# Two UCSD Research Projects Awarded NIH Counter-terrorist Grants

*Countermeasure Against Chemical Threats (CounterACT) grants total $6.75 million*

October 12, 2006

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Two projects designed to develop new and improved medical countermeasures against chemical threats, directed by faculty members at the University of California, San Diego (UCSD) School of Medicine and Skaggs School of Pharmacy and Pharmaceutical Sciences, have been funded with five-year grants from the National Institutes of Health (NIH), Department of Health and Human Services, for Countermeasures Against Chemical Threats (CounterACT) Cooperative Research Projects.

Gerald R. Boss, M.D., professor of medicine, has been awarded $3.3 million for pre-clinical and clinical studies of a detoxifying agent for cyanide, a highly toxic compound that could be used as a weapon of mass destruction. Palmer Taylor, Ph.D., Sandra & Monroe Trout Professor of Pharmacology and Dean of UCSD's Skaggs School of Pharmacy and Pharmaceutical Sciences, received $3.46 million to develop novel means for degrading nerve gas and eliminating toxicity after exposure.

The CounterACT grants are designed to support research to develop new and improved therapeutics and diagnostic techniques to enhance the nation's medical response capabilities in the event of a terrorist chemical threat. Chemical threats are defined by the NIH as toxic chemical agents that could be used in a terrorist attack against civilians, or those that could be released at toxic levels by accident or natural disaster. The NIH intends to commit about $10 million this year for 10-15 CounterACT projects nationwide.

*Finding a safe and effective antidote to cyanide poisoning* Cyanide has been used as a weapon in warfare during World Wars I and II, and during the Iraq/Iran conflict. It has the potential to come into the hands of terrorists because it is readily available in industrial settings and relatively easy to synthesize from inexpensive, widely obtainable reagents, according to Boss. It would be particularly lethal if released as a gas in closed spaces such as an airport or train station.

Boss's project aims to study the safety and efficacy of cobinamide, a promising antidote for cyanide poisoning. Boss hypothesizes that cobinamide - a compound produced in the biosynthesis of cobalamin (vitamin B12) - would be an ideal agent for treating cyanide-exposed victims. It has a very high binding affinity for cyanide, rendering it inert; appears to be non-toxic; and can be administered promptly by injection into the muscle.

Currently, only two cyanide antidotes are available in the United States, sodium thiosulfate and nitrates in the form of sodium and amyl nitrite. Both agents have significant side effects and serious limitations in treating large number of victims as they must be either administered intravenously (sodium thiosulfate and sodium nitrate) or inhaled for several minutes (amyl nitrite.)

Boss has already shown cobinamide to detoxify cyanide in mice and fruit flies. Stanford Research Institute in Palo Alto, California, will subcontract to conduct pre-clinical studies during the first three grant years, allowing the investigators to move on to performing Phase I and IIa clinical studies during the fourth and fifth years, after receiving FDA approval.

The Phase II studies would be performed on patients being treated with nitroprusside, a blood pressure drug used in acute hypertensive emergencies. Nitroprusside therapy is limited by cyanide toxicity, therefore if effective, cobinamide would allow hypertensive patients to be treated with that drug for longer period and at higher doses.

"In addition, cobinamide could be used to treat smoke inhalation victims, occupational and industrial cyanide exposures, and even cigarette smokers," said Boss. He envisions developing a therapy similar to the epi-pens used by highly allergic patients in the event of a bee sting, that could be used within minutes by soldiers or others exposed to cyanide gas to counteract its effect.

*Degrading the toxicity of nerve gas agents* Nerve gas is another chemical weapon that was used by Sadam Hussien on Kurdish citizens and in the scud missile attacks by Iraq in the 1980s. Another recent example is notorious attack by a terrorist group using sarin in the Tokyo subway system.

Taylor 's project focuses on creating a modified, synthetic version of AChE, an enzyme in nerve tissue that is the target protein of nerve gas agents. AChE accelerates or catalyzes the breakdown of the neurotransmitter acetylcholine, allow ing normal neural transmissions across synapses in nerve and muscle tissue to occur. But when a nerve agent interacts with this protein, the normal transmissions of these neurotransmitters are disrupted.

His research involves using recombinant DNA to create a synthetic AChE that, in addition to acetylcholine , catalyzes breakdown of nerve gases. The synthetic, modified human AChE enzyme would be injected into the patient's blood in the case of contact with a nerve gas agent, together with a standard oxime antidote. This would allow the toxic agent to be quickly degraded in the blood, before reaching vitally important nerve and muscle tissues.

This scientific process, called "oxime-assisted catalysis," couples the modified AChE with an oxime, an antidote that has been used for the past 50 years to reactivate inhibited AChE. Taylor has been investigating the structure of AChE and the genes that encode this enzyme of the nervous system since 1975. Selective oximes and other chemical compounds are being developed by K. Barry Sharpless, Ph.D., at The Scripps Research Institute, a collaborating principal investigator on the project.

"Many insecticides used in agriculture, which are especially prevalent in California, cause toxicity upon exposure similar to nerve gas," said Taylor. "The same technology we are developing to deactivate nerve gas can be used as an antidote to accidental insecticide poisoning that can occur with home and garden pesticides as well."

The project will utilize AChE/nerve agent adducts produced by government labs in initial *in-vitro* studies. As the modified enzyme distribution is limited to the bloodstream, oxime-assisted catalysis can readily be tested in human blood samples in later stages of the project, avoiding animal or human exposure.

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