cumulative $^{14}$C-VX penetration for the no decontamination control and DKP-1 Mk3 (from 7 hours) and microfiber cloth decontamination (from 12 hours). The likely discrepancy in decontamination efficacy lies with the skins micro relief. The furrows and wrinkles present in skin make it difficult to decontaminate with the weave of the microfiber cloth. Future work will evaluate a range of decontamination candidates against a range of nerve agents prior to testing in an *in vivo* model with therapeutic intervention administration. *1. Dalton, C.H., Graham, S.J., and Jenner, J. "Effect of exposure area on nerve agent absorption through skin* in Vitro" *Toxicology* in vitro *30 (1) 454-461 (2015)* 

## PS 2155 Genetic-Based, Differential Susceptibility to Exposure to Combined Organophosphate and Increased Glucocorticoid in a Mouse Model of Gulf War Illness

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In 1990-1991, the USA sent 700,000 troops to the first Gulf War. Approximately 25% of the deployed soldiers developed a chronic multisymptom illness with many features of "sickness behavior." This disorder now has been termed Gulf War Illness (GWI) and, remarkably, for those so afflicted, most have symptoms that persist to this day, nearly 30 years later. The cause of GWI has been thought to center on a variety of exposures that occurred in theater, including organophosphate nerve agent (sarin) and insecticides (e.g. chlorpyrifos). We have developed an animal model of GWI that combines exposure to corticosterone as a physiological stressor mimic with diisofluorophosphate (DFP) (as nerve agent analogue) to mirror some of the exposure/conditions that occurred in theater. The model was developed in the C57BL/6 (B6) mouse strain. The question raised was while 25-30% of the troops became ill, what about those who did not -- all else being equal? The B6 mouse strain is one of the founders of a large panel of recombinant strains (BXD) derived from crossing with the DBA/2 (D2) strain. The mouse model of individual differences in susceptibility to combined OP and high circulating glucocorticoid (corticosterone -- CORT) is to test the D2 strain and several of the BXD strains (and both sexes). The protocol involved adding corticosterone to the drinking water (20mg%) of the mice for 7 days followed on the 8th day by injection of diisopropyl-flurophosphate (DFP, 4mg/kg) followed 6h later by euthanasia and harvesting the frontal cortex. The index for neuroinflammation was change in expression of proinflammatory cytokine genes, IL1beta, IL6 and TNFalpha. The results showed that the D2 mice were less sensitive to CORT+DFP than the B6 and that there were large differences among 30 of the BXD strains. We then performed genome-wide mapping of the IL1beta results and found a significant marker (quantitative trait locus) on distal chromosome 7. Searching that area on Chromosome for possible candidate genes, we identified Spondin 1 as candidate. The gene is cis-regulated and its expression is significantly correlated ($r=0.76$, $p<0.01$) with the expression of IL1beta expression under exposure to CORT+DFP. These results show that susceptibility to GWI likely has a genetic component and we will show that further testing of the BXD mice will produce more candidates. We can then identify biochemical pathways that differ and possibly develop treatments and means of prevention.

## PS 2156 Neuroinflammation Detected by Longitudinal TSPO Positron Emission Tomography (PET) Is Associated with Deficits in Learning and Memory in a Rat Model of Acute Organophosphate (OP) Intoxication [BH1]

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Current medical countermeasures for acute OP poisoning do not protect against chronic cognitive impairment, underscoring the need for preclinical models that enable longitudinal monitoring of novel therapies. Previous studies using a rat model demonstrated neuroinflammation coincident with progressive neuronal necrosis following acute intoxication with the OP diisopropylfluorophosphate (DFP), suggesting neuroinflammatory mechanisms of chronic deficits. The goal of the current study was to determine whether OP-induced neuroinflammation, assessed by PET imaging with the TSPO radioligand [18F]PBR111, was associated with cognitive impairment. Adult male Sprague Dawley rats were treated with pyridostigmine (0.1 mg/kg, im) prior to administration of DFP (4 mg/kg, sc), atropine sulfate (2 mg/kg, ip) and 2PAM (25 mg/kg, im), with a subset receiving a benzodiazepine (BDZ) (5 mg/kg diazepam, ip or 0.7 mg/kg midazolam, im) 45 min post DFP. TSPO expression in the brain was imaged using a Siemens F120 or Inveon DPET microPET scanner; anatomic registration was obtained using a Bruker 7T MRI. Animals were imaged on a Bruker 7T MRI at 3, 7, 28, 65, 91, 182 d post-DFP. DFP elicited moderate-to-severe seizure activity in all rats as determined using a modified Racine scale. DFP significantly increased TSPO labeling within multiple brain regions, including the hippocampus, thalamus, amygdala and piriform cortices. Regional quantification of [18F]PBR111 uptake was significantly correlated with deficits in learning and memory assessed by cued and contextual fear conditioning. The results demonstrate that BDZ therapy attenuates, but does not prevent, significant regional neuroinflammation following acute DFP intoxication. These findings suggest this neuroinflammation may contribute to cognitive impairment observed in survivors of acute OP intoxication. *Supported by NIH CounterACT program (NS079202).*

## PS 2157 Crossing the Blood-Brain Barrier to Combat Nerve Agent

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Organophosphorus (OP) nerve agents inhibit the acetylcholinesterase (AChE) enzyme, disrupting the hydrolysis of acetylcholine. An excess of acetylcholine can lead to seizure activity, convulsions, respiratory distress, and even death. Oximes reactivate OP-inhibited AChE by detaching the OP from the enzyme. Pralidoxime (2-PAM) is the standard oxime countermeasure used by the US Army; however, 2-PAM is unable to cross the blood-brain barrier, making it ineffective against the central effects of nerve agent. Here, serum carboxylesterase knockout (Es1 KO) mice were used to investigate the *in vivo* reactivation of OP-inhibited AChE by the novel oximes SwRI-80 and SwRI-144, as compared to 2-PAM. Since carboxylesterase is an endogenous bioscavenger of nerve agent in mice, Es1 KO mice are comparable to a human model of OP toxicity. AChE activity was measured via Ellman's assay for brainstem, cerebellum, cerebral cortex, hippocampus, midbrain, diaphragm, heart, and skeletal muscle. One-way ANOVAs were performed to compare controls, which received the nerve agent sarin (GB), cyclosarin (GF), or VX followed by saline, to groups which received the corresponding nerve agent followed by one of three doses (n=8-9 per group) of 2-PAM, SwRI-80 or SwRI-144. 2-PAM significantly reactivated GB-inhibited AChE in heart, and VX-inhibited AChE in heart and diaphragm, but did not significantly reactivate GF-inhibited AChE in any tissues. SwRI-80 had no significant effect against GB-inhibited AChE, but it significantly reactivated VX-inhibited AChE in skeletal muscle and two brain regions (hippocampus and cerebellum) not affected by 2-PAM. Against GF, SwRI-80 also significantly reactivated AChE in skeletal muscle and two brain regions (midbrain and cerebellum) not affected by 2-PAM. SwRI-144 significantly reactivated GF and GB-inhibited AChE in all tissues, except GB-inhibited cerebellum AChE and GF-inhibited cortex AChE. Similarly, SwRI-144 significantly reactivated VX-inhibited AChE in all tissues, except cortex. The SwRI compounds appear to cross the blood-brain barrier and reactivate OP-inhibited AChE in various brain regions as well as skeletal muscle not affected by the standard oxime countermeasure 2-PAM.

## PS 2158 An *Ex Vivo* and *In Vivo* Comparative Study with MMB4 and 2-PAM to Determine Liabilities Associated with Toxic Levels of the Oximes

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Oximes represent the standard of care against nerve agent poisoning, but several studies have shown that they can also induce striated muscle paralysis and cardiovascular changes. MMB4 has been proposed a potentially safer and more efficacious alternative to 2-PAM, the current therapeutic standard. These experiments evaluated the potential liabilities, and their mechanisms, of MMB4 at supra-therapeutic doses, both *ex vivo* and *in vivo*. The diaphragmatic/neuromuscular effects of MMB4 were evaluated *ex vivo* using stimulated (2V at 2Hz) phrenic nerve-hemidiaphragm preparations isolated from Sprague Dawley rats. MMB4 was given in escalating log concentrations and the force of diaphragmatic contractions were recorded. *In vivo*, the cumulative effects of either MMB4 (6 mg/kg/min) or 2-PAM (2.5 mg/kg/min) on cardiovascular (left ventricular pressures/derived indices) and neuromuscular end-points (diaphragmatic and skeletal muscle contractions) were simultaneously evaluated using anesthetized (isoflurane) and mechanically-ventilated


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