AWARD NUMBER: W81XWH-19-1-0631

TITLE: Inner and Outer Nuclear Layer Atrophy of the Retina as Novel and Distinguishing Biomarkers for Defining and Tracking Progressive Multiple Sclerosis

PRINCIPAL INVESTIGATOR: Dr. Shiv Saidha

CONTRACTING ORGANIZATION: Johns Hopkins University

REPORT DATE: Sept 2020

TYPE OF REPORT: Annual Report

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

DISTRIBUTION STATEMENT: Approved for Public Release;
                                              Distribution Unlimited

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REPORT DOCUMENTATION PAGE

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1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
Sept 2020	Annual	Aug 15, 2019 – Aug 14, 2020

4. TITLE AND SUBTITLE

Inner and Outer Nuclear Layer Atrophy of the Retina as Novel and Distinguishing Biomarkers for Defining and Tracking Progressive Multiple Sclerosis

5a. CONTRACT NUMBER

5b. GRANT NUMBER
W81XWH-19-1-0631

5c. PROGRAM ELEMENT NUMBER

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5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Development Command

1120 Fort Detrick, Frederick, MD 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

Progressive multiple sclerosis (PMS) is a form of multiple sclerosis (MS) characterized by steady and gradual accumulation of disability. Optical coherence tomography (OCT) has emerged as a complementary tool to magnetic resonance imaging (MRI) with utility for tracking neurodegeneration in relapsing-remitting MS (RRMS). However, PMS is less well understood, hindering development of effective treatments. Herein, this project seeks to address these gaps by confirming and validating the predominance of INL (inner nuclear layer) and ONL (outer nuclear layer) retinal atrophy in PMS and evaluate their utility for the development of more specific PMS outcomes, and shedding light on the pathobiology of PMS. This project uses OCT and other data acquired from the SPRINT-MS trial, a 96-week, randomized, double-blind, placebo controlled study of the phosphodiesterase inhibitor ibudilast in 255 primary and secondary PMS patients. The project's first year milestones have been successfully completed, including all steps in the process of regulatory approval and data transfer. Work towards year two milestones of year two, specifically OCT segmentation, is underway. This is the first step towards obtaining high quality data to study whether rates of atrophy of ganglion cell + inner plexiform layer (GCIPL), INL and ONL are lower in ibudilast versus placebo treated PMS patients, and the relationships of OCT captured treatment effects with a broad spectrum of clinical and MRI measures.

15. SUBJECT TERMS
Multiple sclerosis, progressive multiple sclerosis, optical coherence tomography, ibudilast, ganglion cell and inner plexiform layer, inner nuclear layer, outer nuclear layer.

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT	**b. ABSTRACT**	**c. THIS PAGE**	Unclassified	8	**19b. TELEPHONE NUMBER** *(include area code)*
Unclassified	Unclassified	Unclassified			

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1. INTRODUCTION

There is currently an incomplete understanding of disease mechanisms in Progressive Multiple Sclerosis (PMS), and a lack of validated, reliable, and specific biomarkers (clinical, imaging, other) for identifying and tracking PMS. These factors represent major obstacles in PMS research, routine monitoring, the clinical care of PMS patients, and have hindered the development of PMS treatments. The overarching objective of this proposal is to overcome these gaps and identify novel, specific correlates of disease progression in PMS. The principal hypothesis underlying this proposal is that distinct and specific retinal changes occur in PMS, namely INL and ONL atrophy.

The first aim of this study is to confirm and validate that INL and ONL retinal atrophy predominate in PMS and have specific utility for tracking PMS. The second aim of this study is to determine whether rates of GCIPL, INL and ONL atrophy are lower in ibudilast versus placebo treated PMS patients, and evaluate the relationships of OCT captured treatment effects with broad spectrum clinical and MRI measures. To achieve the objectives and specific aims, this project is utilizing pre-existing OCT and other data acquired from a well-characterized, adequately controlled, study of ibudilast in patients with PMS with sufficiently powered cohorts as part of the SPRINT-MS trial (a 96-week, randomized, double-blind, placebo controlled study of the phosphodiesterase inhibitor ibudilast in 255 primary and secondary PMS patients - 126 randomized to placebo and 129 to ibudilast treatment). Study participants underwent clinical and imaging (including OCT) assessments every 24 weeks. The study found that relative to placebo, ibudilast reduced rates of whole brain atrophy in PMS by 48% and may indeed be neuroprotective, highlighting the study cohort as opportune to meet the objectives of the current project.

2. KEYWORDS

Multiple sclerosis, progressive multiple sclerosis, optical coherence tomography, ibudilast, phosphodiesterase inhibitior, ganglion cell and inner plexiform layer, inner nuclear layer, outer nuclear layer.

3. ACCOMPLISHMENTS

What were the major goals of the project?

<u>Aim 1:</u> To confirm and validate that INL and ONL retinal atrophy predominate in PMS and have specific utility for tracking PMS.

<u>Aim 2:</u> To determine whether rates of GCIPL, INL and ONL atrophy are lower in ibudilast versus placebo treated PMS patients, and the relationships of OCT captured treatment effects with broad spectrum clinical and MRI measures.

What was accomplished under these goals?
In order to achieve the aims of this study, high quality segmentation of OCT data for both the placebo and ibudilast arms is required. Significant progress was made towards these project goals, with completion of all of the first year milestones of this three-year project:
1) A Materials Transfer Agreement was executed between Johns Hopkins University and Cleveland Clinic Foundation.
2) IRB approval from the Johns Hopkins IRB was obtained as was HRPO Approval.
3) With the MTA and approvals in place, all clinical and MRI trial data were transferred to Johns Hopkins.
4) Johns Hopkins received the OCT data for all study visits (baseline, weeks 24, 48, 72, and 96) for both the placebo and ibudilast treatment arms of the SPRINT MS trial. Data for both arms were delivered via an encrypted USB-drive. Spectralis OCT scans from both arms (307 visits, with usually 2 scans of each eye) were exported as .vol files. Cirrus OCT data comprising 874 visits (with usually 2 scans of each eye) were exported

as .img files. As this was completed, initial quantitative and qualitative quality control of all raw OCT scans was carried out.

All tasks planned to be performed during the first year of this study have been satisfactorily completed in accordance with our pre-planned statement of work, and are more than on track towards successfully completing the goals of the second and third years of this study. The next ongoing step is the segmentation of all OCT scans, which was projected to start in month ten and conclude by month sixteen. Progress has been satisfactory, with nearly half of the scans being successfully segmented through this reporting period.

What opportunities for training and professional development has the project provided?
The project has provided opportunities for post-doctoral fellows in the Saidha lab to learn several of the techniques required for this project, specifically, training on the use of the Johns Hopkins segmentation and quality control of OCT imaging as well as the management and systematic organization of clinical data.

How were the results disseminated to communities of interest?
Nothing to report, as yet. However, preliminary analyses are to be performed in the coming months, which will be associated with abstract submissions and initial publications stemming from our work

What do you plan to do during the next reporting period to accomplish the goals?
Over the course of the next reporting period, we will complete high quality segmentation of all OCT data from the placebo and ibudilast arms. Additionally, all images will be reviewed for quality control with any issues reviewed. Following this, we will begin on the next goal of the project: evaluation of retinal atrophy in PMS and its relationship to clinical and MRI changes. In order to achieve this goal, all OCT, clinical, and MRI data will be organized into a relational database to allow data analysis in a timely and efficient manner.

4. IMPACT

What was the impact on the development of the principal discipline(s) of the report?
Nothing to report, as yet. Preliminary analyses with initial abstract submissions and publications will begin during the second year of this three-year project.

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
When initial quantitative and qualitative quality control of all raw OCT scans was carried out, we determined that we received nearly twice as many OCTs scans than initially anticipated. Due to the time and date stamps of the scans, we attributed this to an image acquisition protocol in which each scan was taken in pairs for each eye and each study time point. This was confirmed by our collaborator and co-investigator, Dr. Robert Bermel, who oversaw the central OCT reading center for the SPRINT-MS trial. As we were slightly ahead on our year 1 milestones, we were able to adjust our segmentation timeline and use the availability of redundant scans to select the highest quality scan at each time point so as to provide the best quality data. This will have no impact on the overall aims or achievement of project milestones.

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

The OCT data were received in a different file format than initially anticipated. We adjusted our methods for segmentation, including the acquisition of new software technologies, and this problem was resolved. No delays were encountered and this will have no impact on the overall aims or project.

Changes that had a significant impact on expenditures
Nothing to report.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents
Nothing to report, as yet.

6. PRODUCTS

Publications, conference papers, and presentations
- **Journal publications:** Nothing to report
- **Books or other non-periodical, one-time publications**: Nothing to report
- **Other publications, conference papers, and presentations**: Nothing to report

Website(s) or other Internet site(s)
Nothing to report.

Technologies or techniques
Nothing to report.

Inventions, patent applications, and/or licenses
Nothing to report.

Other products
Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

Name: Project Role: Research Identifier: Nearest Person Month: Contribution to Project:	Shiv Saidha PI N/A 2.40 Dr. Saidha oversees all facets of the project as outlined in the main body of the application.
Name: Project Role: Research Identifier: Nearest Person Month: Contribution to Project:	Jerry Prince Co-Investigator N/A 1 Maintains the optimization of the OCT segmentation software package
Name: Project Role: Research Identifier: Nearest Person Month: Contribution to Project:	Jeffrey Lambe Post-Doctoral Associate N/A 6 Performs quality control assessments of all imported/transferred OCT data, and quality control of the segmentation data.

Name:	Henrik Ehrhardt
Project Role:	Post-Doctoral Associate
Research Identifier:	N/A
Nearest Person Month:	1
Contribution to Project:	Performs quality control assessments of all imported/transferred OCT data, and quality control of the segmentation data.

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?
- Organization Name: Cleveland Clinic
- Partner's contribution to the project: Provided access to and will provide knowledge of the study-specific data necessary to perform the analyses proposed in the current proposal and interpret the results.
- Facilities: Nothing to report.
- Personnel exchanges: Nothing to report.
- Other: Nothing to report.

8. SPECIAL REPORTING REQUIREMENTS

Collaborative awards
Nothing to report.

Quad charts
Nothing to report.

9. APPENDIX

Award chart

W81XWH-19-1-0631: Inner and Outer Nuclear Layer Atrophy of the Retina as Novel and Distinguishing Biomarkers for Defining and Tracking Progressive Multiple Sclerosis

PI: Dr. Shiv Saidha, Johns Hopkins University, Maryland   **Budget:** $936,683.00

Topic Area: Multiple Sclerosis Research Program   **Mechanism:** W81XWH-18- MSRP-IIRA

Research Area(s): 0417, 0505, 0701, 0704, 0714, 0803, 0807, 1405, 1407   **Award Status:** Aug 15, 2019 - Aug 14, 2020 (Year 1)

Study Goals:

Use optical coherence tomography (OCT) to identify novel, specific correlates of disease progression in progressive multiple sclerosis (PMS) and examine the effects on the new phosphodiesterase inhibitor ibudilast in relation to both imaging and clinical outcomes.

Specific Aims:

Aim 1: To confirm and validate that INL (inner nuclear layer) and ONL (outer nuclear layer) retinal atrophy predominate in PMS and have specific utility for tracking PMS.

Aim 2: To determine whether rates of GCIP (ganglion cell inner plexiform layer), INL and ONL atrophy are lower in ibudilast versus placebo treated PMS patients in the recent SPRINT-MS Trial, and to examine the relationships of OCT-captured treatment effects with a broad spectrum of clinical and MRI measures.

Key Accomplishments and Outcomes:

Publications: none to date

Patents: none to date
Funding Obtained: none to date

All first year milestones for this three-year project have been completed:
1) A Materials Transfer Agreement was executed between Johns Hopkins University and Cleveland Clinic Foundation.
2) IRB approval from the Johns Hopkins IRB was obtained as was HRPO Approval.
3) With the MTA and approvals in place, all clinical and MRI data were transferred to Johns Hopkins.
4) Johns Hopkins received the OCT data for all study visits from the SPRINT MS trial, initial quantitative and qualitative quality control of all raw OCT scans was carried out.

Second year milestone progress: OCT scan segmentation is proceeding in accordance with projected timeframe