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MEETING ABSTRACTS

CATALYTIC SCAVENGERS PROVIDE BROAD-SPECTRUM PROTECTION AGAINST ORGANOPHOSPHORUS NERVE AGENTS

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Efforts to develop a single enzyme capable of catalyzing the hydrolysis of a broad spectrum of organophosphorus (OP) compounds into non-toxic products have produced multiple candidate enzymes on different structural scaffolds. While protection against multiple OPs from a single enzyme has been obtained, no single enzyme has been identified that can provide protection against all G- and V-type OP nerve agents. The most promising candidate enzyme platform is the bacterially produced recombinant variant of organophosphorus hydrolase (OPH) from *B. diminuta*. *In vivo* protective efficacy of candidate OPH scavengers as prophylactics was tested in guinea pigs by administering the enzyme via a carotid catheter, followed 20 minutes later by a subcutaneous injection of increasing doses of the OP nerve agents GA, GB, GD, GF, VX, VR, or VM. A stage-wise, adaptive dosing experimental design was used to determine the median lethal dose (LD_{50}) of each OP in the context of enzyme prophylaxis. We report that a combination of two different OPH variants is capable of providing protection against at least 2 x LD_{50}s of all of the OPs tested. The results indicate that broad spectrum prophylactic protection against OP intoxication can be provided with a cocktail of two different catalytic scavengers with appropriate catalytic activity. Formulation of the enzymes to promote circulatory stability will be discussed.

Keywords: catalytic scavenger; prophylaxis; organophosphorus hydrolase

The views expressed in this abstract are those of the author(s) and do not reflect the official policy of the Department of Army, Department of Defense, or the U.S. Government. The experimental protocol was approved by the Animal Care and Use Committee at the United States Army Medical Research Institute of Chemical Defense and all procedures were conducted in accordance with the principles stated in the Guide for the Care and Use of Laboratory Animals and the Animal Welfare Act of 1966 (P.L. 89-544), as amended. This work was supported by the NIH CounterACT Center of Excellence grant U54 NS058183 (to D.M.C.) and by the Defense Threat Reduction Agency-Joint Science and Technology Office, Medical S&T Division.

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