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TITLE: Metabolomics in Gulf War Illness: A Systems Biology Approach to Dissecting Mechanisms of Disease

PRINCIPAL INVESTIGATOR: Dr. W. Ian Lipkin, MD

CONTRACTING ORGANIZATION: Columbia University

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

Gulf War Illness (GWI), Myalgic encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) and Post Treatment Lyme Disease (PTLD) have significant symptom overlap, which suggest studying them in parallel may enable discovery of common triggers for disease in addition to diagnostic and prognostic biomarkers, and insights that can lead to therapeutic interventions. We are analyzing the metabolomic profiles of Gulf War veterans with and without Gulf War Illness (GWI) to determine disturbances that provide insights to GWI and similar diseases. During this reporting period, we analyzed metabolomic data on plasma for primary metabolites, biogenic amines, and complex lipids. We identified two dipeptides significantly elevated and one primary metabolite significantly reduced in veterans with GWI. Sphingomylins, a major component of cell membranes, were significantly reduced in veterans with GWI. A reduction in sphingomylins has also been identified in ME/CFS patients, which supports a dysregulation in lipid metabolism for both conditions.

15. SUBJECT TERMS

Gulf War Illness, ME/CFS, Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, metabolomics, proteomics, database

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

We are analyzing the metabolomic profiles of Gulf War veterans with and without Gulf War Illness (GWI) to determine disturbances that provide insights to GWI and similar diseases. GWI, Myalgic encephalomyelitis/Chronic Fatigue Syndrome and Post Treatment Lyme Disease have significant symptom overlap. With the data obtained in this study, we will perform comparative anlaysis with data we have for similar conditions to enable discovery of common triggers for disease, diagnostic and prognostic biomarkers, and insights for therapeutic interventions.

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

Gulf War Illness, ME/CFS, Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, metabolomics, proteomics, database

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.

Original major goals:
Aim 1: Profile metabolites in plasma of 100 GW veterans with GWI and 100 GW veteran controls without GWI who are matched 1:1 for age (+/- 5 years), sex, race, and socioeconomic status.
Aim 2: Profile metabolites in plasma of 50 GW veterans with GWI and 50 GW veteran and civilian controls without GWI at baseline and 24 hours after an ETT.
Aim 3: Integrate metabolomic data well as clinical metadata from Sullivan and Klimas in an effort to identify pathways that can provide insight into the pathogenesis of GWI, ME/CFS, and PTLD as well as targets for intervention in animal models and clinical trials.

Changes to the original major goals:
Provision of adequate samples became an obstacle to conducting the studies as originally proposed. The revised aims are:
Aim 1: Profile metabolites in plasma of 100 GW veterans with GWI and 44 GW veteran controls without GWI who are matched 1:1 for age (+/- 5 years), sex, race, and socioeconomic status.
Aim 2: Integrate metabolomic data with clinical metadata from Sullivan in an effort to identify pathways that can provide insight into the pathogenesis of GWI, ME/CFS, and PTLD as well as targets for intervention in animal models. and clinical trials.

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.

We performed metabolomics on plasma of 77 GW veterans with GWI and 40 age- and sex-matched GW veteran controls without GWI. Untargeted metabolomics data were acquired using three chromatography/mass spectrometry-based assays (MS): (1) Primary metabolites were measured by gas chromatography/time-of-flight mass spectrometry (GC-TOF MS) (Fiehn, 2016) including data alignment and compound annotation using the BinBase database algorithm (Kind, et al., 2009)]; (2) Biogenic amines were measured by hydrophilic interaction liquid chromatography/quadrupole time-of-flight mass spectrometry (HILIC-QTOF MS); (3) Complex lipids were analyzed by liquid chromatography (LC)/quadrupole time-of-flight mass spectrometry (CSH-QTOF MS) (Cajka, Smilowitz, & Fiehn, 2017). All LC-MS/MS data included diverse sets of internal standards. LC-MS data were processed by MS-DIAL vs. 4.0 software (Tsugawa, et al., 2015), and the compounds were annotated based on accurate mass, retention time and MS/MS fragment matching using LipidBlast (Tsugawa, et al., 2020) and Massbank of North America libraries (Wohlgemuth, et al., 2016). MS-FLO was used to remove erroneous peaks and reduce the false discovery rate in LC datasets (DeFelice, et al., 2017). A total of 967 metabolites were annotated, including 131 primary metabolites (PM), 416 biogenic amines (BA), and 420 complex lipids (CL). Data were normalized by SERRF (Fan , et al., 2019). Residual technical errors were assessed by coefficients of variation (CV) for known metabolites. We applied adjusted logistic regression models combined with Bayesian analyses to identify altered chemical compounds with significant GWI associations (Brydges, Che, Lipkin, & Fiehn, 2022) (Jeffreys, 1961) The dipeptides glutamyl-alanine ($p < 0.01$; BayesFactor = 13.89) and alanine-glutamate ($p < 0.01$; BayesFactor = 5.57) were significantly elevated in GW veterans with GWI compared to GW veterans without GWI, whereas the primary metabolite N-acetylornithine was significantly reduced ($p < 0.01$; BayesFactor = 5.01). Chemical enrichment analyses of the results from the logistic regression models were performed using ChemRICH (Barupal & Fiehn, 2017) to determine chemical clusters that were significantly altered. The chemical cluster sphingomyelin (SM) was significantly reduced (altered ratio = 1, $p < 0.01$), and the chemical cluster dipeptides was significantly elevated (altered ratio = 1, $p < 0.01$) in GW veterans with GWI, as compared to GW veterans without GWI. SMs are sphingolipids that are integral components of membrane lipid microdomains and regulate membrane transport (Rogasevskaia & Coorssen, 2006). Reductions in SMs impair membrane integrity (Gulshan, Brubaker, Wang, Hazen, & Smith, 2013). Previous plasma metabolomics studies have reported dysregulations in sphingomyelin metabolism in GWI (Naviaux, et al., 2019) (Oberlin, et al., 2022). In a recent plasma metabolomics study, we reported abnormalities in lipid metabolism with reductions in SMs in ME/CFS (Che, et al., 2022). Our data provides evidence for dysregulations in lipid metabolism with reduced SM levels that are consistent in GWI and ME/CFS.

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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.

Postdoctoral fellow Ayan Roy was recruited to the project and the field of GWI research. Principal investigator W. Ian Lipkin presented study results to the Research Advisory Committee on Gulf War Veterans' Illnesses meeting in Washington DC, on September 22, 2022.

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.

Principal investigator W. Ian Lipkin presented study results to the Research Advisory Committee on Gulf War Veterans' Illnesses meeting in Washington DC, on September 22, 2022.

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

We will perform targeted metabolomics of the plasma samples using bioactive oxylipin assay. We plan to employ machine learning algorithms on integrated untargeted and targeted plasma metabolomics data of GWI subjects to assess the utility of metabolomics as GWI biomarkers. The metabolomics data will be integrated with clinical metadata in an effort to identify pathways that can provide insights into the pathogenesis of GWI. Study results will be submitted for publication with co-investigators Sullivan and Klimas.

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.

Results obtained provide insights into overlap with other chronic illnesses that have symptom overlap including ME/CFS and Long Covid.

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.

After a long-effort to obtain from repositories the quantity of plasma samples originally envisioned, a revised approach was discussed with the Grant's Officer Representative and formed the basis of our No Cost Extension request. We have revised our statistical approach so that comparisons between the 100 GWI and 44 controls samples are valid and can be used for comparative studies. The original Aim 2 needed to be eliminated since samples collected from exercise tolerant tests were not accessible.

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.

Sample acquisition was a formidable problem. We altered our statistical approach so that the research could proceed.

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.

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

Nothing to Report

Significant changes in use or care of vertebrate animals.

Nothing to Report

Significant changes in use of biohazards and/or select agents

Nothing to Report

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

- *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.*

Results obtained will be placed into the NIH Metabolomics database (https://www.metabolomicsworkbench.org).

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."

Example:

Name:	*Mary Smith*
Project Role:	*Graduate Student*
Researcher Identifier (e.g. ORCID ID):	*1234567*
Nearest person month worked:	*5*
Contribution to Project:	*Ms. Smith has performed work in the area of combined error-control and constrained coding.*
Funding Support:	*The Ford Foundation (Complete only if the funding support is provided from other than this award).*

Name:	W. Ian Lipkin
Project Role:	Principal Investigator
Researcher Identifier:	ORCID ID: 0000-0002-8768-9386
Nearest person month worked:	1
Contribution to Project:	Dr. Lipkin directed and guided the research being performed.

Funding Support (if other than this award):

Dr. Ayan Roy, postdoctoral fellow and Dr. Xiaoyu Che, Assistant Professor, also contributed to this work, albeit at less than 1 calendar month effort. Dr. Roy performed ontological analyses. Dr. Che performed statistical 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.

The following awards became active:
TITLE: Center for Solutions for ME/CFS (PI: Lipkin, W. I.); PROJECT NUMBER: 4U54AI138370; SOURCE OF SUPPORT: NIH; PROJECT/PROPOSAL START AND END DATE (MM/YYY): 09/2022 – 03/2023; TOTAL AWARD AMOUNT (INCLUDING INDIRECT COSTS): $600,000; EFFORT: 00.70 person months

TITLE: VirCapSeq: A platform for detection of pandemic threats and differential diagnosis of infectious diseases (PI: Lipkin, W.I.); PROJECT NUMBER: 75A50122C00012; SOURCE OF SUPPORT: ASPR/DHHS; PRIMARY PLACE OF PERFORMANCE: Columbia University; PROJECT/PROPOSAL START AND END DATE (MM/YYY): 03/2022 – 09/2023. TOTAL AWARD AMOUNT (INCLUDING INDIRECT COSTS): $749,000; EFFORT: 00.60 person months

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://ebrap.org** 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.