a carrier comprising a polymeric backbone having attached positively charged branching groups, wherein the association between the carrier and the botulinum toxin is non-covalent.

2. A composition according to claim 1 in which the botulinum toxin is a botulinum toxin derivative.

3. A composition according to claim 1 in which the botulinum toxin comprises a recombinant botulinum toxin.

4. A composition according to claim 1 in which the botulinum toxin comprises a modified botulinum toxin.

5. A composition according to claim 1 in which the botulinum toxin is selected from botulinum toxin serotypes A, B, C, D, E, F and G.

6. A composition according to claim 5 in which the botulinum toxin is botulinum toxin A.

7. A composition according to claim 5 in which the botulinum toxin is botulinum toxin B.

8. A composition according to claim 5 in which the botulinum toxin is botulinum toxin C_1.

9. A composition according to claim 5 in which the botulinum toxin is botulinum toxin D.

10. A composition according to claim 5 in which the botulinum toxin is botulinum toxin E.

11. A composition according to claim 1 in which the carrier comprises a polypeptide having attached positively charged branching groups selected from –$(gly)_{n1}$-$(arg)_{n2}$, HIV-TAT, Antennapedia PTD, and fragments of HIV-TAT or of Antennapedia PTD, in which the subscript n1 is an integer of from 0 to about 20, and the subscript n2 is independently an odd integer of from about 5 to about 25.

12. A composition according to claim 11 in which the carrier comprises a polypeptide having positively charged branching groups selected from $-(gly)_{n1}-(arg)_{n2}$ in which the subscript n1 is an integer of from about 0 to about 20 and the subscript n2 is independently an odd integer of from about 5 to about 25.

13. A composition according to claim 12 in which the subscript n1 is an integer of from 0 to about 8.

14. A composition according to claim 12 in which the subscript n1 is an integer of from about 2 to about 5.

15. A composition according to claim 12 in which the subscript n2 is an odd integer of from about 7 to about 17.

16. A composition according to claim 12 in which the subscript n2 is an odd integer from about 7 to about 13.

17. A composition according to claim 11 in which the carrier comprises a polypeptide having attached positively charged branching groups selected from HIV-TAT and fragments thereof.

18. A composition according to claim 17 in which the branching groups are positively charged HIV-TAT fragments that have the formula $(gly)_p$-RGRDDRRQRRR-$(gly)_q$, $(gly)_p$-YGRKKRRQRRR-$(gly)_q$, or $(gly)_p$-RKKRRQRRR-$(gly)_q$, wherein the subscripts p and q are each independently an integer of from 0 to 20.

19. A composition according to claim 1 in which the positively charged branching groups comprise at least about 0.05 % by weight of the total carrier weight.

20. A composition according to claim 1 in which the positively charged branching groups comprise from about 0.5% to about 45% by weight of the total carrier weight.

21. A composition according to claim 1 in which the positively charged branching groups comprise from about 0.1 % to about 30% by weight of the total carrier weight.

22. A composition according to claim 1 in which the backbone comprises a positively charged polypeptide.

23. A composition according to claim 22 in which the backbone comprises a positively charged polylysine.

24. A composition according to claim 23 in which the polylysine has a molecular weight of from about 10,000 to 1.500,000.

25. A composition according to claim 23 in which the polylysine has a molecular weight of from about 25,000 to about 1,200,000.

26. A composition according to claim 23 in which the polylysine has a molecular weight of from about 100,000 to about 1,000,000.

27. A composition according to claim 1 in which the backbone comprises a positively charged nonpeptidyl carrier.

28. A composition according to claim 27 in which the backbone comprises a positively charged polyalkyleneimine.

29. A composition according to claim 28 in which the polyalkyleneimine is a polyethyleneimine.

30. A composition according to claim 29 in which the polyethyleneimine has a molecular weight of from about 10,000 to about 2,500,000.

31. A composition according to claim 29 in which the polyethyleneimine has a molecular weight of from about 100,000 to about 1,800,000,

32. A composition according to claim 29 in which the polyethyleneimine has a molecular weight of from about 500,000 to about 1,400,000.

33. A composition according to claim 1 having a pH of from about 4.5 to about 6.3.

34. A composition according to claim 1 that is stable when stored at room temperature or under refrigerated conditions.

35. A controlled release composition according to claim 1.

36. A liquid composition according to claim 1.

37. A gel composition according to claim 1.

38. A composition according to claim 1 that is a cream, lotion or ointment.

39. A composition according to claim 1 further comprising saline.

40. A composition according to claim 1 further comprising saline and a pH buffer system.

41. A kit for administration of a botulinum toxin to a subject comprising a botulinum toxin and an effective amount for transdermal delivery thereof, of a carrier comprising a polymeric backbone having attached positively charged branching groups, wherein the association between the carrier and the botulinum toxin is non-covalent.

42. A kit according to claim 41 further comprising a custom applicator.

43. A kit according to claim 42 in which the custom applicator is designed for use by a health care professional.

44. A kit according to claim 42in which the custom applicator is designed for self-administration by a subject.

45. A kit according to claim 41 comprising a pre-formulated composition comprising the botulinum toxin and the carrier.

46. A kit according to claim 41 in which the botulinum toxin and the carrier are separately formulated for combining prior to administration.

47. A kit according to claim 41 in which the botulinum toxin is contained in a device for administering the botulinum toxin to a subject via the skin.

48. A kit according to claim 47 in which the device is a skin patch.

49. A kit for administration of a botulinum toxin to a subject comprising a device for delivering the botulinum toxin to the skin and a composition comprising a carrier comprising a polymeric backbone having attached positively charged branching groups selected from – $(gly)_{n1}$-$(arg)_{n2}$, HIV-TAT and fragments thereof, and Antennapedia PTD, in which the subscript n1 is an integer of from 0 to about 20, and the subscript n2 is independently an odd integer of from about 5 to about 25.

50. A kit according to claim 49 in which the device is a skin patch.

51. A method of administering a botulinum toxin to a subject comprising topically applying to the skin or epithelium of the subject the botulinum toxin in conjunction with an effective amount of a carrier comprising a polymeric backbone having attached positively charged branching groups, wherein the association between the carrier and the botulinum toxin is non-covalent.

52. A method according to claim 51 comprising topically applying to the skin or epithelium of the subject an effective amount of a composition according to claim 1.

53. A method according to claim 51 in comprising separately applying the botulinum toxin and the carrier to the skin or epithelium of the subject.

54. A method according to claim 51 in which the botulinum toxin is administered to achieve a desired biologic effect.

55. A method according to claim 54 in which the botulinum toxin is administered to achieve an aesthetic or cosmetic benefit.

56. A method according to claim 54 in which the botulinum toxin is applied to reduce or prevent an immune response.

57. A method according to claim 56 in which the reduced or prevented immune response improves therapeutic response on later repeat re-administrations of the composition.

58. A method according to claim 54 in which the botulinum toxin is administered for prevention or reduction of symptoms associated with subjective or clinical hyperhidrosis.

59. A method according to claim 54 in which the botulinum toxin is applied topically for prevention or reduction of subjective or clinical dystonic contractions or dystonia.

60. A method according to claim 54 in which the botulinum toxin is applied topically for prevention or reduction of symptoms associated with muscle spasm.

61. A method according to claim 60 in which the botulinum toxin is applied topically to the lower back of the subject.

62. A method according to claim 60 in which the botulinum toxin is topically applied to the neck of the subject.

63. A method according to claim 60 in which the botulinum toxin is topically applied to at least one leg of the subject.

64. A method according to claim 51 in which the botulinum toxin is applied topically to the face of the subject, or to a portion thereof.

65. A method according to claim 51 in which the botulinum toxin is applied topically to the axilla of the subject, or to a portion thereof.

66. A method according to claim 51 in which the botulinum toxin is applied topically to the palms of the hands or to the feet of the subject, or to a portion thereof.

67. A method according to claim 51 in which the botulinum toxin is applied topically to the back or neck of the subject, or to a portion thereof.

68. A method according to claim 51 in which the botulinum toxin is applied topically to the groin of the subject, or to a portion thereof.

69. A method according to claim 51 in which the composition is applied topically to the hands or feet of the subject, or to a portion thereof.

70. A method according to claim 51 in which the botulinum toxin is applied topically to the elbows, upper arms, knees, or upper legs of the subject, or to a portion thereof.

71. A method according to claim 51 in which the botulinum toxin is applied topically to the buttocks of the subject or to a portion thereof.

72. A method according to claim 51 in which the botulinum toxin is applied topically to the torso of the subject or to a portion thereof.

73. A method according to claim 51 in which the botulinum toxin is applied topically to the pelvis of the subject or to a portion thereof.

74. A method according to claim 51 in which the botulinum toxin is applied to generate or enhance an immune response.

75. A method according to claim 51 in which the botulinum toxin is applied topically for prevention or reduction of symptoms associated with migraine headache.

76. A method according to claim 51 in which the botulinum toxin is applied topically for prevention or reduction of acne.

77. A method according to claim 51 in which the botulinum toxin is a botulinum toxin derivative.

78. A method according to claim 51 in which the botulinum toxin comprises a recombinant botulinum toxin.

79. A method according to claim 51 in which the botulinum toxin comprises a modified botulinum toxin.

80. A method according to claim 51 in which the botulinum toxin is selected from botulinum toxin serotypes A, B, C, D, E, F and G.

81. A method according to claim 51 in which the botulinum toxin is botulinum toxin A.

82. A method according to claim 51 in which the botulinum toxin is botulinum toxin B.

83. A method according to claim 51 in which the botulinum toxin is botulinum toxin C.

84. A method according to claim 51 in which the botulinum toxin is botulinum toxin D.

85. A method according to claim 51 in which the botulinum toxin is botulinum toxin E.

86. A method according to claim 51 in which the carrier comprises a polymeric backbone having attached positively charged branching groups selected from $-(gly)_{n1}-(arg)_{n2}$, HIV-TAT, Antennapedia PTD, and fragments of HIV-TAT or of Antennapedia PTD, in which the subscript n1 is an integer of from 0 to about 20, and the subscript n2 is independently an odd integer of from about 5 to about 25.

87. A method according to claim 86 in which the carrier comprises a polypeptide having positively charged branching groups selected from $-(gly)_{n1}-(arg)_{n2}$ in which the subscript n1 is an integer of from about 0 to about 20 and the subscript n2 is independently an odd integer of from about 5 to about 25.

88. A method according to claim 87 in which the subscript n1 is an integer of from 0 to about 8.

89. A method according to claim 87 in which the subscript n1 is an integer of from about 2 to about 5

90. A method according to claim 87 in which the subscript n2 is an odd integer of from about 7 to about 17.

91. A method according to claim 87 in which the subscript n2 is an odd integer from about 7 to about 13.

92. A method according to claim 86 in which the carrier comprises a polypeptide having attached positively charged branching groups selected from HIV-TAT and fragments thereof.

93. A method according to claim 92 in which the branching groups are positively charged HIV-TAT fragments that have the formula $(gly)_p$-RGRDDRRQRRR-$(gly)_q$, $(gly)_p$-YGRKKRRQRRR-$(gly)_q$, or $(gly)_p$-RKKRRQRRR-$(gly)_q$, wherein the subscripts p and q are each independently an integer of from 0 to 20.

94. A method according to claim 51 in which the positively charged branching groups comprise at least about 0.05 % by weight of the total carrier weight.

95. A method according to claim 51 in which the positively charged branching groups comprise from about 0.5% to about 45% by weight of the total carrier weight.

96. A method according to claim 51 in which the positively charged branching groups comprise from about 0.1 % to about 30% by weight of the total carrier weight.

97. A method according to claim 51 in which the backbone comprises a positively charged polypeptide.

98. A method according to claim 97 in which the backbone comprises a positively charged polylysine.

99. A method according to claim 98 in which the polylysine has a molecular weight of from about 10,000 to 1.5 million.

100. A method according to claim 98 in which the polylysine has a molecular weight of from about 25,000 to about 1,200,000.

101. A method according to claim 98 in which the polylysine has a molecular weight of from about 100,000 to about 1,000,000.

102. A method according to claim 51 in which the backbone comprises a positively charged nonpeptidyl carrier.

103. A method according to claim 102 in which the positively charged nonpeptidyl polymer is polyalkyleneimine.

104. A method according to claim 102 in which the polyalkyleneimine is a polyethyleneimine.

105. A method according to claim 104 in which the polyethyleneimine has a molecular weight of from about 10,000 to about 2,500,000.

106. A method according to claim 104 in which the polyethyleneimine has a molecular weight of from about 100,000 to about 1,800,000.

107. A method according to claim 104 in which the polyethyleneimine has a molecular weight of from about 500,000 to about 1,400,000.

108. A method according to claim 51 in which the botulinum toxin comprises a recombinant botulinum toxin.

109. A method according to claim 51 in which the botulinum toxin is applied in a composition having a pH of from about 4.5 to about 6.3.

110. A method according to claim 51 in which the botulinum toxin is applied in a controlled release composition.

111. A method according to claim 51 in which the botulinum toxin is contained in a liquid composition.

112. A method according to claim 51 in which the botulinum toxin is contained in a gel composition.

113. A method according to claim 51 in which the botulinum toxin is contained in a composition that is a cream, lotion or ointment.

114. A method according to claim 51 in which the botulinum toxin is contained in a composition further comprising saline.

115. A method according to claim 51 in which the botulinum toxin is contained in a composition further comprising saline and a pH buffer system.

116. A method according to claim 51 in which the botulinum toxin is contained in a device for dispensing the botulinum toxin, which device is applied topically to the skin or epithelium of the subject.

117. A method according to claim 116 in which the device is a skin patch.

118. A method according to claim 117 in which the device is a cell-encapsulating device.

119. A method according to claim 54 in which the botulinum toxin is applied topically for prevention or reduction of symptoms associated with mucous secretion.

120. A method according to claim 54 in which the botulinum toxin is applied topically for prevention or reduction of obesity or symptoms thereof.

121. A method according to claim 54 in which the botulinum toxin is applied topically for prevention or reduction of inflammation or symptoms thereof.

122. A method according to claim 121 in which the botulinum toxin is applied topically for prevention or reduction of symptoms associated with psoriasis.

123. A method according to claim 122 in which the composition is applied in conjunction with other treatment modalities.

124. A method according to claim 54 in which the botulinum toxin is applied topically for prevention or reduction of snoring.

125. A method according to claim 54 in which the botulinum toxin is applied topically for prevention or reduction of cutaneous symptoms associated with diabetes.

126. A method according to claim 54 in which the botulinum toxin is applied topically for improvement of wound healing.

127. A method according to claim 54 in which the botulinum toxin is applied topically for prevention or reduction of symptoms associated with autonomic nerve dysfunction.

128. A method according to claim 54 in which the botulinum toxin is applied topically for prevention or reduction of symptoms associated with cerebral palsy.

129. A method according to claim 54 in which the botulinum toxin is applied topically for prevention or reduction of symptoms associated with Hashimoto's thyroiditis.

130. A method according to claim 54 in which the botulinum toxin is applied topically for prevention or reduction of symptoms associated with mammary gland disorders.

131. A method according to claim 54 in which the botulinum toxin is applied topically for alteration of hair growth.

132. A method according to claim 54 in which the botulinum toxin is applied topically for prevention or reduction of symptoms associated with parathyroid disorders.

133. A method according to claim 54 in which the botulinum toxin is applied topically for prevention or reduction of symptoms associated with movement disorders.

134. A method according to claim 133 in which the botulinum toxin is applied topically for prevention or reduction of symptoms associated with parkinson's disease.

135. A method according to claim 133 in which the botulinum toxin is applied topically for prevention or reduction of symptoms associated with tremors.

136. A method according to claim 54 in which the botulinum toxin is applied topically for prevention or reduction of symptoms associated with epilepsy.

137. A method according to claim 54 in which the botulinum toxin is applied topically for prevention or reduction of symptoms associated with inner ear disorders.

138. A method according to claim 54 in which the botulinum toxin is applied topically for prevention or reduction of symptoms associated with urologic disorders.

139. A method according to claim 54 in which the botulinum toxin is applied topically for prevention or reduction of other cholinergic-controlled secretions.

140. A method according to claim 54 in which the botulinum toxin is applied topically for prevention or reduction of symptoms associated with neuropshychiatric disorders.

141. A method according to claim 54 in which the botulinum toxin is applied topically for prevention or reduction of symptoms associated with injured muscles.

142. A method according to claim 54 in which the botulinum toxin is applied topically for prevention or reduction of symptoms associated with ear disorders.

143. A method according to claim 54 in which the botulinum toxin is applied topically for prevention or reduction of symptoms associated with cancer.

144. A method according to claim 54 in which the botulinum toxin is applied topically for prevention or reduction of symptoms associated with nerve entrapment disorders.

145. A method according to claim 54 in which the botulinum toxin is applied topically for prevention or reduction of symptoms associated with hypercalcemia.

146. A method according to claim 51 in which the botulinum toxin comprises a fusion protein.

147. A composition according to claim 5 in which the botulinum toxin is botulinum toxin F.

148. A composition according to claim 5 in which the botulinum toxin is botulinum toxin G.

149. A method according to claim 51 in which the botulinum toxin is botulinum toxin F.

150. A method according to claim 51 in which the botulinum toxin is botulinum toxin G.

WHAT IS CLAIMED IS:

1. Use of a composition comprising:

a botulinum toxin, and

a positively charged carrier comprising a positively charged polymeric backbone having attached positively charged efficiency groups,

wherein the botulinum toxin is not covalently modified and wherein the positively charged carrier and the botulinum toxin non-covalently and directly associate;

in the manufacture of a medicament for use in treatment of:

(a) symptoms associated with urological disorders;

(b) symptoms associated with subjective or clinical hyperhidrosis;

(c) symptoms associated with subjective or clinical dystonic contractions or dystonia;

(d) symptoms associated with muscle spasm;

(e) symptoms associated with migraine headache

(f) symptoms associated with acne;

(g) symptoms associated with mucous secretion;

(h) symptoms associated with obesity;

(i) symptoms associated with inflammation;

(j) symptoms associated with psoriasis;

(k) snoring;

(l) cutaneous symptoms associated with diabetes;

(m) wound healing;

(n) symptoms associated autonomic nerve dysfunction;

(o) symptoms associated with cerebral palsy;

(p) symptoms associated with Hashimoto's thyroiditis;

(q) symptoms associated with mammary gland disorders

(r) altering hair growth;

(s) symptoms associated with parathyroid disorders;

(t) symptoms associated with movement disorders;

(u) symptoms associated with parkinson's disease;

(v) symptoms associated with tremors;

(w) symptoms associated with epilepsy;

(x) symptoms associated with inner ear disorders;

(y) symptoms associated with cholinergic-controlled secretions;

(z) symptoms associated with neurophychiatric disorders;

(aa) symptoms associated with injured muscles;

(bb) symptoms associated with ear disorders;

(cc) symptoms associated with cancer;

(dd) symptoms associated with nerve entrapment disorders; or

(ee) symptoms associated with hypercalcemia.

2. Use of a composition comprising:

a botulinum toxin; and

a positively charged carrier comprising a positively charged polymeric backbone having attached positively charged efficiency groups;

wherein the botulinum toxin is not covalently modified, and wherein the positively charged carrier and the botulinum toxin non-covalently and directly associate;

in the manufacture of a medicament for treating, preventing, or reducing symptoms associated with subjective or clinical hyperhidrosis in a subject in need thereof, wherein the medicament is to be topically applied to the skin or epithelium of the subject.

3. Use of a composition comprising:

a botulinum toxin; and

a positively charged carrier comprising a positively charged polymeric backbone having attached positively charged efficiency groups;

wherein the botulinum toxin is not covalently modified, and wherein the positively charged carrier and the botulinum toxin non-covalently and directly associate;

in the manufacture of a medicament for treating, preventing, or reducing the severity of fine lines and/or wrinkles in a subject in need thereof, wherein the medicament is to be topically applied to the skin or epithelium of the subject.

4. Use of a composition comprising:

a botulinum toxin; and

a positively charged carrier comprising a positively charged polymeric backbone having attached positively charged efficiency groups;

wherein the botulinum toxin is not covalently modified, and wherein the positively charged carrier and the botulinum toxin non-covalently and directly associate;

in the manufacture of a medicament for treating urologic disorder in a subject in need thereof, wherein the medicament is to be topically applied to the skin or epithelium of the subject.

5. Use of a composition comprising:

a botulinum toxin; and

a positively charged carrier comprising a positively charged polymeric backbone having attached positively charged efficiency groups;

wherein the botulinum toxin is not covalently modified, and wherein the positively charged carrier and the botulinum toxin non-covalently and directly associate;

in the manufacture of a medicament for treating neurologic pain; migraine headache pain or other headache pain; or relieving muscle spasm-related pain in a subject in need thereof, wherein the medicament is to be topically applied to the skin or epithelium of the subject.

6. Use of a composition comprising:

a botulinum toxin; and

a positively charged carrier comprising a positively charged polymeric backbone having attached positively charged efficiency groups;

wherein the botulinum toxin is not covalently modified, and wherein the positively charged carrier and the botulinum toxin non-covalently and directly associate;

in the manufacture of a medicament for enhancing or reducing an immune response.

7. The use of a composition according to any one of claims 1-6, wherein the one or more positively charged efficiency groups is selected from:

-$(gly)_{n1}$-$(arg)_{n2}$ (SEQ ID NO. 1) in which the subscript n1 is an integer of from 0 to 20, and the subscript n2 is independently an odd integer of from 5 to 25;

Antennapedia PTD and fragments thereof retaining Antennapedia PTD activity; HIV-TAT; and

fragments of HIV-TAT having the amino acid sequences $(gly)_p$-RGRDDRRQRRR-$(gly)_q$ (SEQ ID NO. 2), $(gly)_p$-YGRKKRRQRRR-$(gly)_q$ (SEQ ID NO. 3), or $(gly)_p$-RKKRRQRRR-$(gly)_q$ (SEQ ID NO. 4) wherein the subscripts p and q are each independently an integer selected from a range of 0 to 20; a range of 0 to 8; or a range of 2 to 5.

8. The use of a composition according to claim 7, wherein the one or more positively charged efficiency groups are -$(gly)_{n1}$-$(arg)_{n2}$ (SEQ ID NO. 1) in which the subscript n1 is an integer of from 0 to 20 and the subscript n2 is independently an odd integer of from 5 to 25.

9. The use of a composition according to claim 8, wherein the subscript n1 is an integer of from 0 to 8.

10. The use of a composition according to claim 8, wherein the subscript n1 is an integer of from 2 to 5.

11. The use of a composition according to claim 8, wherein the subscript n2 is an odd integer of from 7 to 17.

12. The use of a composition according to claim 8, wherein the subscript n2 is an odd integer from 7 to 13.

13. The use of a composition according to claim 7, wherein the one or more positively charged efficiency groups are selected from $(gly)_p$-RGRDDRRQRRR-$(gly)_q$ (SEQ ID NO. 2), $(gly)_p$-YGRKKRRQRRR-$(gly)_q$ (SEQ ID NO. 3), or $(gly)_p$-RKKRRQRRR-$(gly)_q$ (SEQ ID NO. 4), wherein the subscripts p and q are each independently an integer of from 0 to 20.

14. The use of a composition according to claim 13, $(gly)_p$-RKKRRQRRR-$(gly)_q$ (SEQ ID NO. 4), wherein the subscripts p and q are each independently an integer of from 0 to 20.

15. The use of a composition according to any one of claims 1-6, wherein the botulinum toxin is selected from botulinum toxin serotypes A, B, C, D, E, F and G or comprises a recombinant botulinum toxin or comprises a fusion protein.

16. The use of a composition according to claim 15, wherein the botulinum toxin is botulinum toxin A.

17. The use of a composition according to any one of claims 1-6, wherein the positively charged efficiency groups comprise at least 0.05 % by weight of the total carrier weight.

18. The use of a composition according to claim 17, wherein the positively charged efficiency groups comprise from 0.5% to 45% by weight of the total carrier weight.

19. The use of a composition according to claim 18, wherein the positively charged efficiency groups comprise from 0.1% to 30% by weight of the total carrier weight.

20. The use of a composition according to any one of claims 1-6, wherein the backbone comprises a positively charged polypeptide.

21. The use of a composition according to claim 20, wherein the positively charged polypeptide is polylysine.

22. The use of a composition according to claim 21, wherein the polylysine has a molecular weight from 10,000 to 1,500,000.

23. The use of a composition according to any one of claims 1-6, wherein the backbone comprises a positively charged nonpeptidyl carrier.

24. The use of a composition according to claim 23, wherein the positively charged nonpeptidyl carrier is a polyalkyleneimine.

25. The use of a composition according to claim 24, wherein the positively charged nonpeptidyl carrier is a polyethyleneimine.

26. The use of a composition according to claim 25, wherein the polyethyleneimine has a molecular weight from 10,000 to 2,500,000.

27. The use of a composition according to any one of claims 1-6, wherein the composition is suitable for topical application to the skin or epithelium having a pH of from 4.5 to 6.3, wherein the composition is optionally a controlled release composition, a liquid composition, cream, lotion, ointment or a gel composition, or a pharmaceutical composition or a cosmetic composition.

28. The use of a composition according to claim 27, wherein the composition is stable when stored at room temperature or under refrigerated conditions.

29. The use of a composition according to claim 27, wherein the composition is formulated to have a controlled release.

30. The use of a composition according to claim 27, wherein the composition is a liquid.

31. The use of a composition according to claim 27, wherein the composition is a gel.

32. The use of a composition according to claim 27, wherein the composition is a cream, lotion or ointment.

33. The use of a composition according to claim 27, the composition further comprising saline or saline and a pH buffer system.

34. The use of a composition according to any one of claims 1-6, wherein the one or more positively charged efficiency groups comprises $(gly)_p$-RKKRRQRRR-$(gly)_q$ (SEQ ID

NO. 4), wherein the botulinum toxin is botulinum toxin A, wherein the backbone comprises a positively charged polylysine having a molecular weight from 10,000 to 1,500,000 and wherein the composition is suitable for topical application to the skin or epithelium having a pH of from 4.5 to 6.3.