

CLAIMS

1. A botulinum neurotoxin (BoNT) Heavy Chain Binding domain (H_C/TAB) having a N-terminal end (H_{CN}) and a C-terminal end (H_{CC}), wherein the H_C/TAB comprises:
 - a) a synaptotagmin (Syt) receptor binding site, and
 - 5 b) a synaptic associated vesicle 2 (SV2) receptor binding site, and
 - c) a ganglioside (Gang) receptor binding site,and wherein said H_C/TAB is adapted to synergistically bind to a synaptotagmin (Syt) receptor, a synaptic associated vesicle 2 (SV2) receptor and a ganglioside (Gang) receptor.
- 10 2. The H_C/TAB according to claim 1, wherein the sequences forming the Gang receptor binding site originates from any Gang receptor binding BoNT serotype and their subtypes.
3. The H_C/TAB according to any of claims 1 or 2, wherein the sequences forming the Syt receptor binding site originates from any Syt receptor binding BoNT serotype and their
15 subtypes.
- 4 The H_C/TAB according to any of claims 1-3, wherein the sequences forming the SV2-receptor binding site originates from any SV2 receptor binding BoNT serotype and their subtypes.
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5. The H_C/TAB according to any of claims 1-4, wherein the H_{CN} sequence originates from any SV2 receptor binding BoNT serotype and their subtypes.
6. The H_C/TAB according to any of the claims 1-5, characterized in that the H_{CC} domain is
25 composed interchangeably of sequences from BoNT serotype A (BoNT/A) and BoNT serotype B (BoNT/B).
7. The H_C/TAB according to any of the claims 1-6, characterized in that said H_{CC} end is composed according to a sequence A₁B₁A₂B₂A₃, wherein A indicates a sequence from BoNT/A
30 and B indicates a sequence from BoNT/B.

8. The H_C/TAB according to claim 7, wherein the sequences of B₁, A₂ and B₂ comprise mutations and/or deletions to create stable intramolecular interfaces for the entire H_C/TAB.
9. The H_C/TAB according to any of the claims 1-8, wherein the sequences forming the
5 Gang receptor binding site originate from BoNT/B.
10. The H_C/TAB according to any of the claims 7-8, wherein the sequences forming the Gang receptor binding site are located in B₂.
- 10 11. The H_C/TAB according to any of the claims 1-10, wherein the sequences forming the Syt receptor binding site originate from BoNT B, DC or G.
12. The H_C/TAB according to any of the claims 7-8 or 10, wherein the sequences forming the Syt receptor binding site are located in B₁ and B₂.
- 15 13. The H_C/TAB according to any of the claims 1-12, wherein the H_{CN} sequence originates from BoNT/A.
14. The H_C/TAB according to any of the claims 7-8, 10 or 12, wherein the sequences
20 forming the SV2 receptor binding site are located in H_{CN} and in A₁ and A₃ in the H_{CC}.
15. The H_C/TAB according to any of claims 1-14, having an amino acid sequence which is at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% identical to the sequence of SEQ. ID. No. 1.
- 25 16. A polypeptide comprising the H_C/TAB according to any of the claims 1-15, coupled to any one or more other protein, polypeptide, amino acid sequence or fluorescent probe, directly or via a linker.
17. The polypeptide according to claim 16, wherein said polypeptide is a BoNT polypeptide
30 (BoNT/TAB), characterized in that said BoNT/TAB in addition to the H_C/TAB comprises a Heavy Chain Translocation domain (H_N), a Light chain (LC) and a protease site positioned between the LC and H_N in the polypeptide sequence, wherein the H_N and the LC, respectively and

independently of each other, originate from any of the BoNT serotypes A, B, C, D, DC, E, En, F, G or X and their subtypes.

18. The polypeptide according to claim 17, further comprising any other protein,
5 polypeptide, amino acid sequence or fluorescent probe, linked thereto, directly or via a linker.

19. The polypeptide according to any of the claims 17 or 18, wherein the protease site is an exoprotease site.

10 20 The polypeptide according to any of claims 16-19, having an amino acid sequence which is at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% identical to the sequence of any of SEQ. ID. No.3, SEQ. ID. No. 5, SEQ. ID. No. 6, SEQ. ID. No. 8, SEQ. ID. No. 10 or SEQ. ID. No. 12.

15 21. A vector comprising a nucleic acid sequence encoding the H_C/TAB according to any of the claims 1-15 or the polypeptide according to any of the claims 16-20.

22. A vector according to claim 21, comprising a nucleic acid sequence which is at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, or 95% identical to the sequence of any of SEQ. ID. No. 4, SEQ. ID. No. 7, SEQ. ID. No. 9, SEQ. ID. No. 11 or SEQ. ID. No. 13.
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23. A H_C/TAB according to any of the claims 1-15, or a polypeptide according to any of the claims 16-20, for use in a therapeutic method or in a cosmetic method.

25 24. The H_C/TAB or polypeptide for use according to claim 23, wherein the therapeutic method or cosmetic method is a treatment to dampen and/or inactivate muscles.

25. The H_C/TAB or polypeptide for use according to any of the claims 23 or 24, wherein the therapeutic method is treatment and/or prevention of a disorder chosen from the group
30 comprising neuromuscular disorders and spastic muscle disorders.

26. The H_c/TAB or polypeptide for use according to any of the claims 23-25, wherein the disorder is chosen from the group comprising 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, sports injuries, and depression.
27. A polypeptide according to claim 16 for use in a pharmacological test, to investigate the role of said protein, polypeptide, amino acid sequence or fluorescent probe in a synaptic process.
28. A H_c/TAB according to any of the claims 1-15 for use as a vehicle for effectively transporting any protein, polypeptide amino acid sequence or fluorescent probe coupled thereto to a neuronal surface.
29. A BoNT/TAB according to any of the claims 17-20 for use as a vehicle for effectively transporting any protein, polypeptide amino acid sequence or fluorescent probe into a neuronal cytosol using a toxin translocation system.
30. A pharmaceutical or cosmetic composition comprising the H_c/TAB according to any of the claims 1-15 or the polypeptide according to any of the claims 16-20.
31. A kit of parts comprising the composition of claim 30 and directions for therapeutic administration of the composition.
32. A method of treating a condition associated with unwanted neuronal activity, the method comprising administering a therapeutically effective amount of the H_c/TAB of any of the claims 1-15 or the polypeptide of any of the claims 16-20, or the pharmaceutical composition of claim 30, to a subject to thereby treat the condition, wherein the condition is

chosen from the group comprising 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, 5 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, sports injuries, and depression, and dermatological or aesthetic/cosmetic conditions.