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TITLE: UTE MRI: A Novel Biomarker for Remyelination in Multiple Sclerosis Patients

PRINCIPAL INVESTIGATOR: Peder Larson, PhD

CONTRACTING ORGANIZATION: University of California, San Francisco, CA

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<b>13. SUPPLEMENTARY NOTES</b>					
<b>14. ABSTRACT</b> Hypothesis UTE MRI can be applied to MS patients undergoing myelin repair therapy and provide specific measurements of myelin non-invasively across the entire brain. Objectives Apply UTE MRI to MS patients undergoing remyelinating therapy; analyze the imaging results in comparison to electrophysiology, in known lesions, and across the white matter Rationale The scientific premise of this proposal is that the capability of UTE MRI to directly measure signals from the myelin phospholipid membranes has the potential to transform non-invasive assessment of myelin by providing a more specific measurement of myelin density and structure.					
<b>15. SUBJECT TERMS</b> None listed.					
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## TABLE OF CONTENTS

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

## 1. INTROUCTION:

Inflammation mediated myelin loss is the hallmark of multiple sclerosis (MS). Restoration of the myelin sheath is an unrealized therapeutic goal in the treatment of MS that promises to help with functional recovery and prevention of long-term disability. This objective of this project is to apply a new, non-invasive measurement using magnetic resonance imaging (MRI) for measuring remyelination in multiple sclerosis patients. This technique, called “Ultrashort echo time” MRI, or UTE MRI, is different from other MRI scans because it can measure signals from the myelin itself, whereas previous techniques measure signals from nearby water. This proposal addresses the FY20 MSRP IIRA Focus Area: “Central Nervous System Regenerative Potential in Demyelinating Conditions”, where a major limitation for developing and evaluating remyelinating therapies is the lack of techniques to accurately measure myelin across the brain. In order to address this limitation, we propose UTE MRI measurements in MS patients undergoing myelin repair therapy. We will compare these measurements to visual evoked potentials (VEPs) which have been proven to measure myelin but are limited to measuring myelin in the visual pathway, whereas MRI can measure myelin across the entire brain.

2. **KEYWORDS:** Multiple Sclerosis, myelin, remyelination, MRI, ultrashort echo time (UTE) MRI

## 3. ACCOMPLISHMENTS:

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

- Specific Aim 1: Apply UTE-MRI in MS patients undergoing myelin repair therapy
  - Major Task 1: Setup Myelin Repair Clinical Trial – The original goal of completion was month 6, and this was completed in month 14.
  - Major Task 2: Data Collection Methods – The original goal of completion was month 6, and we completed this in month 20.
  - Major Task 3: Acquire MRI, VEP, and clinical assessments – This task began in month 22, and will continue until the end of the project period.
- Specific Aims 2 & 3: (2) Compare UTE-MRI metrics to electrophysiology for assessing remyelination; (3) Evaluate treatment response as measured by UTE-MRI across the brain
  - Major Task 1: Processing Pipelines for Study Data – We have completed all Milestones in this task.
  - Major Task 2: Statistical Analyses – We have begun extracting biomarkers from the data, but this task will not be completed until the study data collection has completed.
  - Major Task 3: Multi-parametric Model Development - This task has not begun as it relies on the collected study data.

### ○ What was accomplished under these goals?

- Specific Aim 1: Apply UTE-MRI in MS patients undergoing myelin repair therapy
  - Major Task 1: Setup Myelin Repair Clinical Trial – In this task we (imaging team) have been working extensively with the clinical repair trial team (PI: Ari Green) who are responsible for setting up the clinical trial that the imaging will be added onto. The UCSF IRB approval of the application was completed in November 2022.
  - Major Task 2: Data Collection Methods – We completed this task in June 2023 of setting up UTE MRI method, state-of-the-art MRI methods, VEP measurement protocols, and determined other clinical assessments that will be used in data analysis. The major challenge we faced after IRB and HRPO approval was the

clinical repair trial team discovered that some of their equipment for performing electrophysiology measurements was not functioning, which caused additional delays prior to recruitment. They worked with the vendor and were able to resolve the equipment issues in May 2023.

In the meantime, we were able to further improve and optimize the UTE MRI data collection methods. During setup and optimization we validated the MRI methods in healthy volunteers.

- Major Task 3: Acquire MRI, VEP, and clinical assessments – This task has begun, and will continue while the trial is running.
- Specific Aims 2 & 3: (2) Compare UTE-MRI metrics to electrophysiology for assessing remyelination; (3) Evaluate treatment response as measured by UTE-MRI across the brain
  - Major Task 1: Processing Pipelines for Study Data – We have established the processing pipelines for study data, including identifying data storage and databases for the project, training staff to run VEP processing, training staff to run UTE processing, setting up brain segmentation tools, and setting up lesion segmentation pipelines. This was completed in June 2023
  - Major Task 2: Statistical Analyses – We have begun extracting biomarkers from the data.
  - Major Task 3: Multi-parametric Model Development - This task has not begun as it relies on the collected study data.
- **What opportunities for training and professional development has the project provided?**
  - Nothing to Report
- **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?**
  - Now the trial and data collection is running, so we will continue to obtain the UTE MRI data in this trial.
  - We will monitor the UTE MRI data continuously as it is acquired for data quality as well as image reviews in comparison to the standard of care MRI measurements to begin observing patterns across the MRI methods.

#### 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?**
  - Through this project we have now implemented our myelin UTE MRI method on two major MRI vendors, GE Healthcare and Siemens Healthineers, and in the process simplified some

of our approach. We believe supporting multiple vendors with a simpler protocol will allow for greater adoption of this technology, first in the research community but ultimately we hope by commercial partners.

- We have additionally filed a patent application on the optimization of the UTE MRI methods, which is also described below.
- **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 delays in Major Task 1 and 2 in Specific Aim 1, which the goal is to support the setup of the clinical trial that the UTE MRI will be added onto. The major source of delays in the setup of the clinical trial came from re-evaluation of the trial design, which required additional gathering imaging metrics as well as new statistical analyses. An additional delay was encountered when the electrophysiology hardware was discovered to be malfunctioning, which required several rounds of service to correct. This issues are now all resolved, and the data collection in the trial has begun.
- **Changes that had a significant impact on expenditures**
  - None.
- **Significant changes in use or care of human subjects: None.**
- **Significant changes in use or care of vertebrate animals. N/A**
- **Significant changes in use of biohazards and/or select agents N/A**

## 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**
  - Xin Shen, Uzay Emir, Peder Larson. "MULTIPLE CONTRAST BIOLOGICAL MATERIAL IMAGING USING THREE-DIMENSIONAL BALANCED STEADY STATE FREE PRECESSION ULTRA-SHORT ECHO TIME MRI". US Patent Application # 63/520,032. Filed August 16, 2023

- **Other Products** Nothing to Report.

## 7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

- **What individuals have worked on the project?**

Name:	Peder Larson, PhD
Project Role:	Principal Investigator
Researcher Identifier (e.g. ORCID ID):	0000-0003-4183-3634
Nearest person month worked:	1
Contribution to Project:	Dr. Larson is the principal investigator overseeing the entire project. He is also overseeing all aspects of the UTE MRI pulse sequence.

Name:	Ari Green, MD
Project Role:	Co-investigator
Researcher Identifier (e.g. ORCID ID):	0000-0001-9275-3066
Nearest person month worked:	1
Contribution to Project:	Dr. Green is a Neurologist who has expertise in multiple sclerosis patient care and remyelination therapy. He is overseeing study design and integration of non-imaging metrics.

Name:	Roland Henry, PhD
Project Role:	Co-investigator
Researcher Identifier (e.g. ORCID ID):	0000-0002-8232-7562
Nearest person month worked:	1
Contribution to Project:	Dr. Henry is a neuroimaging expert who oversees the MRI protocol and analysis for multiple sclerosis at UCSF, and will oversee these aspects in this study.
Name:	Eduardo Caverzasi, MD
Project Role:	Co-investigator
Researcher Identifier (e.g. ORCID ID):	0000-0002-0350-0460
Nearest person month worked:	1
Contribution to Project:	Dr. Caverzasi is a neuroradiologist who will perform the interpretation of the imaging results, including identification of MS lesions.

Name:	Nikhil Deveshwar
Project Role:	Graduate Student
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	2
Contribution to Project:	Mr. Deveshwar is doing his PhD on the UTE MRI pulse sequence and associated analysis used in this project.

Name:	Shivany Condor Montes
Project Role:	Clinical Research Coordinator
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	3
Contribution to Project:	Ms. Condor Montes is responsible for preparing regulatory documents (e.g. IRB), coordinating subject recruitment, and coordinating the study design.

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**
  - Updated Other Support of the PIs and current Senior personnel (Drs. Green and Henry) are attached.
- **What other organizations were involved as partners?**
  - Nothing to Report

## 8. SPECIAL REPORTING REQUIREMENTS

- **QUAD CHARTS:** Attached

## 9. APPENDICES: N/A