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Antibody-Assisted Protection from Paraoxon and Nerve Agent Model Compounds

It is estimated that globally, there are 750,000 to 3,000,000 annual human intoxications due to exposure to organophosphorus compounds (OPs). OPs constitute a diverse class of chemicals that include flame retardants and chemical warfare agents (i.e., nerve agents) but are most widely recognized as insecticides. Agricultural workers that handle OP insecticides are at risk of exposure because there are more than 100 different OP forms used worldwide. Parathion is an example of a widely used insecticide that is profoundly toxic following oxidative conversion to paraoxon. The number of OP exposures worldwide and the possible toxic consequences underscores the need to develop new approaches to OP detoxication.

Medicinal chemists and biochemists at the Human BioMolecular Research Institute (HBRI), in San Diego, CA, reported on the development of a catalytic antibody that degraded the OP paraoxon.

The acute toxic effects of OPs arise from inhibition of acetylcholinesterase (AChE) to form a relatively stable OP-AChE moiety that is a covalent phosphorylated enzyme adduct. AChE inhibition results in rapid accumulation of excess acetylcholine that leads to prolonged stimulation of acetylcholine receptors that can produce convulsions and other neurotoxicity. In addition to AChE inhibition, OPs also covalently modify other proteins including butyrylcholinesterase (BChE) and serum albumin. As a class of chemicals, the pronounced reactivity and indiscriminate modification of target and non-target proteins renders OPs a considerable concern to human health.

Known countermeasures to combat exposure to OPs include therapeutics, protein-based scavengers (e.g., BChE), anti-convulsants and sedatives. The current standard of care (SOC) includes the AChE reactivator 2-PAM, the muscarinic receptor blocker atropine, and midazolam or diazepam, and supportive care such as oxygen, fluids etc. Benzodiazepines work to suppress seizures at indirect targets. These countermeasures mainly address AChE post-inhibitory toxicity but not clearance or degradation of OPs. Once exposed to an OP, it is critical to minimize exposure to the brain and other key organs because certain OPs and some oxon metabolites are long-lived and can continuously inhibit/re-inhibit AChE or modify other proteins that lead to acute and delayed neurotoxicities.

Development of a new therapeutic that degrades toxic OPs that directly limit brain and other critical organ penetration would be a useful addition to the countermeasure armamentarium and enhance SOC usefulness. While progress has been made with bioscavengers that decrease OP toxicity by decreasing the net levels of circulating OP, new approaches are needed that can overcome their poor biodistribution, selectivity and reactivity toward OPs. We developed a new approach utilizing a monoclonal antibody (mAb) assisted by 2-PAM to degrade the OP paraoxon into the innocuous materials diethyl phosphate and *p*-nitro phenol. In an *in vivo* setting, use of such a combination therapy with the SOC could result in a decrease in circulating paraoxon, and a decrease in paraoxon entering the brain and other vital organs.

We tested the hypothesis that design of haptens used to elicit mAbs that degraded paraoxon from transition state analog analysis would afford a way to simulate the reaction between paraoxon and 2-PAM on the surface of an antibody. The concept was to bring 2-PAM and paraoxon together on the surface (i.e., combining site) of the mAb to accelerate degradation of paraoxon to harmless byproducts. Others have used biomolecular reactions to accelerate mAb-mediated catalysis but this is the first report of pairing or bringing together of a catalytic mAb with a proxy nucleophile (i.e., 2-PAM) to afford acceleration of OP degradation.

The report showed that application of designed mAbs with or without 2-PAM to degrade paraoxon helped to define chemical determinants responsible for mAb action. In parallel, we observed that the catalytic mAb with or without 2-PAM was flexible enough to degrade a nerve agent model compound of sarin.

This paper was featured in the *Journal of Medicinal Chemistry* in July, 2026.

"The finding that "a catalytic antibody" using "transition state mimetic" technology with a "proxy nucleophile" was successful is important because it showed that antibody engineering can be done efficiently using these approaches" explains co-author Dr. Jorge Gomez-Galeno. *"By efficiently degrading paraoxon and a nerve agent model compound, protection against OPs could be realized."* Given its potency, these new antibodies may be of utility to protect against neurotoxicity.

"*The new antibodies may lead to treatment applications in a whole host of toxic OP exposure conditions that may prove efficacious in vivo*" explains co-author Dr. John Cashman. "*As neuroprotective catalytic antibody technology progresses, we expect new antibodies to be less toxic and more efficacious than current standard of care for OP exposure, and patients will benefit from improved safety, less side effects and possibly significant cost-savings."*

Summary

Medicinal chemists and biologists at HBRI are the first to combine transition state approaches with proxy nucleophiles to design and develop monoclonal antibodies to obtain efficient catalytic antibodies to degrade paraoxon and a nerve agent model compound. To our knowledge, this is one of the first reports to use catalytic antibodies and standard of care to degrade an OP efficiently. Revealing links between antibody development and long-lived neuroprotection from OPs might be fundamentally important and clinically relevant.

Publication

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