

**Toward Better Therapeutics and Prophylaxis:  
Modeling Covalent and Noncovalent Inhibition of Acetylcholinesterase**

**Gerald H. Lushington, Nora M. Wallace, Molecular Graphics and Modeling Laboratory/ Bioinformatics Core Facility, University of Kansas, Lawrence, KS 66045; Jian-Xin Guo, VM Discovery, Inc.** 2006 Annual Kansas City Area Life Sciences Research Day.

Despite being the subject of decades of research, acetylcholinesterase remains a target of vigorous pharmacological interest. One of the more challenging foci of acetylcholinesterase is the development of inhibitors of potential application to a variety of neurodegenerative diseases (Alzheimer's disease, various dementia, etc.), an autoimmune condition called myasthenia gravis, and prophylactics for mitigating the threat of nerve agent exposure. Such applications require the design of inhibitors (either covalent or noncovalent) of differing strength, and also require a careful understanding of toxicity thresholds. In dealing with nerve agent prophylaxis, *in vitro* and *in vivo* testing is inherently hazardous and must be performed under expensive precautionary conditions. For this reason computer modeling is often seen as a highly advantageous first step in many research efforts, thus there has been substantial value attached toward computational methods capable of reliably weighing the numerous factors that influence inhibitive efficacy and toxicity. Herein we report proven methods for accurately predicting the IC<sub>50</sub> values of known non-covalent inhibitors, as well as the LD<sub>50</sub> values of known covalent species. Preliminary optimization strategies are evident from the results.