AWARD NUMBER: W81XWH-17-1-0448

TITLE: Evaluating the metabolic changes associated with exercise in Multiple Sclerosis

PRINCIPAL INVESTIGATOR: Pavan Bhargava, MD

CONTRACTING ORGANIZATION: Johns Hopkins University Baltimore, MD 21218

REPORT DATE: August 2018

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel 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.

-				Form Approved		
L K	EPORT DOC	UMENTATIO	NPAGE		OMB No. 0704-0188	
Public reporting burden for this	s collection of information is estin	nated to average 1 hour per resp	onse, including the time for revie	wing instructions, sear	ching existing data sources, gathering and maintaining the	
this burden to Department of D	Defense, Washington Headquart	ers Services, Directorate for Infor	mation Operations and Reports	(0704-0188), 1215 Jeff	erson Davis Highway, Suite 1204, Arlington, VA 22202-	
4302. Respondents should be	aware that notwithstanding any	other provision of law, no person	n shall be subject to any penalty	for failing to comply with	n a collection of information if it does not display a currently	
1. REPORT DATE		2. REPORT TYPE	200.	3. [	DATES COVERED	
August 2018		Annual		1 4	Aug 2017 - 31 Jul 2018	
4. TITLE AND SUBTIT	LE			5a		
				00.		
Evaluating the me	tabolic changes as	ociated with exercis	e in Multiple Sclerosis		GRANT NUMBER	
				W	31XWH-17-1-0448	
				5c.	PROGRAM ELEMENT NUMBER	
6. AUTHOR(S)				5d.	PROJECT NUMBER	
Pavan Bhargava,	MD			5e.	TASK NUMBER	
0,						
				5f.	WORK UNIT NUMBER	
E-Mail: pbharga2@	⊉ihmi.edu					
7. PERFORMING ORC	GANIZATION NAME(S)	AND ADDRESS(ES)		8. F	PERFORMING ORGANIZATION REPORT	
	(-)	- \ - /		1	IUMBER	
Johns Hopkins Un	iversity					
3400 N Charles St	t -					
Baltimore MD 212	18-2608					
9. SPONSORING / MC	NITORING AGENCY N	AME(S) AND ADDRES	S(FS)	10	SPONSOR/MONITOR'S ACRONYM(S)	
			5(=0)			
U.S. Army Medica	Research and Ma	teriel Command				
Fort Dotrick Mary	and 21702 5012			11	SPONSOR/MONITOR'S REPORT	
					NUMBER(S)	
					NOMBER(0)	
12. DISTRIBUTION / P						
	ic Release: Distribu	tion I Inlimited				
	V NOTES					
13. SUPPLEMENTAR	Y NOTES					
14. ABSTRACT						
Currently available	e pharmacological t	herapies do not imp	rove MS symptoms	, such as weal	kness. Exercise training improves	
multiple symptoms associated with MS, including weakness, fatigue and mood disturbance. Exercise produces alterations in						
multiple metabolic pathways and some of these changes may underlie the beneficial effects of exercise. We hypothesized that						
metabolic alterations produced by strength training will predict symptomatic changes in people with MS. In this study we are						
enrolling adults with MS (N=20) and age- and gender-matched healthy controls (N=20). Participants undergo 12-weeks of						
guided Progressive Resistance Training 3-times weekly. At baseline and end-of-study we collect measures of fatigue, strength						
physical fitness co	onition and overall	impairment in addi	tion to blood for me	tabolomics At	the end of the study plasma	
physical nucess, cognition and overall impainment, in audition to blood for metaboliting and determine their concentrations. Me						
samples will undergo global unitalgeted metabolitios analysis to identify metabolites and december to identify metabolities that are altered with exercise and dec identify metabolities that are related to						
win men periorin analyses to identify metabolites that are altered with exercise and also identify metabolites that are related to abandon in MS symptom solverity. This study has the notantial to identify the machanisms by which systems to the						
changes in wis symptom seventy. This study has the potential to identify the mechanisms by which exercise impacts the						
metabolome in INS patients. Identification of metabolic pathways that are associated with symptomatic benefits could lead to						
the development of alternative treatment strategies, both pharmacologic and neuro-rehabilitative, for targeting these pathways.						
15. SUBJECT TERMS						
Multiple sclerosis, metabolomics, progressive resistance training, rehabilitation						
16. SECURITY CLASS	SIFICATION OF:		17. LIMITATION	18. NUMBER	19a. NAME OF RESPONSIBLE PERSON	
			OF ABSTRACT	OF PAGES	USAMRMC	
a. REPORT	b. ABSTRACT	c. THIS PAGE	1		19b. TELEPHONE NUMBER (include area	
			Unclassified	8	code)	
Unclassified	Unclassified	Unclassified				

## **Table of Contents**

# Page

1. Introduction	1
2. Keywords	1
3. Accomplishments	1
4. Impact	3
5. Changes/Problems	3
6. Products	4
7. Participants & Other Collaborating Organizations	4
8. Special Reporting Requirements	5
9. Appendices	None

## **1. INTRODUCTION:**

Currently available pharmacological therapies do not improve MS symptoms, such as weakness. Exercise training improves multiple symptoms associated with MS, including weakness, fatigue and mood disturbance. Global untargeted metabolomics is a relatively new technology that enables the measurement of multiple metabolites in plasma or serum. Exercise produces alterations in multiple metabolic pathways and some of these changes may underlie the beneficial effects of exercise. Metabolomics analyses reveal differences in the metabolome between people with MS and healthy controls (HC). We propose that the effects of exercise in people with MS may be mediated through its effects on the metabolome, and that utilizing metabolomics, we can link alterations in the metabolome to changes in MS related symptoms.

While the beneficial effects of exercise on MS related symptoms are known, the mechanisms by which exercise produces these pleiotropic effects are not well understood. We propose to use an innovative technology – metabolomics, to investigate the effects of an exercise intervention on the metabolome of MS patients. This study has the potential to identify the mechanisms by which exercise impacts the metabolome in MS patients. This information could help in personalizing care for MS patients by helping to individualize interventions for patients. Additionally, identification of metabolic pathways that are associated with symptomatic benefits could lead to the development of alternative treatment strategies, both pharmacologic and neurorehabilitative, for targeting these pathways.

**2. KEYWORDS:** Multiple Sclerosis, metabolomics, Progressive Resistance Training, rehabilitation

## **3. ACCOMPLISHMENTS:**

#### What were the major goals of the project?

The major goals of the study are -

- 1. Identify alterations in the metabolome produced by strength training in people with MS and healthy controls.
- 2. Determine the extent that metabolite alterations produced by strength training result in improvements to affected metabolic pathways in people with MS.
- 3. Determine the relationship between alterations in metabolites and change in measures of strength, cognition, fatigue and overall impairment.

Below are the lists of tasks as stated in the Statement of Work (SOW):

- a) Major Task 1: Assess protocol for the study
- b) Major Task 2: Coordinate study staff for PRT clinical trial
- c) Major Task 3: Determine logistics for PRT exercise intervention
- d) Major Task 4: Participant recruitment, PRT, Participant evaluation
- e) Major Task 5: Metabolomics analysis
- f) Major Task 6: Data analysis

#### What was accomplished under these goals?

The accomplishments of each stated tasks correspond with each bullet point above.

- a) Assess protocol for study: We refined our study protocol (including study outcomes) and completed associated forms (consent form, etc) and submitted this to local IRB on 8/15/2017 and received approval on 9/14/2017 (<u>Milestone achieved</u>). We also amended the protocol as required by the local IRB and this protocol amendment was approved on 11/2/2017. Required documents were submitted to HRPO for review on 10/11/2017 and approved on 11/30/2017 (<u>Milestone achieved</u>). We also submitted and received approval of our continuing review from the local IRB on 8/14/2018.
- b) Coordinate Study staff for PRT trial: We identified a study coordinator David Buchanan and he was trained in all aspects of conduct of the study by the PI and study physical therapist (<u>Milestone achieved</u>). He however resigned his position and we then trained a back-up coordinator Esther Ogbuokri in all aspects of conduct of the study. We interviewed and hired a new coordinator who unfortunately had to leave his position two weeks after starting the job. We are now in the final stages of hiring a replacement study coordinator who will be trained in all aspects of the study conduct by the PI, the study PT and the current back-up coordinator.
- c) **Determine logistics for PRT intervention**: We identified space to conduct the PRT intervention and obtained necessary equipment for the exercise intervention (<u>Milestone achieved</u>).
- d) Participant recruitment, PRT, Participant evaluation: We assembled a flow chart for the study visits and finalized data collection forms for the PRT and study assessments. As of 7/31/2018 we had enrolled 7 participants in the study, of whom 3 had completed the study intervention (PRT) (<u>Milestone achieved</u>). We are in the process of actively recruiting subjects for the study and have enrolled an additional 4 subjects in August 2018. We expect recruitment to be even more rapid once we have a new study coordinator hired and trained later this month.
- e) **Metabolomics analysis:** We have begun collection and processing of pre- and postintervention blood samples for metabolomics analysis. These samples will undergo analyses at the end of the study.

What opportunities for training and professional development has the project provided? The project has allowed for training on how to administer the neuropsychology battery,

# How were the results disseminated to communities of interest?

Nothing to Report

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

During the next reporting period, we plan to enroll at least one participant per week. We are aggressively screening charts and have a number of potential candidates identified for the study. We will continue to administer the study intervention to eligible participants and collect various

study outcome measures as planned. We will plan to perform metabolomics analyses – once all participants have completed the study intervention and will then proceed with data analysis and manuscript preparation.

#### 4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project? Nothing to Report

What was the impact on other disciplines? Nothing to Report

What was the impact on technology transfer? Nothing to Report

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

#### Actual or anticipated problems or delays and actions or plans to resolve them

We have had slower than expected recruitment for the study. This was primarily due to two issues - 1) study coordinator turnover; 2) injury to study PT.

We had a hiatus in recruitment due to the sudden departure of David Buchanan our initial study coordinator. We then identified a back-up coordinator (Esther Ogbuokri) who helped continue recruitment, however this was not at an optimal pace since she had limited time devoted to the study due to additional responsibilities. We then identified a new coordinator – Austin Gabbala who had to leave the position within two weeks of starting due to personal reasons. Esther Ogbuokri continues to function as the study coordinator at this time and is now devoting more time to the study to help accelerate recruitment. Indeed, we have already recruited 4 new participants in August 2018 and have identified several more potential candidates. We are currently in the process of finalizing the selection of a new study coordinator, who can provide sufficient dedicated time to the study and hence resolve this issue. We anticipate that with recruitment and training of a new coordinator we will be able to speed up recruitment and meet our original goals.

In addition to the study coordinator turnover, we also had to content with our study PT – Jen Keller sustaining an injury resulting in a fractured finger. This caused a short hiatus in study recruitment and in addition to the study coordinator turnover has resulted in a slower than expected rate of recruitment. This problem has now been resolved.

#### Changes that had a significant impact on expenditures

Nothing to Report.

# Significant changes in use or care of human subjects

Nothing to Report

#### 6. PRODUCTS

Nothing to Report

# 7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

# What individuals have worked on the project?

Name: Project Role: Nearest person month worked: Contribution to Project:	<ul> <li>Pavan Bhargava</li> <li>Principal Investigator</li> <li>0.6</li> <li>Dr. Bhargava has performed work in the area of study management and oversight (including drafting/revising protocol and IRB documents, submission of documents to HRPO and training the research coordinator). He is also performing EDSS assessments for all study participants at baseline and end-of-study visits.</li> </ul>
Name: Project Role: Nearest person month worked: Contribution to Project:	Amy Bastian Site-Principal Investigator 0.12 Dr. Bastian has performed work in the area of study oversight in providing oversight of the study physical therapist and logistical support at Kennedy Krieger Institute.
Name: Project Role: Nearest person month worked: Contribution to Project:	Jennifer Keller Co-Investigator 3 Ms. Keller is the study physical therapist and has been involved in training of study coordinator and performing various study interventions and outcome measurements.
Name: Project Role: Nearest person month worked: Contribution to Project:	David Buchanan Study Coordinator 2 Mr. Buchanan was the study coordinator but has now left Johns Hopkins.

Name:Esther OgbuokriProject Role:Back-up Study CoordinatorNearest person month worked:1Contribution to Project:Ms. Ogbuokri was the back-up study coordinator and is<br/>currently responsible for patient recruitment, oversight of<br/>study intervention and performing various patient<br/>assessments at baseline and end of study visits.

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

What other organizations were involved as partners? Nothing to Report

#### 8. SPECIAL REPORTING REQUIREMENTS

Nothing to Report

9. APPENDICES

None