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The Use of Comprehensive Molecular Profiling with Network and Control Theory to Better Understand GWI and Model Therapeutic Strategies

Principal Investigator: KLIMAS, NANCY G**Institution Receiving Award:** SOUTH FLORIDA VETERANS AFFAIRS FOUNDATION FOR RESEARCH AND EDUCATION, INC**Program:** GWIRP**Proposal Number:** GW080152**Funding Mechanism:** Investigator-Initiated Research Award**Partnering Awards:****Award Amount:** \$715,456.00[View Technical Abstract](#)

PUBLIC ABSTRACT

Numerous studies have reported fatigue, pain, cognitive difficulties, and certain other symptoms in veterans deployed to the Persian Gulf (Operation Desert Storm) who developed a fatiguing multi-symptom illness now called Gulf War Illness (GWI). These symptoms overlap with those of Chronic Fatigue Syndrome (CFS). GWI remains a serious health consequence for at least 11,000 veterans deployed during the first Gulf War in the early 1990s. Our group and others have shown problems with the regulation of immune function in both CFS and GWI, although the literature is not uniform. We hypothesize that GWI is a subset of CFS. We have completed a preliminary study in 10 GWI patients and 10 healthy controls, in which we collected blood samples before, immediately after, and 4 hours after, a carefully designed exercise challenge. We used a gene expression-based approach. By looking at the genes that control the immune system, the hormone system, and the nervous system, we showed that this exercise challenge model can help us better understand how these systems interact in healthy people and in patients with GWI. By using this exercise challenge, which forces the systems to work under stress, we showed that the differences between patients and controls become apparent. We also showed that GWI patients had impaired natural killer (NK) cell function as demonstrated by the decreased ability to kill tumor cell targets and altered peripheral blood mononuclear cell expression in genes associated with NK cell function. In addition, this preliminary work indicated that in order to capture changes in cytokine and gene expression that occur early in the exercise challenge we must sample early and frequently, thus this time course sampling period of 10 minutes, with a total of eight blood samples drawn over 2 hours.

In this new study, we propose to recruit 25 patients with GWI and 25 matched controls and to look at gene expression, immune function, endocrine studies, measures of autonomic function, and clinical data at these eight time points, and provide this rich data set to a talented analytic team. We will be able to accurately map out the networks of communication between these systems (endocrine, immune, and neurologic) using new analytic approaches that are very powerful. Our research group includes a team of biologic systems networks experts at the University of Alberta who use a combination of mathematical approaches, some quite unique, to map out these pathways or communication networks. With the use of a supercomputer, and looking at each individual data point in combination, over time, and compared to controls, a model is created that shows just how the ill veterans have a new balance of these systems that sustain the state of illness. This balance, termed homeostasis, allows the veteran to remain ill for many years. But we believe it should be possible to influence the mediators that sustain this balance and shift the balance toward normal, if we better understood the dynamics in play. The systems biologists on our team can both create these models and use them to propose very specific interventions to force the regulatory balance back towards a normal balance and health. Preliminary work has already pointed to novel, hormone-based interventions, and we expect a number of immune-based interventions to result from the proposed work. Ultimately, this work will lead to the definition of a number of clinical trials for effective therapies that are both reasonable and could be started on completion of this study.

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