NEWS RELEASE

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FOR RELEASE
November 12, 2003

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SMALL-MOLECULE INHIBITORS OF BOTULINUM NEUROTOXIN IDENTIFIED
Findings Hold Promise for Developing New Botulism Therapies

Scientists have identified several key molecules that block the activity of a toxin that causes botulism—an important first step in developing therapeutics to counter the disease.

Botulinum neurotoxins (BoNT) are useful as therapeutic agents for treating a wide variety of muscle dysfunctions in humans, and are used cosmetically to reduce wrinkles. Paradoxically, the seven serotypes of BoNT, designated A through G, also are among the most lethal biological substances known.

Botulinum neurotoxins are composed of two peptide chains, a heavy chain (HC) and a light chain (LC). The heavy chain targets and binds to surface receptors on nerve terminals. The toxins are then internalized into the nerve terminal. Once inside, the light chain separates from the heavy chain and cleaves, or cuts, specific proteins that control neuromuscular function. Cleavage of these proteins effectively blocks the release of neurotransmitters that cause the muscle contractions necessary for respiration. The result is a flaccid paralysis that ultimately leads to suffocation and death.

Because botulinum neurotoxins are capable of causing mass casualties, they are classified as biodefense A (top priority) agents by the Centers for Disease Control and Prevention. Currently, no therapeutics exist to counter the threat; thus, identifying and developing compounds that inhibit the neurotoxins is a high priority.

In an article published last month in *Biochemical and Biophysical Research Communications*, and recently highlighted in *Nature Reviews in Drug Discovery*, investigators from the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID), the National Cancer Institute (NCI), and the University of Nebraska Medical Center (UNMC) report using a high-throughput assay to screen a group of 1,990 compounds known as the NCI diversity set. The molecular properties of this group are predictive of a larger set of more than 100,000 compounds.

Using a two-stage assay, the team identified a number of compounds that inhibited the enzymatic action of BoNT serotype A light chain (BoNT/A LC). All inhibitors were further verified by high-performance liquid chromatography. Finally, molecular modeling techniques were used to predict structural features that contribute to inhibitor binding and potency.

These techniques revealed a common pharmacophore—a "scaffold" upon which future therapeutics can be built. This pharmacophore will serve as a basis for directing future efforts to

develop BoNT/A LC inhibitors with enhanced potency. Testing in cell culture will be followed by animal modeling once the most promising candidates have been identified.

Study collaborators were Sina Bavari, James J. Schmidt, and Robert G. Stafford of USAMRIID; Rick Gussio, Daniel W. Zaharevitz, Edward A. Sausville, Douglas J. Lane, Connor F. McGrath, Ann R. Hermone, Tam L. Nguyen, Rekha G. Panchal, and James C. Burnett of NCI; and Jonathan L. Vennerstrom of UNMC.

"This work is the result of a productive collaboration between federal and academic partners," said Colonel Erik A. Henchal, commander of USAMRIID. "These are the relationships that will, in the future, deliver the biodefense products the nation needs."

USAMRIID, located at Fort Detrick, Maryland, is the lead laboratory for the Medical Biological Defense Research Program, and plays a key role in national defense and in infectious disease research. The Institute's mission is to conduct basic and applied research on biological threats resulting in medical solutions (such as vaccines, drugs and diagnostics) to protect the warfighter. USAMRIID is a subordinate laboratory of the U.S. Army Medical Research and Materiel Command.

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