Project Objective: What is the purpose of the overall effort and significance to the goals of CounterACT (1-3 concise sentences)?

Technological Approach: In brief general terms, what are you going to do and how will you do it (4-5 concise sentences)? Please do NOT list Specific Aims (or their status).

Figure(s)/data illustrating significant/exciting new progress or KEY results of the work performed in the current year (include exposure paradigm if in vivo results are illustrated).

Project Year 0X Milestones/Deliverables and Status:
• State milestones EXACTLY as listed on your latest Notice of Grant Award (also state whether “Accomplished” or “In Progress”)

Figure(s)/data illustrating significant/exciting new progress or KEY results of the work performed in the current year (include exposure paradigm if in vivo results are illustrated).

Potential Key Challenges:
•

POC: PI Name/Institute and email address
Enhancing the anti-OP activity of the HuXYZ enzyme
U01 NS012345-0X

**Project Objective:** To develop an effective *in vivo* therapeutic (bioscavenger) against organophosphate (OP) intoxication, to include pesticide and chemical warfare agent poisonings.

**Technological Approach:** Based on computational studies, site-directed mutagenesis will be utilized to generate mutants of the human XYZ enzyme. Mutants will then be expressed and biochemically assayed for catalytic activities against common substrates (phenyl acetate and paraoxon) *in vitro*. Optimal mutants will be characterized against *bona fide* nerve agents *in vitro*. Mutant enzymes with at least 10-fold enhancement in anti-nerve agent activity will be evaluated as potential bioscavengers in animal studies. Definitive analytical methods will be developed as needed throughout the research process.

**Project Year 0X Milestones/Deliverables and Status:**
- Develop a computational model of human XZY based on the structures of mouse XYZ and a OPase-based homolog (*Accomplished*)
- Complete docking simulations of enzyme-substrate complex of HuXYZ with GA, GD, and VX (*In Progress*)
- Identify 10 amino acid residues involved in catalytic machinery (*Accomplished*)
- Generate 5 mutant HuXYZ enzymes with at least 10-fold enhanced activity for paraoxon (*In Progress*)

**Potential Key Challenges:**

**POC:** Dr. Larry Jones; UNV; jonesl@unv.edu