What is claimed:

1. A botulinum neurotoxin (BoNT) polypeptide comprising:
   a) a protease domain;
   b) a protease cleavage site;
   c) a translocation domain; and
   d) a modified receptor binding domain of *Clostridial botulinum* serotype B ($B\text{-}H_c$), comprising one or more substitution mutations corresponding to substitution mutations in serotype B, strain 1, selected from the group consisting of:
   V1118M; Y1183M; E1191M; E1191I; E1191Q; E1191T; S1199Y; S1199F; S1199L; S1201V; and combinations thereof.

2. The BoNT polypeptide of claim 1, wherein the modified ($B\text{-}H_c$) comprises two substitution mutations.

3. The BoNT polypeptide of claim 2, wherein the two substitution mutations correspond to E1191M and S1199L, E1191M and S1199Y, E1191M and S1199F, E1191Q and S1199L, E1191Q and S1199Y, or E1191Q and S1199F.

4. The BoNT polypeptide of one of claims 2-3, wherein the two substitution mutations correspond to E1191M and S1199L.

5. The BoNT polypeptide of one of claims 2-3, wherein the two substitution mutations correspond to E1191M and S1199Y.

6. The BoNT polypeptide of one of claims 2-3, wherein the two substitution mutations correspond to E1191M and S1199F.

7. The BoNT polypeptide of one of claims 2-3, wherein the two substitution mutations correspond to E1191Q and S1199L.

8. The BoNT polypeptide of one of claims 2-3, wherein the two substitution mutations correspond to E1191Q and S1199Y.

9. The BoNT polypeptide of one of claims 2-3, wherein the two substitution mutations correspond to E1191Q and S1199F.

10. A botulinum neurotoxin (BoNT) polypeptide comprising:

a) a protease domain;

b) a protease cleavage site;

c) a translocation domain; and

d) a modified receptor binding domain of *Clostridial botulinum* serotype B ($B\text{-}H_c$), comprising a substitution mutation at a position corresponding to S1199 or S1201 of serotype B, strain 1.

11. The BoNT polypeptide of claim 10 wherein the substitution mutation produces enhanced binding of the modified $B\text{-}H_c$ to human SytII and/or reduced binding of the modified $B\text{-}H_c$ to human Syt I as compared to an identical molecule lacking the substitution mutation.

12. The BoNT polypeptide of claim 10 wherein the substitution mutation produces enhanced binding of the modified $B\text{-}H_c$ to human SytII and/or increased binding of the modified $B\text{-}H_c$ to human Syt I as compared to an identical molecule lacking the substitution mutation.

13. The BoNt polypeptide of any one of claims 11-12 wherein the substitution mutation is selected from the group consisting of A, R, N, D, C, Q, E, G, H, I, L, K, M, F, P, T, W, Y and V substituted for S.

14. The BoNt polypeptide of any one of claims 11-13 wherein the substitution mutation is a non-naturally occurring amino acid substituted for S.

15. The BoNT polypeptide of any one of claims 1 -14, wherein the modified $B\text{-}H_c$ is of strain 1.

16. The BoNT polypeptide of any one of claims 1-15 wherein the protease domain, translocation domain, and protease cleavage site are from serotype selected from the group consisting of A, B, C, D, E, F, G, and combinations thereof.

17. The BoNT polypeptide of claim 16, wherein the protease domain, translocation domain, and protease cleavage site are from serotype B, strain 1.

18. The BoNT polypeptide of claim 16, wherein the protease domain, translocation domain, and protease cleavage site are from serotype A, strain 1.

19. A polypeptide comprising a modified receptor binding domain of Clostridial botulinum serotype B (B-H_c) comprising one or more substitution mutations corresponding to substitution mutations in serotype B, strain 1, selected from the group consisting of V1118M; Y1183M; E1191M; E1191I; E1191Q; E1191T; S1199Y; S1199F; S1199L; S1201V; and combinations thereof.

20. The polypeptide of claim 19, wherein the modified (B-H_c) comprises two substitution mutations.

21. The polypeptide of claim 20, wherein the two substitution mutations correspond to E1191M and S1199L, E1191M and S1199Y, E1191M and S1199F, E1191Q and S1199L, E1191Q and S1199Y, or E1191Q and S1199F.

22. The polypeptide of one of claims 20-21, wherein the two substitution mutations correspond to E1191M and S1199L.

23. The polypeptide of one of claims 20-21, wherein the two substitution mutations correspond to E1191M and S1199Y.

24. The polypeptide of one of claims 20-21, wherein the two substitution mutations correspond to E1191M and S1199F.

25. The polypeptide of one of claims 20-21, wherein the two substitution mutations correspond to E1191Q and S1199L.

26. The polypeptide of one of claims 20-21, wherein the two substitution mutations correspond to E1191Q and S1199Y.

27. The polypeptide of one of claims 20-21, wherein the two substitution mutations correspond to E1191Q and S1199F.

28. A polypeptide comprising a modified receptor binding domain of Clostridial botulinum serotype B (B-H_c) comprising a substitution mutation at a position corresponding to S1199 or S1201 of serotype B, strain 1.

29. The polypeptide of claim 28, wherein the substitution mutation produces enhanced binding of the modified B-H_c to human SytII and/or reduced binding of the modified B-H_c to human Syt I as compared to an identical molecule lacking the substitution mutation.

30. The polypeptide of claim 28, wherein the substitution mutation produces enhanced binding of the modified B-H_c to human SytII and/or increased binding of the modified B-H_c to human Syt I as compared to an identical molecule lacking the substitution mutation.

31. The polypeptide of any one of claims 29-30 wherein the substitution mutation is selected from the group consisting of A, R, N, D, C, Q, E, G, H, I, L, K, M, F, P, T, W, Y and V substituted for S.

32. The polypeptide of any one of claims 29-31 wherein the substitution mutation is a non-naturally occurring amino acid substituted for S.

33. The polypeptide of any one of claims 19 - 32, wherein the modified B-H_c is of strain 1.

34. A chimeric molecule comprising a first portion that is a modified receptor binding domain of *Clostridial botulinum* serotype B (B-H_c) linked to a second portion, wherein the modified B-H_c comprises one or more substitution mutations

corresponding to substitution mutations in serotype B, strain 1, selected from the group consisting of:

V1118M; Y1183M; E1191M; E1191I; E1191Q; E1191T; S1199Y; S1199F; S1199L; S1201V and combinations thereof.

35. The chimeric molecule of claim 33, wherein the modified B-H_c comprises two substitution mutations.

36. The chimeric molecule of claim 35, wherein the two substitution mutations correspond to E1191M and S1199L, E1191M and S1199Y, E1191M and S1199F, E1191Q and S1199L, E1191Q and S1199Y, or E1191Q and S1199F.

37. The chimeric molecule of one of claims 35-36, wherein the two substitution mutations correspond to E1191M and S1199L.

38. The chimeric molecule of one of claims 35-36, wherein the two substitution mutations correspond to E1191M and S1199Y.

39. The chimeric molecule of one of claims 35-36, wherein the two substitution mutations correspond to E1191M and S1199F.

40. The chimeric molecule of one of claims 35-36, wherein the two substitution mutations correspond to E1191Q and S1199L.

41. The chimeric molecule of one of claims 35-36, wherein the two substitution mutations correspond to E1191Q and S1199Y.

42. The chimeric molecule of one of claims 35-36, wherein the two substitution mutations correspond to E1191Q and S1199F.

43. The chimeric molecule of claim 34, wherein the modified B-H_c comprises a modified receptor binding domain of Clostridial botulinum serotype B (B-H_c) comprising a substitution mutation at a position corresponding to S1199 or S1201 of serotype B, strain 1.

44. The chimeric molecule of claim 43, wherein the substitution mutation produces enhanced binding of the modified B-H_c to human SytII and/or reduced binding of the modified B-H_c to human Syt I as compared to an identical molecule lacking the substitution mutation.

45. The chimeric molecule of claim 43, wherein the substitution mutation produces enhanced binding of the modified B-H_c to human SytII and/or increased binding of the modified B-H_c to human Syt I as compared to an identical molecule lacking the substitution mutation.

46. The chimeric molecule of any one of claims 44-45 wherein the substitution mutation is selected from the group consisting of A, R, N, D, C, Q, E, G, H, I, L, K, M, F, P, T, W, Y and V substituted for S.

47. The chimeric molecule of any one of claims 44-46 wherein the substitution mutation is a non-naturally occurring amino acid substituted for S.

48. The chimeric molecule of any one of claims 43 – 47, wherein the modified B-H_c is of strain 1.

49. The chimeric molecule of any one of claims 32-48, wherein the first portion and the second portion are linked covalently.

50. The chimeric molecule of any one of claims 32-48, wherein the first portion and the second portion are linked non-covalently.

51. The chimeric molecule of any one of claims 32-50 wherein the second portion is selected from the group consisting of a small molecule, a nucleic acid, a short polypeptide and a protein.

52. The chimeric molecule of claim 51, wherein the second portion is a bioactive molecule.

53. The chimeric molecule of claim 51 or 52, wherein the second portion is a therapeutic polypeptide or non-polypeptide drug.

54. A nucleic acid comprising a nucleotide sequence that encodes the polypeptide or chimeric molecule of any one of claims 1- 53.

55. A nucleic acid vector comprising the nucleic acid of claim 54.

56. A cell comprising the nucleic acid vector of claim 55 or the nucleic acid of claim 54.

57. A cell expressing the polypeptide or chimeric molecule of any one of claims 1- 53.

58. A pharmaceutical composition comprising the botulinum neurotoxin (BoNT) polypeptide of any one of claims 1-18, or the chimeric molecue of any one of claims 34-53, or the nucleic acid vector of claim 55 or the nucleic acid of claim 54.

59. The pharmaceutical composition of claim 58, further comprising a pharmaceutically acceptable excipient.

60. A kit comprising a pharmaceutical composition of claim 58 or 59 and directions for therapeutic administration of the pharmaceutical composition.

61. A method to produce a botulinum neurotoxin (BoNT) polypeptide, the method comprising the steps of culturing the host cell of claim 57 under conditions wherein said BoNT polypeptide is produced.

62. The method of claim 61 further comprising recovering the BoNT polypeptide from the culture.

63. A method for treating a condition associated with unwanted neuronal activity comprising administering a therapeutically effective amount of the BoNT polypeptide of any one of claims 1-18 to a subject to thereby contact one or more neurons exhibiting unwanted neuronal activity, to thereby treat the condition.

64. The method of claim 63, wherein the condition is selected from the group consisting of , spasmodic dysphonia, spasmodic torticollis, laryngeal dystonia, oromandibular dysphonia, lingual dystonia, cervical dystonia, focal hand dystonia, blepharospasm, strabismus, hemifacial spasm, eyelid disorder, cerebral palsy, focal spasticity and other voice disorders, spasmodic colitis, neurogenic bladder, anismus, limb spasticity, tics, tremors, bruxism, anal fissure, achalasia, dysphagia and other muscle tone disorders and other disorders characterized by involuntary movements of muscle groups, lacrimation, hyperhydrosis, excessive salivation, excessive gastrointestinal secretions, secretory disorders, pain from muscle spasms, headache pain, and dermatological or aesthetic/cosmetic conditions.

65. The botulinum neurotoxin (BoNT) polypeptide of any one of claims 1-18, the pharmaceutical composition of claim 58 or 59, or the chimeric molecule of any one of claims 34-53, or the polypeptide of any one of claims 19-33, for use in medicine.

66. The botulinum neurotoxin (BoNT) polypeptide of any one of claims 1-18, the pharmaceutical composition of claim 58 or 59, or the chimeric molecule of any one of claims 34-53, or the polypeptide of any one of claims 19-33, for use in treating a condition associated with unwanted neuronal activity.

CLAIMS

1. A botulinum neurotoxin (BoNT) polypeptide comprising:

(a) a protease domain;

(b) a protease cleavage site;

(c) a translocation domain; and

(d) a modified receptor binding domain of *Clostridial botulinum* serotype B (B-H_c), comprising one or more substitution mutations corresponding to a Y1183M substitution mutation in serotype B, strain 1.

2. A BoNT polypeptide according to Claim 1, in which the modified (B-H_c) comprises two substitution mutations.

3. A BoNT polypeptide according to Claim 1 or 2, in which the modified B-H_c is of strain 1.

4. A BoNT polypeptide according to Claim 1, 2 or 3, in which the protease domain, translocation domain, and protease cleavage site are from a serotype selected from the group consisting of A, B, C, D, E, F, G, and combinations thereof.

5. A BoNT polypeptide according to Claim 4, in which the protease domain, translocation domain, and protease cleavage site are from serotype B, strain 1.

6. A BoNT polypeptide according to Claim 4, in which the protease domain, translocation domain, and protease cleavage site are from serotype A, strain 1.

7. A polypeptide comprising a modified receptor binding domain of *Clostridial botulinum* serotype B (B-H_c) comprising one or more substitution mutations corresponding to a Y1183M substitution mutation in serotype B, strain 1.

8. A polypeptide according to Claim 7, in which the modified (B-H_c) comprises two substitution mutations.

9. A polypeptide according to Claim 7 or 8, in which the modified B-H_c is of strain 1.

10. A chimeric molecule comprising a first portion that is a modified receptor binding domain of *Clostridial botulinum* serotype B (B-H_c) linked to a second portion, in which the modified B-H_c comprises a substitution mutation Y1183M in serotype B, strain.

11. A chimeric molecule according to Claim 10, in which the modified B-H_c comprises two substitution mutations.

12. A chimeric molecule according to Claim 10 or 11, in which the first portion and the second portion are linked covalently.

13. A chimeric molecule according to Claim 10 or 11, in which the first portion and the second portion are linked non-covalently.

14. A chimeric molecule according to any of Claims 10 to 13 in which the second portion is selected from the group consisting of a small molecule, a nucleic acid, a short polypeptide and a protein.

15. A chimeric molecule according to Claim 14, in which the second portion is a bioactive molecule.

16. A chimeric molecule according to Claim 14 or 15, in which the second portion is a therapeutic polypeptide or non-polypeptide drug.

17. A nucleic acid comprising a nucleotide sequence that encodes a polypeptide or chimeric molecule according to any preceding claim.

18. A nucleic acid vector comprising a nucleic acid according to Claim 17.

19. A cell comprising a nucleic acid vector according to Claim 18 or a nucleic acid according to Claim 17.

20. A cell expressing a polypeptide or chimeric molecule according to any of Claims 1 to 16.

21. A pharmaceutical composition comprising a botulinum neurotoxin (BoNT) polypeptide according to any of Claims 1 to 6, a chimeric molecule according to any of Claims 10 to 16, a nucleic acid vector according to Claim 18 or a nucleic acid according to Claim 17.

22. A pharmaceutical composition according to Claim 21, further comprising a pharmaceutically acceptable excipient.

23. A kit comprising a pharmaceutical composition according to Claim 21 or 22 and directions for therapeutic administration of the pharmaceutical composition.

24. A method of producing a botulinum neurotoxin (BoNT) polypeptide, the method comprising the steps of culturing a host cell according to Claim 20 under conditions in which the BoNT polypeptide is produced.

25. A method according to Claim 24, further comprising recovering the BoNT polypeptide from the culture.

26. A botulinum neurotoxin (BoNT) polypeptide according to any of Claims 1 to 6, a pharmaceutical composition according to Claim 21 or 22, a chimeric molecule according to any of Claims 10 to 16, or a polypeptide according to any of Claims 7 to 9, for use in medicine.

27. A botulinum neurotoxin (BoNT) polypeptide according to any of Claims 1 to 6, a pharmaceutical composition according to Claim 21 or 22, a chimeric molecule according to any of Claims 10 to 16, or a polypeptide according to any of Claims 7 to 9, for use in treating a condition associated with unwanted neuronal activity.

28. A botulinum neurotoxin (BoNT) polypeptide, pharmaceutical composition, chimeric molecule, or a polypeptide according to Claim 26 or 27 for a use as specified therein, in which the method comprises administering a therapeutically effective amount of the BoNT polypeptide to a subject to thereby contact one or more neurons exhibiting unwanted neuronal activity, to thereby treat the condition.

29. A botulinum neurotoxin (BoNT) polypeptide, pharmaceutical composition, chimeric molecule, or a polypeptide according to Claim 26, 27 or 28 for a use as specified therein, in which the condition is selected from the group consisting of spasmodic dysphonia, spasmodic torticollis, laryngeal dystonia, oromandibular dysphonia, lingual dystonia, cervical dystonia, focal hand dystonia, blepharospasm, strabismus, hemifacial spasm, eyelid disorder, cerebral palsy, focal spasticity and other voice disorders, spasmodic colitis, neurogenic bladder, anismus, limb spasticity, tics, tremors, bruxism, anal fissure, achalasia, dysphagia and other muscle tone disorders and other disorders characterized by involuntary movements of muscle

groups, lacrimation, hyperhydrosis, excessive salivation, excessive gastrointestinal secretions, secretory disorders, pain from muscle spasms, headache pain, and dermatological or aesthetic/cosmetic conditions.

30. Use of a botulinum neurotoxin (BoNT) polypeptide according to any of Claims 1 to 6, a chimeric molecule according to any of Claims 10 to 16, or a polypeptide according to any of Claims 7 to 9, in the preparation of a medicament for the treatment of a condition associated with unwanted neuronal activity, preferably a condition set out in Claim 29.