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1 **Hsp90 and Thioredoxin-Thioredoxin Reductase Enable the Catalytic Activity of**
2 **Clostridial Neurotoxins inside Nerve Terminals**

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8 **Keywords:** Thioredoxin Reductase, Thioredoxin, Synaptic Vesicles, Botulinum Neurotoxins,
9 Tetanus Neurotoxin, Hsp90, Geldanamycin, PX-12, Ebselen, inhibitors

10 **ABSTRACT**

11 Botulinum (BoNTs) and tetanus (TeNT) neurotoxins are the most toxic substances known
12 and form the growing family of Clostridial neurotoxins (CNT), the etiologic agents of
13 botulism and tetanus. CNT are composed of a metalloprotease light chain (L), linked via a
14 disulfide bond to a heavy chain (H). H mediates the binding to nerve terminals and the
15 membrane translocation of L into the cytosol, where its substrates, the three SNARE
16 proteins, are localized. L translocation is accompanied by unfolding and, once delivered on
17 the cytosolic side of the endosome membrane, it has to be reduced and reacquire the
18 native fold to be active. The Thioredoxin-Thioredoxin Reductase system (Trx-TrxR)
19 specifically reduces the interchain disulfide bond while the cytosolic chaperone protein
20 Hsp90 mediates L refolding. Both steps are essential for CNT activity and their inhibition
21 efficiently blocks the neurotoxicity in cultured neurons and mice. Trx and its reductase
22 physically interact with Hsp90 and are loosely bound to the cytosolic side of synaptic
23 vesicles, the organelle exploited by CNT to enter nerve terminals and wherefrom L is
24 translocated into the cytosol. Therefore, Trx, TrxR and Hsp90 orchestrate a chaperone-
25 redox molecular machinery that enables the catalytic activity of the L inside nerve
26 terminals. Given the fundamental role of L reduction and refolding, this machinery
27 represents a rational target for the development of mechanism-based antitoxins.

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