

The U.S. Army Medical Research Institute of Chemical Defense is Awarded a \$14.4 Million Center of Excellence Grant from the National Institutes of Health

Center for Catalytic Bioscavenger Medical Defense Research will Advance a Therapeutic Concept Developed by the Department of Defense

The National Institutes of Health (NIH) has announced the award of a "Countermeasures Against Chemical Threats (CounterACT) Research Center of Excellence" grant worth \$14.4 million over 5 years to the U.S. Army Medical Research Institute of Chemical Defense (USAMRICD) at Aberdeen Proving Ground, Maryland. The Institute is the Department of Defense's premiere laboratory for the development of medical products against the effects of toxic chemicals. The NIH CounterACT program addresses the critical need for improved antidotes for civilian populations vulnerable to chemical agent poisoning by a terrorist attack. The competitive funding opportunity was available for all U.S. academic, industrial, and government laboratories.

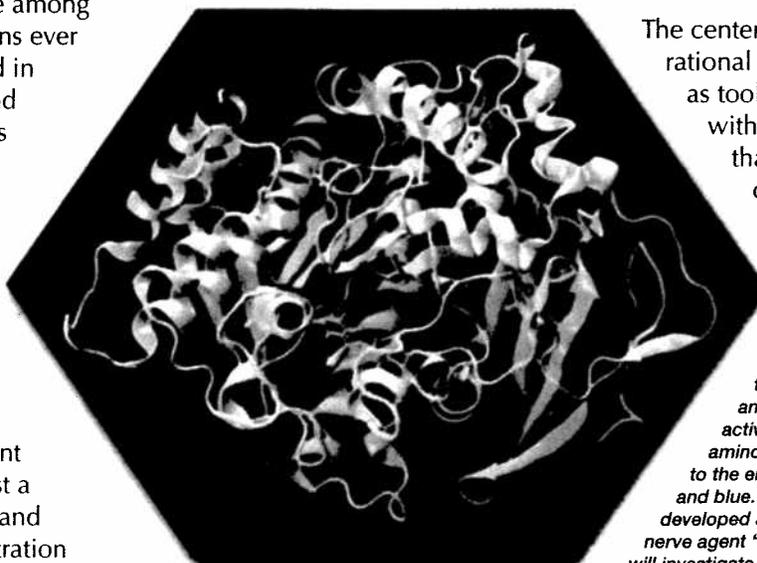
Led by the center's principal investigator, Dr. David Lenz, the new NIH Center for Catalytic Bioscavenger Medical Defense Research at the USAMRICD will build upon the established infrastructure and personnel resources at the USAMRICD and at the national and international collaborating institutions. The partner organizations include the Human Biomolecular Research Institute, San Diego; The Weizmann Institute in Israel; the Department of Plant, Cellular, and Molecular Biology, The Ohio State University; The Biodesign Institute at Arizona State University; and the Department of Chemistry, The Ohio State University.

"Nerve agents, such as sarin, are among the most lethal chemical weapons ever developed. They have been used in wars as recently as the 1980s and by terrorist organizations such as in the subway attacks in Japan in the mid-1990s," says Dr. David Moore, Director of Strategic Research Program Development at the USAMRICD. The possibility of future use of these nerve agents by terrorists requires the urgent development of effective and safe antidotes. A pretreatment (or prophylactic) effective against a broad spectrum of nerve agents and capable of reducing the concentration

of nerve agent in the blood before it can reach its site of action should be particularly effective as an antidote. Likewise, a very rapid onset therapy that could specifically reduce the concentration of the nerve agent poison in circulation would be more advantageous than the currently available therapeutic drugs. The concept of designing a safe and effective nerve agent bioscavenger addresses the strategic need for improved preventative and therapeutic drugs.

The Center will provide for a comprehensive collection of scientific and technological capabilities needed to address this novel drug discovery and drug production challenge. The Center will align collaborative research efforts between the USAMRICD and five other research groups. The USAMRICD is responsible for the overall administration of the Center and the management of the \$14.4 million award over 5 years.

The Center for Catalytic Bioscavenger Medical Defense Research is based on two interlocking themes, one based on biochemical and molecular biological approaches to the design of human proteins with unique catalytic activity, and one based on genetic engineering of plants such that they will express proteins of human origin in high yield, both bolstered by the ability to provide critical facilities for demonstrating proof of concept sufficient for transition of a potential drug for advanced development and human clinical trial testing.



The center places heavy emphasis on both rational design and molecular evolution as tools for the design of human proteins with unique catalytic activity such that they can catalyze the hydrolysis of all currently identified nerve agent chemical warfare threats,

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The structure for human butyrylcholinesterase is shown as a ribbon diagram form, with those portions of the molecule that are structurally similar to each other depicted in purple or yellow. The amino acids that play a role in the catalytic activity of the enzyme are shown in red, and those amino acids that assist in binding of the substrate to the enzyme are depicted in green, orange, yellow and blue. Human butyrylcholinesterase is being developed as a potential nerve agent prophylaxis or nerve agent "scavenger". The new "Center" at USAMRICD will investigate and develop additional bioscavengers.

MRICD Grant *cont.*

i.e., those poisons that act by inhibiting the enzyme critical for nervous transmission, acetylcholinesterase (AChE). These efforts will be informed by research into the basic physiochemical processes that define catalytic activity using techniques, such as computational chemistry, protein structural analysis by NMR and X-ray crystallography, and fast flow kinetics. Those efforts, coupled with the evaluation of catalytic efficiency, *in vitro* and, ultimately, *in vivo*, of the mutated proteins, will provide the basis for optimization of the requisite catalytic activity.

The center will focus not only on the design of a protein with high catalytic efficiency for the detoxification of nerve agents *in vivo*, but will also address the equally challenging problem of expression of such a protein in high yields at a potentially economically viable cost. To that end, two unique approaches will be utilized to express human proteins in plant systems. Plants offer several advantages as sources of human proteins, not the least of which is the scalability of these systems. In addition, one of their major advantages is that they are higher eukaryotic organisms that possess an endomembrane system and secretory pathway that is very similar to that of mammalian cells. As a result, complex proteins are generally efficiently assembled with the appropriate post-translations modifications.

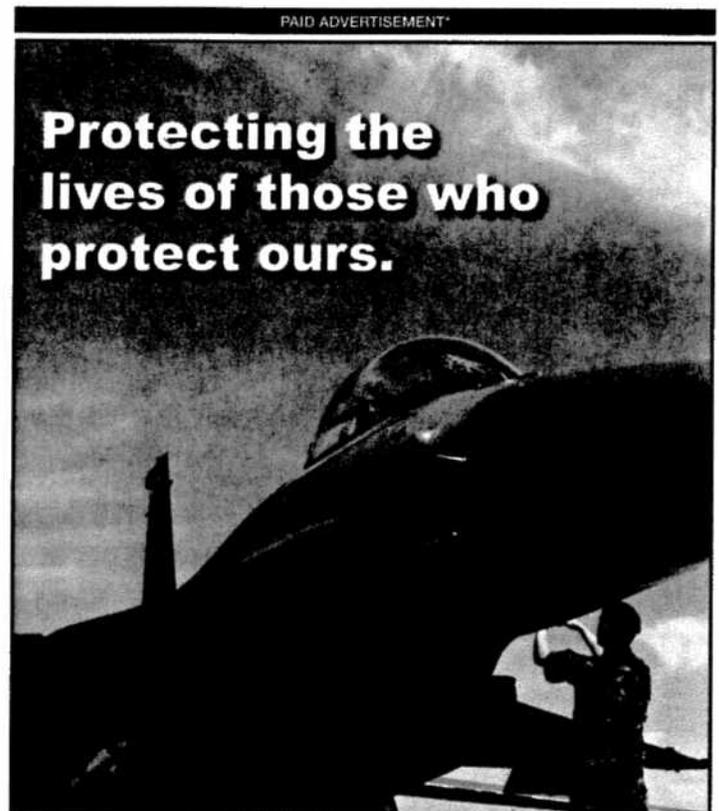
The center has unique facilities for testing the resultant rationally designed or gene-shuffled, transiently expressed enzymes with respect to their ability to catalyze the hydrolysis of the actual threat nerve agents. Likewise, these same facilities at the USAMRICD will be used to test the products from the high expression plant systems. This unique capability will allow for immediate evaluation of proteins to allow for a rank-ordering based on *in vitro* results prior to further testing *in vivo*, resulting in a significant conservation of animal resources. It will also provide rapid feed-back to both the emerging computational chemistry data base and to the rational design efforts for improved activity. Finally the center will be able to perform *in vivo* evaluation of the efficacy of candidate proteins, thereby ensuring that the most promising candidates are selected for advanced development. This will save time and money, both critical commodities in drug development programs.



COL Brian Lukey, Commander of USAMRICD congratulates Dr. David Lenz on the award of the five year Center of Excellence grant from the National Institutes of Health.

that the NIH has recognized the considerable talents resident at the USAMRICD, as well as the quality of the research team organized by Dr. Lenz to address this important problem".

"The work of this new center will lead to a paradigm shift in how to treat nerve agent exposure and will lead to therapeutics with less toxic potential and reduced immunogenicity," says Dr. Lenz. Colonel Brian Lukey, commander of the USAMRICD, says, "We are delighted



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