AWARD NUMBER: W81XWH-16-1-0558

TITLE: Examination of Plasma PON1 Paraoxonase Activity and Genotype in Gulf War Veterans

PRINCIPAL INVESTIGATOR: Linda Chao

RECIPIENT: Northern California Institute for Research and Education (NCIRE)
San Francisco, CA 94121

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Fort Detrick, Maryland 21702-5012

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6. AUTHOR(S): **Linda Chao**

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7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

NCIRE
4150 Clement Street
San Francisco, CA 94121

8. PERFORMING ORGANIZATION REPORT

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
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13. SUPPLEMENTARY NOTES

14. ABSTRACT

The goal of this project is to evaluate the extent to which $PON1_{192}$/Gulf War (GW)-related exposure interactions contribute to the risk for Gulf War Illness (GWI), as defined by the Centers for Disease Control and Prevention (CDC) and Kansas case definitions in a large sample of GW veterans. Specifically, we will: (1) determine the associations between GWI and GW-related exposures with the potential for "cholinergic" effects (e.g., personal pesticide use, exposure to OP nerve agents) in subgroups of veterans with different $PON1_{192}$ genotype. (2) determine the associations between GWI and each GW-related "cholinergic" exposure in subgroups of veterans with different PON1 activity levels and (3) calculate prevalence odds ratios for GWI/exposure associations separately for sugbroups of veterans with different $PON1_{192}$ genotypes and PON1 activity levels.

15. SUBJECT TERMS
Gulf War Illness (GWI), Paraoxonase-1 (PON1), organophosphates (OP), Gulf War-related exposures

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER	19a. NAME OF RESPONSIBLE PERSON
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Unclassified	Unclassified	Unclassified	Unclassified	16	

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1. **INTRODUCTION:** Narrative that briefly (one paragraph) describes the subject, purpose and scope of the research.

The goal of this project is to evaluate the extent to which PON1$_{192}$/Gulf War (GW)-related exposure interactions contribute to the risk for Gulf War Illness (GWI), as defined by the Centers for Disease Control and Prevention (CDC) and Kansas case definitions in a large sample of GW veterans. Specifically, we will: (1) determine the associations between GWI and GW-related exposures with the potential for "cholinergic" effects (e.g., personal pesticide use, exposure to OP nerve agents) in subgroups of veterans with different PON1$_{192}$ genotype. (2) determine the associations between GWI and each GW-related "cholinergic" exposure in subgroups of veterans with different PON1 activity levels and (3) calculate prevalence odds ratios for GWI/exposure associations separately for sugbroups of veterans with different PON1$_{192}$ genotypes and PON1 activity levels.

2. **KEYWORDS:** Provide a brief list of keywords (limit to 20 words).

Gulf War Illness (GWI), Paraoxonase-1 (PON1), organophosphates (OP), Gulf War-related exposures

3. **ACCOMPLISHMENTS:** The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction.

What were the major goals of the project?
List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project, identify these dates and show actual completion dates or the percentage of completion.

1. Obtain information about GW-related exposures from participants of the completed DoD-funded GW study for whom we have PON1$_{192}$ genotype and PON1 activity data (by 10th month).
2. Obtain PON1$_{192}$ genotype and PON1 activity levels for veterans participating in the on-going VA Merit GW study at the SF VAMC (by month 17).
3. Obtain PON1$_{192}$ genotype and PON1 activity levels on biosamples from the Gulf War Illness Consortium (GWIC) (by month 27).
4. Obtain PON1$_{192}$ status and PON1 activity levels for veterans participating in the re-evaluation study of the Ft. Devens cohort (by month 15).
5. Analyze PON1 and self-reported GW-exposure data (by month 33).

What was accomplished under these goals?
For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.

Major activities and achievements:

A. Dr. Furlong's laboratory has established PON1 status, genotype, and phenotype for **372** samples to date.

B. Dr. Lea Steele's laboratory has conducted preliminary analyses on the associations between Kansas GWI case status with potential "cholinergic" exposures (e.g., pesticides, PB, hearing chemical alarms) and a noncholinergic exposure (e.g., oil fire smoke) by PON1 genetic subgroup status (QQ, RR, QR).

1. There were no significant differences in gender, race, PON1 activity, or PON1 genotype between Kansas GWI cases and controls.

2. Kansas GWI case status was associated with "cholinergic" exposures (hearing chemical alarms sound > 7 days, Odds Ratio, OR = 2.64, $p<0.05$ and using cream/spray pesticide on skin > 7 days, OR = 3.43, $p<0.001$) but not with the non-cholinergic exposure of oil fire smoke > 7 days (OR = 0.82).

3. The table below summarizes the association of Kansas GWI case status with deployment exposures (cholinergic and non-cholinergic) in the 3 different PON1 genetic subgroups. Preliminary analyses suggest substantial variations between the association of Kansas GWI case status with "cholinergic" exposures, which differ by PON1 genotype.

Experience/Exposure	QQ genotype (N=110)	QR genotype (N=97)	RR genotype (N=43)
Saw oil fire smoke > 7 days (non-cholinergic)	OR = 1.10	OR = 0.41	OR = 0.49
Heard chemical alarms sound > 7 days (cholinergic)	OR = 1.66	OR = 2.92	OR = 7.63*
Used cream/spray pesticide on skin > 7 days (cholinergic)	OR = 7.20**	OR = 3.49*	OR = 2.22

Multivariable logistic regression: full model includes all 4 exposures)
*OR significant $p<0.05$; **OR significant $p<0.001$

What opportunities for training and professional development has the project provided?
If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.

Nothing to report.

How were the results disseminated to communities of interest?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.

Nothing to report.

What do you plan to do during the next reporting period to accomplish the goals?
If this is the final report, state "Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

The Boston VA/BVARI site expects to have 20-30 samples that they will send to Dr. Furlong's laboratory for PON1 analysis.

The GWIC has 50 additional samples that they will send to Dr. Furlong's for PON1 analysis, with potentially 30 more samples by Spring, 2020.

Dr. Steele's group will continue to analyze the data in more detail, looking at other exposures and optimizing the statistical models. We expect analysis of the larger dataset will help to power analyses in the various subgroups.

4. **IMPACT:** Describe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

The preliminary findings support our hypothesis and suggest that there are differences in the impact of exposures to deployment-related "cholinergic" exposures on GWI by PON1 genotype.

What was the impact on other disciplines?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.

Nothing to report.

What was the impact on technology transfer?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to report.

What was the impact on society beyond science and technology?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Nothing to report.

5. **CHANGES/PROBLEMS:** The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

Changes in approach and reasons for change
Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.

Nothing to report.

Actual or anticipated problems or delays and actions or plans to resolve them
Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

No actual or anticipated problems.

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting

Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.

Significant changes in use or care of human subjects

There are no significant deviations or changes in approved protocols for the use of human subjects. The current IRB approval dates are:

SF VAMC site: initially approved: 03/30/2016; current expiration date: 12/08/2020
Boston University site: initially approved 6/23/16, current expiration date: 6/22/20
Boston VA site: initially approved 11/14/16, current expiration date: 5/6/20
Baylor College of Medicine site: initially approved: 9/13/16, current expiration date: 5/9/20

The University of Washington IRB determined that the UW site is not "engaged" in human subject research. Therefore, the UW IRB decided that IRB approval for the activities conducted by the UW research team is not required.

Significant changes in use or care of vertebrate animals.

N/A

Significant changes in use of biohazards and/or select agents

N/A

6. **PRODUCTS:** List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."

- **Publications, conference papers, and presentations**

Report only the major publication(s) resulting from the work under this award.

Journal publications. *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to report.

Books or other non-periodical, one-time publications. *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: Author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

Nothing to report.

Other publications, conference papers, and presentations. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

Nothing to report.

- **Website(s) or other Internet site(s)**
  List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.

Nothing to report.

- **Technologies or techniques**
  Identify technologies or techniques that resulted from the research activities. In addition to a description of the technologies or techniques, describe how they will be shared.

Nothing to report.

- **Inventions, patent applications, and/or licenses**
  Identify inventions, patent applications with date, and/or licenses that have resulted from the research. State whether an application is provisional or non-provisional and indicate the application number. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.

Nothing to report.

- **Other Products**
  Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment, and/or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:
  - *data or databases;*
  - *biospecimen collections;*
  - *audio or video products;*
  - *software;*
  - *models;*
  - *educational aids or curricula;*
  - *instruments or equipment;*
  - *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
  - *clinical interventions;*
  - *new business creation; and*
  - *other.*

N/A

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?
Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change."

Name:	Linda Chao
Project Role:	PI
Researcher Identifier:	0000-0002-8593-2434 (eRA Commons: lindachao)
Nearest person month worked:	0.6 calendar months
Contribution to Project:	Dr. Chao has work closely with Drs. Furlong, Sullivan, Steele, Krengel, and Klimas to coordinate all aspects of project, from study procedures, data collection, to data quality control.
Name:	Nancy Klimas
Project Role:	Co-Investigator
Researcher Identifier:	0000-0003-1459-3268
Nearest person month worked:	0.24 calendar months
Contribution to Project:	Dr. Klimas' laboratory houses all the GWIC samples. She will oversee the preparation and sending of the GWIC biorepository to Dr. Furlong's laboratory for PON1 analyses.

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.

Name: Linda Chao
Changes: 1. The federally funded support details for Dr. Chao remained unchanged since the previous annual report.

Name: Kimberly Sullivan
Changes:
1. DOD/CDMRP grant "Defining and Characterizing GWI Pathobiology using Longitudinal Brain Imaging Biomarkers of White Matter Integrity and Hemodynamic Response" has been funded. Dr. Sullivan is PI at X calendar months.
2. NIEHS grant "HMGB1, Chlorpyrifos, and Persistent GWI-like Neuropathology" has been funded. Dr. Sullivan is co-investigator at 0.6 calendar months.
3. DOD/CDMRP grant "Understanding Gut-Microbiome links to Gulf War Illness persistence and development of gut dysbiosis targeted therapy" has been funded. Dr. Sullivan is co-investigator at 0.6 calendar months.
4. DOD/CDMRP grant "Novel Combinatorial screening for Neurotrophis, Neuropoietic cytokines, Matrix Metalloproteinsas, and Complement components in relevance to neuronal Autoantibodies in the serum and CSF of Veterans with Gulf War Illness" has been funded. Dr. Sullivan is co-investigator at 0.6 calendar months.
5. DOD/CDMRP grant "Microtubule-Based Therapy for Neurodegeneration in Gulf War Illness; Studies with hiPSC-Derived Neurons from Gulf War Veterans" has been funded. Dr. Sullivan is co-investigator at 0.36 calendar months.
6. DOD/CDMRP grant "The Gulf War Illness Clinical Trials and Interventions Consortium (GWICTIC)" has been funded. Dr. Sullivan is co-investigator and site-PI at 0.84 calendar months.
7. Dr. Sullivan's efforts on DOD/CDMRP grant "Novel Autoantibody Serum and Cerebrospinal Fluid Biomarkers in Veterans with Gulf War Illness" has ended.
8. Dr. Sullivan's efforts on DOD grant "D-cycloserine –A Novel Treatment for Gulf War Illness" has ended.
9. Dr. Sullivan's effort on DOD/CDMRP grant GW150050P1 has ended.
10. Dr. Sullivan's effort on "A Randomized, Double-blind Placebo-controlled Phase III Trial of Coenzyme Q10 in Gulf War Illness" grant from the Department of Veterans Affairs has been reduced to 1.8 calendar months.

Name:	Clement Furlong 1. UW Center for Process Analysis and Control grant "Advance Surface Plasmon Resonance Sensors" has ended. 2. Dr. Furlong is PI on a University of Washington Center for Process Analysis and Control (CPAC) grant at 0.6 calendar months (annual direct cost: $6,000, dates of project: 10/1/19-9/30/20). 3. Dr. Furlong is co-investigator on a UW Alzheimer's Disease Research Center (ADRC) grant at 0.6 calendar months (annual direct cost: $146,410, dates of project: 05/01/19-04/30/20. PI: Marsillach).
Name:	Lea Steele 1. Dr. Steele's role on Assessment of MRI-Based Marker of Dopaminergic Integrity as a Biological Indicator of Gulf War Illness" (W81XWH-14-1-0622) changed from Co-I to PI and her effort increased from 0.6 to 2.4 calendar months.
Name: Change:	Nancy Klimas 1. NIH grant R01NS090200 has new end date of 1/31/20. 2. Dr. Klimas' contribution to DOD grant W81XWH-13-2-0085 has been increased from 0.72 to 1.2 calendar months. 3. Dr. Klimas' effort on VA Merit grant "A Translational Medicine Approach to Gulf War Illness: From Cells to Therapy" will end on 12/31/19. 4. DOD grant W81XWH-15-1-0537 has been extended. The new end date is 9/30/20 and Dr. Klimas' effort on this project remains 0.6 calendar months. 5. NIH grant R15 NS087604-01A has ended. 6. Dr. Klimas' effort of on DODGWIRP grant W81XWH1820062 has increased from 1.44 to 2.4 calendar months. 7. Dr. Klimas' effort on DOD/GWIRP grant W81XWH-17-2-0063 has increased from 0.36 to 0.6 calendar months. 8. DOD/GWIRP grant W81XWH-17-1-0640 has been extended to 09/14/20. Dr. Klimas' effort on this project has been reduced from 0.2 calendar months to no measurable effort. 9. DOD/CDMRP grant "Defining and Characterizing GWI Pathobiology using Longitudinal Brain Imaging Biomarkers of White Matter Integrity and Hemodynamic Response" has been funded. Dr. Klimas is co-investigator at 0.6 calendar months. 10. Dr. Klimas' effort on DOD/CDMRP grant "Disentangling the Effects of PTSD from GWI for Improved Diagnostics and Treatments" has ended. 11. Dr. Klimas' effort on DOD/CDMRP grant "Improving Diagnostics and Treatments for GWI Females by Accounting for the Effects of PTSD" has ended. 12. Dr. Klimas' effort on DOD/CDMRP grant "High Fidelity Design of Multi-modal Restorative Interventions in Gulf War Illness" has ended. 13. Dr. Klimas' effort on VA Merit grant "A Randomized, Double-blind Placebo-

What other organizations were involved as partners?

Nothing to Report

Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.
Provide the following information for each partnership:
Organization Name:
Location of Organization: (if foreign location list country)
Partner's contribution to the project (identify one or more)

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*

Name:	Clement Furlong
Organization Name:	University of Washington
Project Role:	Site PI
Researcher Identifier:	0000-0002-6489-7211 (eRA Commons: furlong)
Nearest person month worked:	0.6 calendar months
Contribution to Project:	Dr. Furlong is directing Ms. Richter in determination of PON1 status of the Gulf War veterans in the study.
Name:	Rebecca Richter
Organization Name:	University of Washington
Project Role:	Research Scientist in Dr. Furlong's laboratory
Researcher Identifier:	N/A
Nearest person month worked:	3.0 calendar months
Contribution to Project:	Ms. Richter has been working with Dr. Furlong to determine the PON1 status of the 103 Gulf War veterans' plasma samples from Dr. Chao's VA Merit award using the three-substrate assay/analysis protocol.
Name:	Kimberly Sullivan
Organization Name:	Boston University
Project Role:	Site PI
Researcher Identifier:	0000-0001-7940-6123
Nearest person month worked:	0.36 calendar months
Contribution to Project:	Dr. Sullivan is providing serum samples and Gulf War-related exposure data from the Department of Defense-funded (GW120037) multi-site Gulf War Illness consortium (GWIC) for study analysis. Once we receive HRPO clearance for Dr. Klimas' site, which houses all the GWIC samples, 100 GWIC samples will be sent to Dr. Furlong's laboratory.
Name:	Maxine Krengel
Organization Name:	Boston VA/Boston VA Research Institute (BVARI)
Project Role:	Site PI
Research Identifier:	0000-0001-7632-590X
Nearest person month worked:	0.60 calendar months
Contribution to Project:	Dr. Krengel is providing serum samples and Gulf War-related exposure data from her call-back survey study of the Fort Devens cohort. She will send 20 samples this month.
Name:	Lea Steele
Organization Name:	Balyor College of Medicine
Project Role:	Site PI
Research Identifier:	0003-4940-069X
Nearest person month worked:	0.6 calendar months
Contribution to Project:	Dr. Steele has worked with study collaborators on study planning and design.

8. SPECIAL REPORTING REQUIREMENTS: N/A

9. APPENDICES: Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.

N/A