DEVELOPMENT OF A RECOMBINANT BUTYRYLCHOLINESTERASE "PULMONARY BIOSHIELD" TO PROTECT AGAINST OP RESPIRATORY TOXICITY IN MACAQUES

Rosenberg Y.J[1]; Laube B.[2]; Mao L.[1]; Jiang X.[1]; Hernandez-Abanto S.[1]; Adams R[2].

[1]*PlantVax Inc, Rockville, Maryland, USA,*

[2]*Johns Hopkins University School of Medicine, MD, USA*

Objective: The recent use of sarin in Syria highlights the urgent need for nerve agent and toxic pesticide detection and countermeasures necessary for preparedness and emergency responses. Recombinant butyrylcholinesterase (BChE) is a potent, safe and effective organophosphate (OP) and carbamate bioscavenger with broad antidotal properties. However, the requirement for post-translational modification for plasma stability, the large size of the PEG-rMaBChE form (>800,000 MW) and the 1:1 stoichiometry of BChE:OP, means large treatment doses will be required and thus the route of systemic delivery, which determines the pharmacokinetics (PK) of clearance, becomes critical to efficacy and safety. Because of the challenges using parenteral delivery, an aerosolized (aer) rBChE has been used to generate a "pulmonary bioshield", which can neutralize inhaled OP in situ; preventing its entry into the blood and inhibition of RBC-AChE and plasma BChE.

Methods: CHO-derived rBChE was delivered to anesthetized macaques using a microsprayer via an endoscope or nebulizer and aer-paraoxon (Px) was delivered 1-40 hr later. Protection was assessed by the percent inhibition of red blood cell acetylcholinesterase (RBC-AChE) and plasma butryylcholinesterase (BChE) in blood post exposure.

Results: Previous results using a microsprayer via an endotracheal tube for delivery, indicate that unmodified aer-rMaBChE and rHuBChE (~9 mg/kg) pretreatment given 1-40 hr prior to >1 LD50 of aer-paraoxon (Px) prevented inhibition of circulating cholinesterase in a dose-dependent manner. More recently, studies have been performed using a vibrating mesh nebulizer system to mimic pulmonary administration to humans and indicate that 45ug/kg (~3LD50) of inhaled Px. inhibited 90% blood ChEs by one hr. Efficacy studies using inhaled BChE and the ability of oximes to increase the duration of protection will be reported.

Conclusions: These studies are the first to show protection by rBChE against a pesticide such as paraoxon when delivered directly into the lung and bode well for the use of a non-invasive and consumer friendly method of rHuBChE delivery as a human pretreatment to counteract OP and pesticide toxicity.