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Identification of Biological Pathways Implicated in Hippocampal Dysfunction and Cognitive Impairment in Gulf War Illness

Principal Investigator: CRAWFORD, FIONA**Institution Receiving Award:** ROSKAMP INSTITUTE**Program:** GWIRP**Proposal Number:** GW080094**Funding Mechanism:** Investigator-Initiated Research Award**Partnering Awards:****Award Amount:** \$834,000.00[View Technical Abstract](#)

PUBLIC ABSTRACT

Veterans from the 1990-1991 Persian Gulf War conflict exhibit a wide variety of health problems that are more chronic and complex in nature than non-deployed veterans or those deployed elsewhere. The time course of illness and the pattern of symptoms are unique to this specific deployment and are now characterized as Gulf War Illnesses (GWI). Among the symptoms consistently observed in these veterans is the impairment of short-term and delayed memory. This specific pattern of memory impairment is associated with damage to the hippocampal region of the brain and is also characteristic of Alzheimer's disease (AD) and related neurodegenerative disorders. Evidence suggests that agents that were administered for protective reasons during the conflict, such as the anti-nerve gas chemical pyridostigmine bromide (PB), and the pesticides DEET and permethrin, are significant contributors to the presentation of GWI and the hippocampal effects.

We believe that application of these agents to mice will result in memory impairment of hippocampal origin and will allow us to model neurocognitive abnormalities of GWI. Furthermore, we expect that mice with a genetic predisposition to develop memory problems will experience more severe cognitive impairment in response to exposure to these Gulf War agents. Recent technological advances allow detection and quantification of changes in proteins from complex samples, which can then be mapped to biological pathways to predict the functional significance of their altered state. In this proposal, Gulf War agents will be administered to mice, either singly or in combination, in order to compare the different effects of these agents on cognitive and behavioral performance using standard tests that are commonly used in research studies involving mice. We will also investigate changes in brain pathology, and changes in the type and amount of proteins in the hippocampal region of the brain, as well as the influence of genetic predisposition to cognitive dysfunction. The goal will be to identify underlying biological mechanisms relevant to GWI. Once identified, such mechanisms enable the development and testing of novel therapeutics.

By creating mouse models of GWI we will facilitate a comprehensive experimental assessment of the underlying biological causes for hippocampal-based cognitive dysfunction observed in Gulf War veterans, which is not possible in human patients but which will provide invaluable contributions toward finding an effective treatment. Nearly two decades have passed since these conflicts, but the cause and progression of GWI largely remains unresolved. These findings will have a major implication for the discovery of disease mechanisms that may contribute to hippocampal-based cognitive impairment in GWI. This proposal may also reveal that existing treatments for neurodegenerative disorders that are either already approved or are in various stages of clinical development, could prove useful to GWI patients and will thus support the use of such drugs in clinical trials for GWI.

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Last updated April 11, 2008 (ldm)
