

AWARD NUMBER: W81XWH-19-1-0765

TITLE: Clarifying the Role Played by Microglia and Astrocyte Activation in Veterans with Gulf War Illness Using Positron Emission Tomography (PET)

PRINCIPAL INVESTIGATOR: Ronald Killiany, Ph.D.

CONTRACTING ORGANIZATION: Trustees of Boston University, BUMC, Boston, MA

REPORT DATE: October 2020

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Development Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing this collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to Department of Defense, Washington Headquarters Services, Directorate for Information Operations and Reports (0704-0188), 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to any penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number. **PLEASE DO NOT RETURN YOUR FORM TO THE ABOVE ADDRESS.**

1. REPORT DATE October 2020		2. REPORT TYPE Annual		3. DATES COVERED 30Sep2019-29Sep2020	
TITLE AND SUBTITLE Clarifying the Role Played by Microglia and Astrocyte Activation in Veterans with Gulf War Illness Using Positron Emission Tomography (PET)				5a. CONTRACT NUMBER W81XWH-19-1-0765	
				5b. GRANT NUMBER GRANT12744547	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Ronald Killiany, Ph.D. E-Mail:killiany@bu.edu				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) Boston University Medical Campus 25 Buick Street, Suite 200 Boston, MA 02215-1301				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Development Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
13. SUPPLEMENTARY NOTES					
14. ABSTRACT The study objective is to assess whether veterans with GWI will show evidence of a chronic inflammatory process as measured by increased levels of astrocyte and microglial activation. We will determine the regionally specific pattern of astrocyte activation in 20 GW veterans. We will determine if there is regional independence of the astrocyte activation from microglial activation and we will assess the utility of using FDG PET as a marker for activated astrocytes. We have been focusing on obtain appropriate approvals while working with institutions where only limited in person research has been allowed. This study will take place at Mass General Brigham Hospital and Boston University School of Medicine. We have set up the subcontract between these institutes. We have gotten feedback and responded to questions by the MGH IRB. We have the BUMC IRB ready for submission and the BBRAIN study that we expect to recruit from has approval for in person visits allowing us to begin inquiries of interest in this study.					
15. SUBJECT TERMS Microglia, Astrocytes, FDG-PET, Positron Emission Tomography, chronic inflammatory process					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT Unclassified	18. NUMBER OF PAGES 10	19a. NAME OF RESPONSIBLE PERSON
a. REPORT Unclassified	b. ABSTRACT Unclassified	c. THIS PAGE Unclassified			19b. TELEPHONE NUMBER (include area code)

TABLE OF CONTENTS

	<u>Page</u>
1. Introduction	4
2. Keywords	4
3. Accomplishments	5
4. Impact	6
5. Changes/Problems	6
6. Products	8
7. Participants & Other Collaborating Organizations	8
8. Special Reporting Requirements	9
9. Appendices	9

1. Introduction

The study objective is to assess whether veterans with Gulf War Illness will show evidence of a chronic inflammatory process as measured by increased levels of astrocyte and microglial activation. We will determine the regionally specific pattern of astrocyte activation in 20 GW veterans. We will determine if there is regional independence of the astrocyte activation from microglial activation and we will assess the utility of using FDG PET as a marker for activated astrocytes. We believe that information about astrocyte activation in veterans with GWI will help to clarify whether activation of astrocytes and microglia is regionally independent, representing separate processes or regionally related potentially representing a combined process. This is a multimodal PET imaging study that will be conducted in 20 GW veterans (10 GWI cases, 10 controls). GWI cases will be determined by Kansas GWI criteria. All participants will be recruited from the Boston Biorepository and Integrated Network (BBRAIN) for GWI which is conducting cognitive assessments and collecting blood, saliva, urine and other relevant biomarkers to share for GWI relevant studies. The veterans with GWI in this study will be asked to undergo an FDG PET scan at Boston Medical Center, [11C]-I-Deprenyl PET scan at Massachusetts General Hospital and a [11C]PBR28 PET scan at Massachusetts General Hospital. The healthy control veterans will only undergo the FDG PET scan at Boston Medical Center and [11C]-I-Deprenyl PET scan at Massachusetts General Hospital. This study will be a BBRAIN call-back study and the PET imaging data will be included in the BBRAIN repository.

2. Keywords

Gulf War Illness

Microglia

Astrocytes

Positron Emission Tomography

Chronic Brain Inflammation

Fluorodeoxyglucose

Kansas Gulf War Illness Criteria

Boston Biorepository and Integrated Network

Deprenyl PET

PBR28 PET

3. Accomplishments – What were the major goals of the project?

Aim 1: To determine the regionally specific pattern of astrocyte activation using [11C]-I- Deprenyl PET ligand in combination with MRI based anatomical regions in 20 GW veterans (10 GWI cases, 10 controls).

Aim 2: To determine if there is regional independence of the astrocyte activation from microglial activation using the [11C]PBR28 PET ligand in the same 10 veterans with GWI who were imaged under Aim 1. Aim

3: To assess the utility of using FDG PET as a marker for activated astrocytes we will image the same subjects scanned under aim 1 using FDG PET.

Accomplishments – What was accomplished under these goals?

In the first year of this project we have focused on completing the administrative tasks that will make the collection of data and analyses possible in this project. To this end, we have set up a subcontract with Mass General Brigham Hospital (formally known as Massachusetts General Hospital). We have conducted discussions with our colleague Marco Loggia Ph.D. about the proper Positron Emission Tomography to be using in the project and the logistics surrounding the recruitment of participants at Boston University Medical School with consent for both the Boston University and Mass General Brigham Institutional Review Boards (IRB). Our IRB application was submitted and reviewed by the Mass General Brigham IRB board and we have responded back to the questions that they have asked. We anticipate having their approval for this project any day. We have drafted the Boston University Medical School IRB protocol and will be modifying it to accommodate changes made in the Mass General Brigham protocol and then submitting it to the Boston University Medical School IRB for review once we have the Mass General Brigham IRB approval letter. When we have approval from both of our local IRBs we will submit to HARPO. We have had discussions with the Boston Medical Center Radiology department about the logistics that will be involved in this project and have made them aware of our needs for research slots on the PET scanner in the upcoming year. We have also set up a mechanism through the BBRAIN project for the secure transfer of medical images such as those we will be generating in this project between Dr. Loggia's lab and Dr. Killiany's lab.

Accomplishments – What opportunities for training and professional development has the project provided?

This project has provided unique and highly valuable hands on training for our full-time graduate student Renee DeVivo and our half-time graduate student Yashar Rahimpour in the process of working with

Institutional Review Boards, the development of protocols for use with human subjects, strategies for recruitment, methods for ensuring confidentiality and the use of radioligands in human experiments. This experience was enhanced by working with two separate IRBs each with a common mission but unique approaches. Further, this project has provided training for these two students in discussions with radiation safety officials and scientists using radioligands with human subjects. Quite unexpectedly this project has also provided training in the logistics of running in person human studies during the time of a pandemic.

Accomplishments – How were the results disseminated to communities of interest?

Nothing to Report

Accomplishments – What do you plan to do during the next reporting period to accomplish the goals?

In the next reporting period, we expect to have IRB approval from Mass General Brigham's IRB and to have submitted the protocol to Boston University Medical School's IRB. Once we have both approvals in place we will submit to HARPO. We anticipate Dr. Sullivan's BBRAIN project to have permission from Boston University to return to in person research visits/assessments (permission required by BU COVID policy). As a call-back study to the BBRAIN project we will gage the BBRAIN participants interest in taking part in a studies like this one at the time of their on-site visit (no recruitment until all approvals are in place). This will allow us to fast track the recruitment process once we have all IRB approvals in place (including HARPO) and start collecting data sooner.

4. Impact – What was the impact on the development of the principle discipline of the project?

Nothing to Report

Impact – What was the impact on other disciplines?

Nothing to Report

Impact – What was the impact on technology transfer?

Nothing to Report

Impact – What was the impact on society beyond science and technology?

Nothing to Report

5. Changes/Problems – Changes in approach and reasons for change.

Nothing to Report

Changes/Problems – Actual or anticipated problems or delays and actions or plans to resolve them.

The biggest problem/delay that we faced in the past year with this project has been the COVID 19 virus. Boston was affected in early March, 2020 when the international “Biogen Conference” brought individuals with the virus to our community. When this virus began to impact the greater Boston area in it resulted in a shutdown of research and a slowdown of most administrative tasks at both Boston University Medical School and Mass General Brigham Hospital. Only essential staff were allowed on the two campuses with most administrators creating a mechanism for working from home. Building occupancy limits were put in place with preference given to post-doctoral students and graduate students occupying the labs. Faculty and PIs were asked to develop ways for working remotely.

The initial response by both Boston University Medical School and Mass General Brigham Hospital to the COVID 19 crisis was to fast track research into the virus and how to care for those afflicted with it. Administrative and IRB/IACCUC resources were prioritized to this effort.

These events induced delays in our obtaining a subcontract with Mass General Brigham Hospital for this award and delays in the review process of our IRB protocols. At this point in time, we are re-opening for research. Both Mass General Brigham Hospital and Boston University Medical School are supporting in person human research studies with appropriate COVID 19 restrictions. PET scanning for research studies is underway at both institutions. Faculty such as Drs. Loggia and Killiany are still working primarily off-site but we now have the appropriate systems in place to support this. Priorities in terms of lab occupancies are still given to post-doctoral fellows and graduate students so that the hands-on work of collecting research data can be done. We now have appropriate policies in place for consenting human subjects with physicians and or primary investigators interacting with them by phone or video.

As noted above, we anticipate Dr. Sullivan’s BBRAIN project to have permission from Boston University to return to in person research visits/assessments (permission required by BU COVID policy). As an call-back study to the BBRAIN project we will gauge the BBRAIN participants interest in taking part in call-back studies like this one at the time of their on-site visit (no recruitment until all approvals are in place). This

will allow us to fast track the recruitment process once we have all IRB approvals in place (including HARPO) and start collecting data sooner.

Changes/Problems – Changes that had a significant impact on expenditures.

Nothing to Report

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

Nothing to Report

Changes/Problems – Significant changes in use or care of human subjects.

Nothing to Report

Changes/Problems – Significant changes in use or care of vertebrate animals.

Nothing to Report

Changes/Problems – Significant changes in use of biohazards and/or select agents.

Nothing to Report

6. Products – Publications, conference papers and presentations.

Nothing to Report

Products – Websites or other internet sites.

Nothing to Report

Products – Technologies or techniques.

Nothing to Report

Products – Inventions, patent applications and/or licenses

Nothing to Report

Products – Other products

Nothing to Report

7. Participants & Other Collaborating Organizations

What individuals have worked on this project?

Name: Ronald Killiany, Ph.D.

Project Role: Principle Investigator

Research Identifier: ORCID ID 0000-0003-4740-2181

Nearest Person Month Worked: 2

Contribution to the Project: Review of Institutional Review Board applications, administration of MGH subcontract, coordination of return to research for BBRAIN project

Name: Renee DeVivo

Project Role: Full time graduate student

Research Identifier: NA

Nearest Person Month Worked: 12

Contribution to the Project: Drafting of Boston University Medical Center Institutional Review Board protocol, interfacing and preliminary review with Boston University Medical Center Institutional Review Board, consultation on Massachusetts General Institutional Review Board application and response to comments raised.

Name: YASHAR RAHIMPOUR

Project Role: Half-time graduate student

Research Identifier: NA

Nearest Person Month Worked: 6

Contribution to the Project: Editing of Boston University Medical Center Institutional Review Board protocol, discussion with Boston University Radiation Safety office concerning use of multiple PET ligands in the same subjects, responds to IRB preliminary review questions, development of study materials for recruitment.

7. Participants & Other Collaborating Organizations – has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Nothing to Report

Participants & Other Collaborating Organization – What other organizations were involved as partners?

Organization Name: MassGeneral Brigham (formally Massachusetts General Hospital)

Location of Organization: Boston, Massachusetts, USA

Partner's contribution to the project: Subcontracted performance site.

8. Special Reporting Requirements

Nothing to Report

9. Appendices

Nothing to Report