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TITLE: Biomarkers and Brain Mechanisms of Gulf War Illness

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14. ABSTRACT: [no new findings; original abstract provided] Gulf War illness (GWI), a chronic and debilitating pain, headaches, impaired memory and thinking, fatigue, respiratory and gastrointestinal symptoms, and skin abnormalities. Exposure and sensitivity to chemical, pharmaceutical and/or environmental toxins in a combat theater of operations is believed to be causative of the illness. The pathobiological mechanisms of GWI are unknown; there are no validated diagnostic tests, nor are there effective treatments or cures. This is a case-control study consisting of 20 Gulf War veterans affected with GWI and 20 matched non-affected Gulf War veterans, who will serve as the normal control group. All subjects will undergo brain positron emission tomography and magnetic resonance imaging scans for assessments of metabolic or neurochemical disturbances that may be associated with GWI. In all consenting participants, a lumbar puncture will be performed to obtain cerebrospinal fluid (CSF), which will be analyzed for abnormalities in biochemical compounds that may be related to GWI. The derived neuroimaging and CSF metabolic or biochemical data will be compared between the groups to determine if there are abnormal changes in GWI veterans compared to controls, which may shed new light onto the pathophysiology of GWI, as well as serve as biomarkers of the disorder.					
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STANDARD FORM (SF) 298: A sample SF 298 is provided at <https://mrmc.amedd.army.mil/rrpindex.asp>. The abstract shall be provided in Block 14 and shall state the purpose, scope, and major findings and be an up-to-date report of the progress in terms of results and significance. Abstracts will be submitted to the Defense Technical Information Center (DTIC) and shall not contain proprietary information. Subject terms are keywords that may have been previously assigned to the proposal abstract or are keywords that may be significant to the research.

Pages shall be numbered. The number of pages shall include all pages that have printed data (including the front cover, SF 298, table of contents, and all appendices). Page numbers must match the numbering shown on the Table of Contents.

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

The overall objective of this study is to evaluate the suitability of a number of endogenous chemical compounds or metabolites to serve as sensitive brain imaging and cerebrospinal fluid (CSF) biomarkers of pathologic alterations in Gulf War illness (GWI) for use to facilitate early diagnosis, to assess disease progression and/or to monitor therapeutic response in future clinical trials of promising interventions. This is a case-control study that will enroll 20 Gulf War veterans affected with GWI and 20 matched non-affected Gulf War veterans, who will serve as the normal control group. All subjects will undergo brain positron emission tomography (PET) and magnetic resonance imaging (MRI) and spectroscopy (MRS) scans to assess metabolic or neurochemical disturbances that may be associated with GWI. In all consenting participants, a lumbar puncture will be performed to obtain CSF samples, which will be analyzed for abnormalities in biochemical compounds that may be related to GWI. The derived neuroimaging and CSF metabolic or biochemical data will be compared between the groups to determine if there are abnormal changes in GWI veterans compared to controls, which may shed new light onto the pathophysiology of GWI, as well as serve as biomarkers of the disorder.

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

Gulf War illness, Neuroinflammation, Oxidative Stress, Mitochondrial Dysfunction, Magnetic Resonance Imaging, Magnetic Resonance Spectroscopy, Positron Emission Tomography.

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.

RESEARCH-SPECIFIC TASKS:		
For All Specific Aims: Recruitment & Regulatory Approvals	Timeline	Site(s)
Major Task 1: GWI and Non-GWI Subject Recruitment	Months	ALL
Subtask 1: Establish formal contact between Mount Sinai Beth Israel (MSBI) Medical Center and the New Jersey War Related Illness & Injury Study Center [NJ WRIISC] to discuss strategy for recruiting GWI and non-GWI veterans for the study.	1	Dr. Natelson & Dr. Helmer

<u>Subtask 2</u> : Develop complementary or cooperative IRB protocols, including study advertisement material that would enable seamless recruitment/characterization of subjects at NJ WRIISC/MSBI and referral to Weill Cornell Medicine [WCM].	1-3	Drs. Natelson, Helmer & Shungu
<u>Subtask 3</u> : Submit IRB protocols at each participating Institution. Second-tier DoD human subjects regulatory review and approval conducted by the Office of Research Protections, Human Research Protections Office (HRPO).	3-6	Drs. Natelson, Helmer & Shungu; HRPO
<i>Milestone(s) Achieved: All IRB protocols approved; recruitment starts in earnest by month 6 and will continue to end of project</i>	6-30	Drs. Natelson, Helmer
Specific Aim 1: Neuroimaging Biomarkers Studies		
Major Task 2: Conduct <i>in vivo</i> brain ^{11}C -(R)-PK11195 PET to assess neuroinflammation		WCM
<u>Subtask 1</u> : Order supply for producing the radioligand and review chemistry and PET scanning protocol.	1-6	Dr. Babich
<u>Subtask 2</u> : Conduct PET scans in 10 GWI and 10 non-GWI veterans	6-30	Dr. Babich
<i>Milestone(s) Achieved: Availability of radioligand on demand to end of study; clear ability to obtain good PET scans, reproducibly, in each subject using the PK11195 PET technique</i>	30	
Major Task 3: To conduct ^1H and ^{31}P MRS studies for assessment of oxidative stress and mitochondrial dysfunction <i>in vivo</i> . Assess cerebral blood flow using ASL-MRI.		WCM
<u>Subtask 1</u> : Protocols for achievement of this Major Task are already fully developed and being used in an ongoing study in chronic fatigue syndrome that is identical to the one we are proposing in GWI. The protocol will be reviewed with the MR neuroimaging team to ensure its flawless implementation.	1-6	Dr. Shungu
<u>Subtask 2</u> : Conduct ^1H and ^{31}P MRS and scan in 20 GWI and 20 non-GWI veterans to assess oxidative stress and mitochondrial dysfunction; also measure CBF in all 40 subjects using ASL-MRI.	6-30	Dr. Shungu
<i>Milestone(s) Achieved: Clear ability to obtain high-quality ^1H and ^{31}P MR spectra, as well as ASL-MRI CBF maps in each enrolled subject.</i>	30	

Specific Aim 2: CSF Biomarkers		
Major Task 4: Collect CSF samples from all consenting subjects for validation of neuroimaging biomarkers.		WCM
Subtask 1: Collect and cryo-freeze CSF samples using lumbar puncture	6-30	Dr. Mangat
<i>Milestone(s) Achieved: Clear ability to collect and freeze CSF samples for later analyses to determine markers of oxidative stress and neuroinflammation (cytokines, including IL-17).</i>	30	
For Specific Aims 1 & 2: Data Analysis and Hypothesis Testing		
Major Task 5: Data Analysis, Reduction, Statistical Analyses.		WCM
Subtask 1: Analyze/process and reduce the data from all the active tasks, combine with the clinical data in a master database and perform statistical analyses and hypothesis testing.	30-36	All investigators with Dr. Shungu supervising
<i>Milestone(s) Achieved: Determination of whether: (a) neuroinflammation, oxidative stress and mitochondrial dysfunction play a role in GWI pathobiology; and (b) the outcome measures either individually or in concert can serve as biomarkers for GWI and point to potential brain mechanisms for the illness.</i> <i>Submission of at least 3 manuscripts for publication.</i>	36	

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.

The primary activities for the third year of this research were to continue our neuroimaging biomarkers studies on the enrolled GWI and non-GWI subjects, consisting of:

- 1) brain ¹¹C-(R)-PK11195 PET scan to assess neuroinflammation
- 2) ¹H and ³¹P MRS scans to assess oxidative stress and mitochondrial dysfunction in vivo; and ASL-MRI to measure regional cerebral blood flow.
- 3) to collect blood plasma/urine, and in consenting subjects, CSF samples from for corroboration with and validation of neuroimaging biomarkers.

Accomplishment goals to date:

The biggest hurdle to our making progress toward completing this study has been identifying and recruitment qualified healthy and affected Gulf War veterans.

To be able to address this recruitment challenge, we recently requested from the DoD and were granted a second 1-year no-cost extension (NCE) period ending on 08/31/2020, during which we proposed to engage a highly promising recruitment service, named WeHealth.

Currently, within one month of the second NCE period and of implementing WeHealth's recruitment strategy, we have already had 43 subject referrals. Of these, 1 subject met all the inclusion criteria has been enrolled into study, and 3 subjects have passed initial screening and are in the process of undergoing their in-person screen tests.

In summary, since the last Annual Progress Report, 3 subjects completed all study assessments, which has brought to 15 the total number of subjects studied to date. We have now begun the second approved NCE period, during which our ability to identify and recruit eligible Gulf War veterans has jumped nearly 400% thanks to the recruitment service of WeHealth. At this recruitment rate, we anticipate reaching at least 80% of our recruitment target by the end of the NCE period.

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.

As part of our recruitment efforts, we have attended a monthly meeting of Gulf War Veterans support group at the Brooklyn VA Hospital Center, where we presented information on our study and have undertaken similar outreach efforts to involve potential participants from the Manhattan and Bronx VA Hospital Centers.

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 study protocols and procedures have been shown to yield the desired data. Therefore, for the next reporting period, i. e. the no-cost extension period, we’ll describe our progress in advancing the study toward fulfilling its objectives based on our latest outreach efforts.

- 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).

Nothing to report.

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.

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.

Problem: Continuing recruitment challenge.

Remedial Actions:

1. Attended monthly meetings of the VA support group at the Brooklyn VA Center
 - Presented study in-person to potential participants
 - Provided recruitment flyer for dissemination.
2. Contact Manhattan & Bronx VA Centers to similarly present our study in-person to potential participants at these additional VA Centers.
3. Continue tapping into existing websites and social media outlets
 - institutional clinical trials site
 - recruitment specific sites (ClinicalConnection, Craigslist)
 - social media (Facebook)
4. The focus on Google Lab keyword searches, under the guidance of Weill Cornell Joint Clinical Trials Office (JCTO).
5. Post a multimedia video featuring PI, Dr. Shungu, describing the study and explaining why it is important for advancing the understanding of GWI.
6. Engagement of WeHealth recruitment service: show great promise in jump-starting recruitment.

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 objectives at less cost than anticipated.

None to date.

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

None

Significant changes in use or care of vertebrate animals.

Not applicable

Significant changes in use of biohazards and/or select agents

Not applicable

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.*

Nothing to Report.

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: Dikoma C. Shungu, Ph.D.
Project Role: PI
Researcher Identifier (e.g. ORCID ID): orcid.org/0000-0001-9452-2245
Nearest person month worked: 1 calendar Month
Contribution to Project: Dr. Shungu oversees all the MR Neuroimaging aspects the proposed research, as well as its day-to-day coordination of the study.

Name: Xiangling Mao, M.S.
Project Role: Co-I
Researcher Identifier (e.g. ORCID ID): orcid.org/0000-0003-2274-8282
Nearest person month worked: 1 Calendar Month
Contribution to Project: Ms. Mao perform work in the area of regulatory activity, MR Scan and data processing.

Name: Benjamin H. Natelson, M.D.
Project Role: Sub-site PI at BIMC
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 1 Calendar Month
Contribution to Project: Dr. Natelson will perform work in the area of subject recruitment and characterization.

Name: Sarah Khan
Project Role: Study coordinator at BIMC
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 1 Calendar Month
Contribution to Project: Ms. Khan will perform work in the area of subject recruitment.

Name: Michelle Blate
Project Role: Nurse-practitioner at MSBI
Researcher Identifier (e.g. ORCID ID):
Nearest person month worked: 1 Calendar Month
Contribution to Project: Ms. Blate performs work in the area of subject recruitment.

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.

Nothing to Report.

What other organizations were involved as partners?

If there is nothing significant to report during this reporting period, state “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);*
- *Personnel exchanges (e.g., project staff and/or partner’s staff use each other’s facilities, work at each other’s site); and*
- *Other.*

Nothing to Report.

8. SPECIAL REPORTING REQUIREMENTS

COLLABORATIVE AWARDS: For collaborative awards, independent reports are required from BOTH the Initiating PI and the Collaborating/Partnering PI. A duplicative report is

acceptable; however, tasks shall be clearly marked with the responsible PI and research site. A report shall be submitted to <https://ers.amedd.army.mil> for each unique award.

QUAD CHARTS: If applicable, the Quad Chart (available on <https://www.usamraa.army.mil>) should be updated and submitted with attachments.

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.