

## Brookfield Academy Upper School SMART Team

Elizabeth Cinquegrani, Mark Morris, Leah Wang, Harry Kalsi, Shalini Gundamraj, Suneri Kothari, Lena Ding, Srimayi Mylavarapu, Alex Dortzbach, and Juliana Vollmer

Advisor: Dr. Robbyn Tuinstra

Mentor: Madison Zuverink and Joseph T. Barbieri, Ph.D.  
Medical College of Wisconsin Department of Microbiology and Molecular Genetics

### Modeling Botulinum Neurotoxin Type A

**PDB:** 3BTA

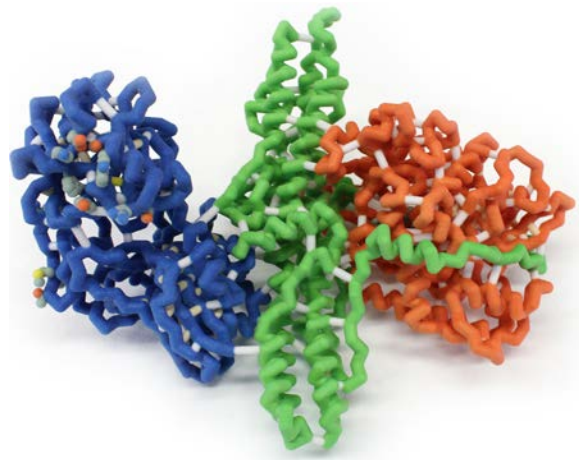
**Primary Citation:** D. Borden Lacy, William Tepp, Alona C. Cohen, Bibhuti R. DasGupta, and Raymond C. Stevens. (1998) Crystal structure of botulinum neurotoxin type A and implications for toxicity. *Nature Structural Biology*. 5: 898-902

**Format:** Alpha carbon backbone

**RP:** Zcorp with plaster

#### Description:

Botulinum neurotoxin type A (BoNT/A) is a potent neurotoxin, causing muscle paralysis in the host by blocking the release of the neurotransmitter, acetylcholine, from motor neurons associated with skeletal muscle. Despite this toxicity, BoNT/A is used pharmaceutically as a treatment for numerous neurological diseases, including migraines, dystonias, and as an anti-wrinkle agent in cosmetic surgery. BoNT/A is one of seven serotypes of botulinum (A-G), which, along with tetanus toxin, are produced by several species of *Clostridium*. All clostridial neurotoxins, such as BoNT/A, are di-chain proteins, consisting of a 50-kDa light chain, the catalytic domain, connected by a disulfide bond to a 100-kDa heavy chain, containing the receptor-binding and translocation domains. BoNT/A intoxication is a multistep process. First, BoNT/A binds to presynaptic nerve endings, through interactions of the receptor-binding domain with the ganglioside, GT1b, and the protein co-receptor, SV2. SV2 is a synaptic vesicle protein that becomes exposed to the neuron cell surface as vesicles fuse with plasma membrane, releasing neurotransmitter into the synapse. BoNT/A then enters the neuron by receptor-mediated endocytosis. Following endocytosis, the synaptic vesicle acidifies, allowing for neurotransmitter uptake, which triggers the translocation domain to insert and transport the catalytic domain into the cytosol. The catalytic domain is a Zn-dependent protease that cleaves SNAP-25, one of three major proteins present in the SNARE complex. The SNARE protein complex is required for the fusion of synaptic vesicles with the neuronal membrane. Cleavage of SNAP-25 inhibits fusion of synaptic vesicles to the plasma membrane to inhibit acetylcholine release and muscle contraction, leading to flaccid paralysis. Brookfield Academy SMART (Students Modeling A Research Topic) Team students modeled BoNT using 3D printing technology, highlighting amino acid residues associated with protease activity in the catalytic domain, and GT1b and SV2 interactions within the receptor binding domain. This model is meant to



help understand and communicate structure/function relationships of BoNT/A and promote potentially therapeutic uses of the toxin.

### **Specific Model Information:**

- Catalytic domain (1-437) backbone is colored red
- Translocation domain (448-872) backbone is colored limegreen
- Receptor-binding Domain (873-1295) backbone is colored blue
- Zn cofactor is displayed as spacefill and is colored orange
- Amino acids Glutamic Acid-261, Histidine-226 and Histidine-222, which coordinate the Zn cofactor, are displayed as ball and stick in CPK coloration.
- Amino acids Glutamic Acid-223, and Tyrosine-365 are also present in the catalytic domain near the Zn cofactor and assist in the catalysis of SNAP-25 hydrolysis. They are displayed as ball and stick in CPK coloration.
- Amino acids Arginine-1155, Tyrosine 1148, Methionine 1143, Threonine 1144, and Threonine 1145, which are present in the receptor-binding domain and interact with SV2 protein, are displayed as ball and stick in CPK coloration.
- Amino acids Trptophan-1265, Glutamic Acid-1202, Serine-1263, histidine-1252, phenylalanine-1251, tyrosine-1116, serine 1274, and arginine-1275, which are present in the receptor-binding domain and interact with GT1B ganglioside, are displayed as ball and stick in CPK coloration.
- Disulfide bridges are displayed in yellow.
- Structural supports are colored ghostwhite.
- H-bonds are colored moccasin

<http://cbm.msoe.edu/smartTeams/index.php>

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