

Oral Presentation - 11

Development of a Recombinant Butyrylcholinesterase “Pulmonary Bioshield” To Protect Against OP Inhalation Exposure in Macaques

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Abstract

Native butyrylcholinesterase (BChE) is a potent, safe and effective organophosphate (OP) and carbamate bioscavenger with very good in vivo stability but of limited availability. Alternative recombinant (r) forms of BChE require PEG-conjugation to achieve similar plasma stability following parenteral delivery (im, sc, iv). However, while BChE has broad antidotal properties, the large size of PEG-rMaBChE (>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 of large molecules and because inhalation OP exposure serves as a major means of intoxication due to rapid accesses of the OP to the blood), we have delivered an aerosolized form of rBChE, which is too large to leave the lung and which can neutralize inhaled OP in situ and prevent its entry into the blood and inhibition of RBC-AChE and plasma BChE. The results to date, indicate that unmodified aer-rMaBChE and rHuBChE (~5-9 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. 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 Carbamate toxicity.