

MICROBIOTIX, INC. RECEIVES SBIR PHASE I GRANT TO DEVELOP QUINOLINE-BASED INHIBITORS OF BoNT/A LC

April 1, 2011. Microbiotix, Inc, a privately held biotechnology company, announced that it was awarded a Phase I Small Business Innovation Research (SBIR) grant from the National Institutes of Health/NIAID. The SBIR Phase I grant entitled, "Quinoline-based Inhibitors of BoNT/A LC" provides two years of support to develop novel drugs to treat botulinum poisoning.

The botulinum neurotoxins (BoNTs) are the most poisonous biological substances known. The lethal intravenous dose of BoNT serotype A (BoNT/A) in humans is 1-5 ng/kg. If accidental exposure to BoNT occurs (e.g. from contaminated foodstuffs), loss of life or life-threatening paralysis can occur. Most importantly, the BoNTs have already been "weaponized" in a highly toxic aerosol form, and they consequently pose a significant threat to both civilian and military populations. Once ingested, BoNTs target the peripheral cholinergic nerve endings and cause death by interrupting autonomic nerve function. The zinc-dependent endopeptidase light chain (LC) portion of BoNTs impairs neuronal exocytosis through proteolysis of essential SNARE (soluble *N*-ethylmaleimide-sensitive factor attachment protein receptor) components of neurotransmission.

The overall goal of this project is to develop small molecule inhibitors of the BoNT/A light chain (LC) metalloprotease activity to treat botulinum poisoning. Our strategy is to optimize a novel chemotype of BoNT/A LC inhibitors to improve potency, selectivity, and drug-like properties. In preliminary studies, we refined the structures to provide a new starting point for medicinal chemistry based on a chemical core with more drug-like properties than the original compound series and with ten-fold better potency. Significant activity was also observed in a chick neuronal cell model of BoNT/A intoxication. These validated early lead compounds are more suitable lead compounds for BoNT/A inhibitor drug discovery than were the original series, and they form the basis for this optimization program to generate an advanced lead compound.

The aims of this research program are as follows: (1) Design and synthesize novel inhibitors of BoNT/A LC.; (2) Demonstrate potent, selective inhibitory activity in cellular models of BoNT/A action.; (3) Identify BoNT/A inhibitor lead compounds that are active in an *in vivo* rodent model of BoNT/A intoxication. (4). Identify BoNT/A inhibitors with favorable *in vitro* ADME-T properties suitable for further pre-clinical development.

John D. Williams, Ph.D., Senior Scientist, will serve as the Principal Investigator of the grant.

About Microbiotix

Founded in 1998, Microbiotix, Inc. is a product-focused biopharmaceutical company engaged in the research and development of novel, small-molecule, anti-infective drugs that address commercially significant medical markets. The company currently has several active research programs in the fields of anti-bacterial and anti-viral discovery, with three compound series in pre-clinical development. More information can be found on the company's web site, www.microbiotix.com.