AWARD NUMBER: W81XWH-21-1-0399

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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Larson, Peder

E-Mail: peder.larson@ucsf.edu

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

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.

15. SUBJECT TERMS
None listed.

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
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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. We are 95% complete with this task.
    - Major Task 2: Data Collection Methods – The original goal of completion was month 6, and we completed this in month 9.
    - Major Task 3: Acquire MRI, VEP, and clinical assessments – This task has not begun, and will be able to begin once the myelin repair trial has received all regulatory approvals.
  - 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 had several goals at month 7, which we completed in month 7. This task continues until month 30. We are 40% complete with this task.
    - Major Task 2: Statistical Analyses – This task has not begun as it relies on the collected study data.
    - 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. This trial is nearly setup, with most recently completing a response to the UCSF IRB review of the application, which will re-review in September 2022. The responses

were relatively straightforward to address and we are optimistic to have approvals within a few months.

- Major Task 2: Data Collection Methods – We completed this task in June 2022 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. One challenge we faced was moving our UTE MRI technique to a new MRI scanner in the Department of Neurology from a different MRI vendor (Siemens) than we had previously used (GE). This required obtaining research prototypes from Siemens, working with on-site scientists to evaluate UTE MRI on their system, and finally validating the approach. Using this system, however, will provide a major benefit for comparing with other MRI methods that have been extensively optimized on this system as well as for patient recruitment and retention as this MRI scanner is the most conveniently located to the majority of their clinic appointments as well as the VEP and clinical assessments.

- Major Task 3: Acquire MRI, VEP, and clinical assessments – This task has not begun, and will be able to begin once the myelin repair trial has received all regulatory approvals.

- 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 begun to establish 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. In particular we evaluated our image segmentation pipelines in prior data from UCSF in multiple sclerosis patients and applied this to perform an analysis of size and size distribution of lesions identified on imaging.

  - Major Task 2: Statistical Analyses – This task has not begun as it relies on the collected study 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?**

  - Following UCSF IRB approval, we will obtain HRPO approval. This is the next major activity. We have prepared for this activity by reviewing the draft IRB application with HRPO personnel to get feedback on proper preparation of the IRB application.

  - Before data collection, we will finalize our data collection pipelines and setup procedures for data quality control review

  - We will begin to data collection in Year 2 following completion of regulatory approvals.

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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.

   - **What was the impact on society beyond science and technology?**

     - Nothing to Report

5. **CHANGES/PROBLEMS:**

   - **Changes in approach and reasons for change**

     - We made minor changes to the statement of work in regards to the study design and imaging timepoints that were approved by our Scientific Officer. These changes were a result of changes in the design for the associated clinical trial that were aimed to increase the statistical power. We performed a new power analysis for the imaging data to validate the new design, and reviewed this with the Scientific Officers as well.

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

     - We have had delays in Major Task 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. The final trial design is now completed and is nearing completion of UCSF IRB approval. As this delay unfolded, we reviewed the draft study application with HRPO to mitigate any future delays.

   - **Changes that had a significant impact on expenditures**

     - None.

   - **Significant changes in use or care of human subjects: None. IRB approval ispending.**

   - **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.**
    - Deveshwar, Nikhil; Caverzasi, Eduardo; Yao, Jingwen; Green, Ari; Henry, Roland; Larson, Peder. “Brain Ultrashort-T2* component measurements in patients with multiple sclerosis”. Proceedings of the Annual Meeting of the International Society for Magnetic Resonance in Medicine, May 2022, London, UK, #3986.
    - Yao, Jingwen; Deveshwar, Nikhil; Larson, Peder “Iterative decomposition of multi-compartment relaxometry with least square estimations (IDMCR) for UTE relaxometry in brain” Proceedings of the Annual Meeting of the International Society for Magnetic Resonance in Medicine, May 2022, London, UK, #4092.

- **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

- **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. Dr. Caverzasi has now left UCSF.

- **What other organizations were involved as partners?**
    - Nothing to Report

8. **SPECIAL REPORTING REQUIREMENTS**
    - **QUAD CHARTS:** Attached
9. **APPENDICES:** N/A

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

Log number: MS200272, Multiple Sclerosis Research Program
Award number: W81XWH-21-1-0399

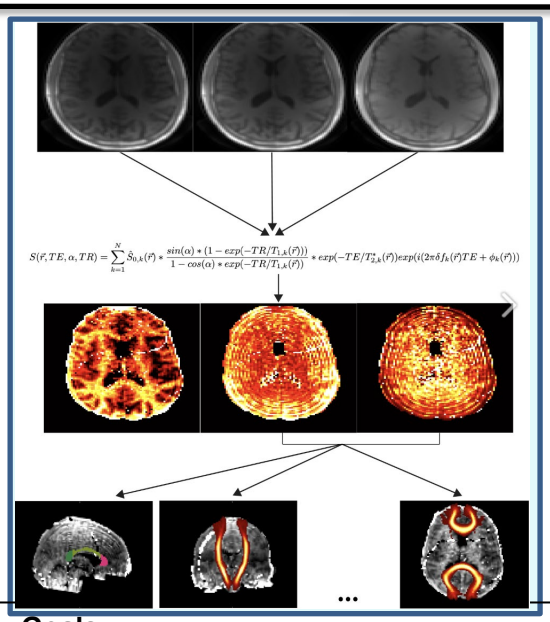
PI: Peder Larson, PhD **Org:** University of California – San Francisco **Award Amount:** $969,000

Study Aims

1. Apply UTE-MRI in MS patients undergoing myelin repair therapy
2. Compare UTE-MRI metrics to electrophysiology for assessing remyelination
3. Evaluate treatment response as measured by UTE-MRI across the brain

Approach

This project aims to apply a new imaging approach, ultrashort echo time (UTE) MRI for measuring remyelination in Multiple Sclerosis Patients. This new approach is based on MRI signals originating within the myelin phospholipid membranes, whereas all other MRI techniques rely on signals from surrounding or trapped water. UTE MRI, other myelin MRI scans, and visual evoked potentials will all be compared in subjects who are undergoing remyelination with clemastine fumarate.



Accomplishments: Our novel UTE MRI technique starts with (top) a series of images acquired a different echo times and flip angles, (middle) which is fit to a signal model to extract parameter maps of the myelin component. (bottom) When applying this to the MS patients, will examine lesions as well as regions of interest (e.g. corpus callosum, optic radiation) to look for evidence of local and global remyelination.

Timeline and Cost

Activity	Y1	Y2	Y3
Apply UTE-MRI in MS patients undergoing myelin repair therapy			
Compare UTE-MRI metrics to electrophysiology for assessing remyelination			
Evaluate treatment response as measured by UTE-MRI across the brain			
Estimated Budget	$323k	$323k	$323k

Updated: 8/31/2022

Goals:

Y1 Goals

Setup Myelin Repair Clinical Trial – 95% complete
Finalize Data Collection Methods – complete

Y2 Goals

Begin Data Collection and subject enrollment
Initial Data analyses

Y3 Goals

Complete Data Collection
Perform Final Data Analyses

Comments/Challenges/Issues/Concerns

- Delays in setup of the myelin repair clinical trial due to further investigation of study design. Nearly complete (IRB application has gone through 1 review cycle)

Budget Expenditure to Date

Projected Expenditure: $323,000 (total costs)
Actual Expenditure: $197,060 (total costs)

PREVIOUS/CURRENT/PENDING SUPPORT

Name: Peder Larson

Current

Title: MRI methods for high resolution imaging of the lung
Time Commitments: 0.12 calendar
Supporting Agency: NIH/NHLBI, R01HL136965-02, (Larson, P.E.Z)
Address: National Institute of Diabetes and Digestive and Kidney Diseases
Contracting/Grants Officer: Aruna Natarajan
Performance Period: 04/15/2018 – 03/31/2023
Level of funding:
Project Goals: The overall goal of this research is the development of high-resolution, multi-parametric magnetic resonance imaging (MRI) techniques for robust evaluation of lung disease in pediatric populations.
Specific Aims: 1. Develop acquisition strategies for improving SNR, minimizing motion, and creating contrast in the lung. 2. Develop reconstruction strategies for high-resolution imaging in the presence of motion.
3. Perform pediatric lung MRI studies in lung nodules and other pathologies.
Overlap: No scientific or budgetary overlap with the proposal

Title: Imaging Metabolism and Cellular Transport in Cancer
Time Commitments: 0.12 calendar
Supporting Agency: ACS, RSG-18-005-01-CCE, (Larson, P.E.Z)
Address: American Cancer Society, Inc. 3380 Chastain Meadows Pkwy NW Suite 200 Kennesaw, GA 30144
Contracting/Grants Officer: Ellie Daniels
Performance Period: 07/01/2018-06/30/2023
Level of funding:
Project Goals: The goal of this project is to translate our novel lactate production and efflux imaging method into clinical studies to improve distinction of low grade from high grade disease.
Specific Aims:
Overlap: No scientific or budgetary overlap with the proposal

Title: Hyperpolarized 13C Metabolic MRI for Noninvasive Monitoring of Kidney Injury
Time Commitments: 0.54 calendar
Supporting Agency: NIH/NIDDK, 1 R21 DK130002-01 (Larson, P.E.Z & Wang, Z.J)
Address: National Institute of Diabetes and Digestive and Kidney Diseases
Contracting/Grants Officer: Norma G DeGuzman
Performance Period: 07/01/2021-04/30/2023
Level of funding:
Project Goals: This project aims to develop hyperpolarized 13C metabolic MRI technology as a tool specifically for assessing kidney injury. It includes technique development and a pilot study in kidney transplant patients.
Specific Aims: We will develop a novel kidney metabolic imaging tool based on the emerging hyperpolarized 13C magnetic resonance imaging modality to non-invasively investigate kidney energy metabolism as a biomarker of kidney injury. This project includes technology development of innovative image acquisition and data analysis strategies that will be evaluated in human subject studies. This tool has an outstanding potential to advance our understanding of energy metabolism in kidney disease, a major public health problem in the United States, and to improve its timely diagnosis and therapy monitoring for both clinical research and clinical care.
Overlap: No scientific or budgetary overlap with the proposal

Title: Development of Sodium Fluoride PET-MRI for Quantitative Assessment of Knee Osteoarthritis
Time Commitments: 0.6 calendar
Supporting Agency: NIH/NIAMS, 5 R01 AR 074492-03, (Larson, P.E.Z (Subcontract PI) (PI: Gold, G. Stanford))
Address: National Institute of Arthritis and Musculoskeletal and Skin Disease
Contracting/Grants Officer: Xincheng Zheng
Performance Period: 08/01/2019-06/30/2024
Level of funding: $330,345
Project Goals: The goal of this project is to develop NaF PET-MRI methods that can provide improved, quantitative assessments of knee degeneration associated with osteoarthritis. The subcontract will develop and implement methods for quantitative PET using MR-based attenuation correction that will improve the power of the proposed approach.
Specific Aims: Aim 1: PseudoCT Generation of Bone and Hardware from MRI for Automated MR-Attenuation Correction "New PET/MR systems present an opportunity to simultaneously acquire metabolic, biochemical and anatomic data but still have many unsolved challenges. Quantitative accuracy of PET tracer uptake requires careful attenuation correction from bony anatomy and MRI hardware in PET/MRI systems, which are challenging due to varying geometry and their lack of signal on MRI. We propose to develop a patient-specific method to directly synthesize pseudoCT images from Dixon and zero echo-time (ZTE) MR images using deep learning models." The successful completion of the pseudo CT generation method in Aim 1 will be the responsibility of our UCSF team. This will include algorithm development. We will provide all associated data and derived methods for all investigators. The majority of this work will be completed in Years 1 & 2, and we will work on optimizing the methods to ensure the success of the entire project in Years 3-5.
Overlap: No scientific or budgetary overlap with the proposal

Title: Translating Hyperpolarized ^{13}C Metabolic MRI to Predict Renal Tumor Aggressiveness
Time Commitments: 1.8 calendar
Supporting Agency: NIH/NCI, 5 R01 CA 249909-02 (Wang, Z.J. & Larson, P.E.Z.)
Address: National Cancer Institute
Contracting/Grants Officer: Huiming Zhang
Performance Period: 01/01/2021-12/31/2025
Level of funding: $3,066,265
Project Goals: The goal of this study is to apply a powerful imaging technology, hyperpolarized 13C metabolic MRI, to renal tumors for the first time to address an unmet need for noninvasive predictors of tumor aggressiveness. Successful completion of this work will aid in future management of patients with renal tumors by reducing the current overdiagnosis and treatment of indolent tumors while enabling early detection of aggressive renal cancers that require timely surgery.
Specific Aims: Aim 1- we will optimize the MRI acquisition strategies for renal tumor metabolic evaluation. Aim 2- we will investigate the value of HP 13C pyruvate MRI for differentiating between benign tumors, low grade RCCs, and high grade RCCs. We will also compare HP 13C data to advanced 1H MRI and radiomics analyses, and develop multi-parametric model to assess whether it can improve the prediction. Aim 3- we will determine the repeatability of HP 13C pyruvate MRI of renal tumors, and evaluate new analysis methods to further improve the robustness of metabolism quantification. Successful completion of this project will provide the first data on the value of HP 13C pyruvate MRI in predicting renal tumor aggressiveness, and will pave the way for future larger clinical studies. HP 13C pyruvate has already been shown to be safe, and we envision the 13C metabolic imaging markers to be incorporated into a state-of-the-art multi-parametric MRI to reduce the current overdiagnosis of indolent tumors while enabling the early detection of aggressive RCCs, and help safely select patients for active surveillance.
Overlap: No scientific or budgetary overlap with the proposal

Title: UTE MRI: a Novel Biomarker for Remyelination in Multiple Sclerosis Patients
Time Commitments: 0.96 calendar
Supporting Agency: USMRAA, W81XWH2110399 (Larson, P.E.Z)
Address: USA MED RESEARCH ACQ ACTIVITY 820 CHANDLER ST, FORT DETRICK MD 21702-5014
Contracting/Grants Officer: Jason Kuhns
Performance Period: 08/01/2021-07/31/2024
Level of funding: $969,000
Project Goals: The major goal of this project is to measure the ability of UTE MRI to measure remyelination in MS patients, we propose to study patients undergoing myelin repair therapy. We propose to study relapsing MS patients with chronic demyelinating optic neuropathy where pattern-reversal visual-evoked potentials (VEPs) have been used as a primary outcome for assessing myelin repair therapy.
Specific Aims: 1. Apply UTE-MRI in MS patients undergoing myelin repair therapy. 2. Compare UTE-MRI metrics to electrophysiology for assessing remyelination. 3. Evaluate treatment response as measured by UTE-MRI across the brain.
Overlap: No scientific or budgetary overlap with the proposal

Title: Hyperpolarized Carbon-13 Metabolic MRI of the Human Heart Time Commitments
Time Commitments: 1.62 calendar
Supporting Agency: NIH/NHLBI, 1 R33 HL161816-01 (Larson, P.E.Z. & Abraham, M.R.)
Address: National Heart, Lung and Blood Institute
Contracting/Grants Officer: Narasimhan Danthi
Performance Period: 02/01/2022-01/31/2024
Level of funding: $965,076
Project Goals: Alterations in cardiac metabolism are implicated in a broad range of heart diseases, including cardiomyopathies, ischemia, and early heart failure. The project proposes to develop a novel imaging modality, hyperpolarized 13C MRI, for metabolic imaging to assess heart disease. Hyperpolarized 13C MRI has transformative potential by providing unique quantifications of metabolic fluxes for earlier and more precise diagnoses, improving understanding of pathogenesis, and rapid assessments of treatment response.
Specific Aims: Aim 1: Develop robust cardiac hyperpolarized 13C MRI methods. We propose imaging technology developments including real-time calibrations, fast imaging of multiple metabolites with whole heart coverage, image reconstructions with off-resonance correction, and cardiovascular signal models for quantifying metabolism.
Aim 2: Perform in vivo validations in human subjects. We propose a series of studies that will establish robust imaging protocols and characterize the reproducibility and repeatability of this technique. These studies include evaluation of subject preparation methods, normalization of metabolic imaging data with correlative blood measurements, test-retest characterizations in healthy volunteers and patients, and same-session repeatability for multiple injection studies.
Overlap: No scientific or budgetary overlap with the proposal

Title: Co-Clinical Quantitative Imaging of Small Cell Neuroendocrine Prostate Cancer Using Hyperpolarized 13CMRI
Time Commitments: 1.38 Calendar
Supporting Agency: NIH/NCI, 5 U24 CA253377-02 (Kurhanewicz,J)
Address: National Cancer Institute
Contracting/Grants Officer: Huiming Zhang
Performance Period: 09/01/2020-08/31/2025
Level of funding: $3,351.115
Project Goals: The successful outcome of this Co-Clinical Imaging Research Program proposal is the establishment of an online resource of quantitative HP 13C MRI protocols, data analyses tools, and correlative biology data allowing for a consensus on how quantitative HP 13C MRI can be used in co-clinical imaging

trials to improve the assessment of therapeutic response and resistance. While this project focuses on advanced prostate cancer, these new quantitative metabolic imaging techniques could ultimately benefit the clinical management of other cancers and diseases.
Specific Aims: Aim 1: Optimize and validate appropriate preclinical HP 13C MRI protocols and analyses that are consistent with those utilized in patient studies using realistic PDX models of metastatic SCNC.
1a. Evaluate the optimal radiofrequency (RF) coil set-ups for imaging SCNC tumors in liver and bone.
1b. Optimize a dynamic fast HP 13C echoplanar imaging MRI acquisition to acquire metabolic data of high spatial and temporal resolution with sufficient signal-to-noise ratio.
1c. Develop metabolic phantoms to test reproducibility and robustness of kPL measurements using optimized RF coils and pulse sequences (from Aims 1a and 1b)
1d. Evaluate the inputless model to calculate kPL, and validate using metabolic phantoms (Aim 1c) and preclinical murine models.
Aim 2: Implement the optimized preclinical dynamic HP 13C MRI protocols and data modeling approaches developed in Aim 1 to assess whether kPL can be used as a biomarker of therapeutic response or resistance.
2a. Assess the changes in kPL of SCNC PDX tumors in liver and bone to platinum-based chemotherapy as a marker of response or resistance. The preclinical HP 13C MRI findings will be used to inform on HP 13C MRI studies of patients with
SCNC of liver and bone metastases before and after platinum-based chemotherapy.
Aim 3: Establish a web-based repository of co-clinical imaging data and protocols, associated molecular and pathological characterization of PDX models, processed data and processing pipelines, as well as the analytical tools developed. 3a. Characterize the transcriptomic and metabolic profiles of the PDX lines in the two different metastatic sites and supplement a comprehensive information resource on Oncology Models Forum.
3b. Institute an online portal to establish a repository of data, protocols and tools for image acquisition and quantitative processing.
Overlap: No scientific or budgetary overlap with the proposal

Title: Hyperpolarized C-13 MRI Techniques to Monitor Radiation Therapy Response in Prostate Cancer Patients
Time Commitments: 0.6 calendar
Supporting Agency: NIH/NCI, 1 R01 CA 238379-01A1 (Vigneron, D.B. & Bok R.A.)
Address: National Cancer Institute
Contracting/Grants Officer: Piotr Grodzinski
Performance Period: 07/01/2021-06/30/2026
Level of funding: $3,326,471
Project Goals: The goal of this project is to develop new techniques and apply an innovative MR molecular imaging approach to monitor HP pyruvate metabolism in prostate cancer patients pre- and post-radiation therapy for the first time. While this study focuses on prostate cancer radiation therapy, these methods are designed to be applicable to other radiation therapy HP MRI studies and in general to other cancer investigations.
Specific Aims: Aim 1: HP 13C Technical Developments and Translation for Prostate Cancer RT Studies.
Aim 2: Application of the New HP 13C MRI Exam Before and After Prostate Cancer SBRT.
Aim 3: Detection of Progressive Disease in Post-RT Patients.
Overlap: No scientific or budgetary overlap with the proposal

Title: Development and Translation of Hyperpolarized C-13 Prostate Cancer MRI Methods
Time Commitments: 0.6 calendar
Supporting Agency: NIH/NIBIB, 5 U01 EB026412-04 (Gordon/Vigneron)
Address: National Institute of Biomedical Imaging and Bioengineering
Contracting/Grants Officer: Guoying Liu
Performance Period: 06/01/2019-02/28/2024

Level of funding: $6,046,631
Project Goals: The goal of this Bioengineering Research Partnership project (with partners/collaborators at Stanford, MD Anderson, UCB, UFlorida, GE & Isotec) is to develop new techniques and test them through early-phase studies in primary and metastatic prostate cancer to create the most reliable, cost-effective, high quality HP C-13 MRI exams possible to benefit individual patients and future clinical trials. While this project focuses on prostate cancer, these bioengineering developments are designed to be generally applicable to human HP MRI studies benefiting a broad variety of studies.
Specific Aims: Aim 1: Improve HP Pharmacy Methods for Producing Sterile HP 13C-pyruvate.
Aim 2: Develop New Robust HP 13C MR Technology for Primary Prostate Cancer.
Aim 3: Specific Technical Developments for Metastatic Prostate Cancer Exams.
Overlap: No scientific or budgetary overlap with the proposal

Title: Measuring Metabolic Activity in Prostate Cancer Bone Metastases Using Hyperpolarized 13C Pyruvate MRI for Improved Targeted Therapy Monitoring
Time Commitments: 0.48 calendar
Supporting Agency: NIH/NCI, 5 R01 CA 256740-02 (Vigneron, D.B. & Aggarwal, R)
Address: National Cancer Institute
Contracting/Grants Officer: Huiming Zhang
Performance Period: 12/01/2020-11/30/2025
Level of funding: $3,281,374
Project Goals: The goal of this project is to investigate a new molecular imaging approach for novel measurements of drug target inhibition in an early-phase feasibility clinical research study in prostate cancer patients with bone metastases. While this early-stage feasibility clinical research study focuses on prostate cancer, these methods are designed to be applicable to other metastatic cancer MRI studies and in general to other cancer investigations.
Specific Aims: Aim 1: Develop specialized quantitative 13C-pyruvate HP MRI for the metabolic characterization of bone metastases in prostate cancer patients.
Aim 2: Define the molecular and metabolic signature of response and resistance to AR targeting therapies in prostate cancer bone metastases.
Aim 3: Integrate HP 13C-pyruvate MRI as a drug development tool for a novel MYC-targeting therapies in advanced prostate cancer.
Overlap: No scientific or budgetary overlap with the proposal

Title: Hyperpolarized C-13 MRI for Early Detection of Aggressive Prostate Cancer in Active Surveillance Patients
Time Commitments: 0.6 calendar
Supporting Agency: NIH/NCI, 5 U01 CA232320 – 04, (Vigneron, D.B. & Bok, R.A.)
Address: National Cancer Institute
Contracting/Grants Officer: Richard V Mazurchuk
Performance Period: 04/01/2019-03/30/2024
Level of funding: $3,246,811
Project Goals: The goal of this prostate imaging project is to investigate the addition of a new safe, non-radioactive 5-minute hyperpolarized 13C-pyruvate MR scan to a clinical mpMRI exam in order to create a metabolic imaging solution for the unmet clinical need for the detection of aggressive cancer in the prostate in patients prior to and enrolled in “Active Surveillance”. Success of this project would improve the detection of aggressive cancer missed by biopsy sampling error enabling earlier treatment decisions or increased confidence in selecting Active Surveillance for more patients; thus reducing overtreatment.
Specific Aims: Aim 1: Higher Resolution 3D HP 13C-Pyruvate Acquisition and Analysis Techniques for Detection of Aggressive Prostate Cancer Within the Prostate.
Aim 2: HP 13C-Pyruvate Detection of Organ-confined Aggressive Prostate Cancer in Patients Prior to

Enrollment or on Active Surveillance with Correlations to Image Guided Biopsy Data.
Aim 3: Early Prediction of Progression to Aggressive Prostate Cancer in Untreated AS Patients using Serial HP 13CPyruvate mpMRI.
Overlap: No scientific or budgetary overlap with the proposal

Title: Hyperpolarized MRI Technology Resource Center
Time Commitments: 1.2 calendar
Supporting Agency: NIH/NIBIB, 5 P41 EB 013598-11 (Vigneron, D.B.)
Address: National Institute of Biomedical Imaging and Bioengineering
Contracting/Grants Officer: Guoying Liu
Performance Period: 08/01/2011-02/28/2027
Level of funding: $6,556,185
Project Goals: This NIH NIBIB National Center for Biomedical Imaging and Bioengineering (NCBIB) focuses on the technological development of new preclinical hyperpolarized carbon-13 MRI. It is based on three Technology Research and Development projects for: 1) the development of new dynamic nuclear polarization (DNP) and HP-MRI techniques; 2) New HP probes and cell/tissue HP-techniques; 3) Specialized HP MRI reconstruction and analysis techniques. These technical resource developments are driven by Collaborative Projects and then disseminated to Service Projects and then the general scientific community.
Specific Aims: Aim 1: Continual Improvement of the HMTRC Infrastructure and Interactions. Aim 2: HMTRC Training and Dissemination. Aim 3: TRD1 Technology Development for Polarizer and Detector Instrumentation Aim 4: TRD2 Development of Novel Hyperpolarized MR Molecular Imaging Probes Tested in Realistic Preclinical Models and Correlative Science Studies. Aim 5: TRD3 Acquisition and Analysis Methods for Hyperpolarized MR Data
Overlap: No scientific or budgetary overlap with the proposal

Previous

Title: Hyperpolarized C-13 Diffusion MRI Measures of Cellular Transport and Metabolism
Time Commitments: 1.65 Calendar
Supporting Agency: NIH/NIBIB, R01EB016741
Address:
Contracting/Grants Officer: Guoying Liu
Performance Period: 09/17/2014 - 05/31/2019
Level of funding: $315,458
Project Goals: We aim to provide new imaging biomarkers for perfusion, transport and metabolism non-invasively with hyperpolarized 13C diffusion-weighted MRI to improve the characterization of disease states such as cancer.
Specific Aims: This project proposes (1) rapid and efficient methods for dynamic metabolic imaging to provide localized perfusion, uptake and rate information that are unavailable in current techniques. (2) New sources of contrast with hyperpolarized carbon-13 are also proposed, including a method to distinguish flowing metabolites from those within tissues and development of specialized techniques for multiple carbon-13 agents. (3) Preclinical studies in normal animals will be used for investigation of the new imaging methods.

Title: Novel Ultrashort Echo Time Sequences for Brain MRI
Time Commitments: 1.08 Calendar
Supporting Agency: NIH/NINDS, R21NS089004
Address:
Contracting/Grants Officer: Debra Babcock
Performance Period: 04/01/2016 – 03/31/2019
Level of funding: $150,000

Project Goals: In this project we propose to explore a new source of contrast for imaging myelin, which plays a critical role in neuronal networks throughout the brain. We will develop and apply novel ultra-short echo time magnetic resonance imaging (MRI) methods to provide new information that maybe extremely valuable for studying brain development as well as diagnosis, localization, surgical planning, and monitoring response to treatment in many neurodegenerative disorders, such as multiple sclerosis, leukodystrophies, and Alzheimers disease. This project will also explore the clinical potential of these novel methods through studies in multiple sclerosis patients with known demyelinating lesions.
Specific Aims: (1) We first propose to characterize its MRI properties in human studies, both in healthy volunteers of various ages as well as multiple sclerosis patients with previously identified demyelinating lesions. (2) Since these complete characterization studies will require long scan times, we will also develop SNR and contrast efficient imaging methods based on UTE MRI in order to enable widespread measurements of this source of contrast in future clinical evaluation studies

Title: Development and Translation of Hyperpolarized C-13 Prostate Cancer MRI Methods
Time Commitments: 1.8 calendar
Supporting Agency: NIH/NIBIB, R01 EB017449 (Vigneron & Kurhanewicz)
Address:
Contracting/Grants Officer: Guoying Liu
Performance Period: 8/15/2013 - 7/31/2018
Level of funding: $784,145
Project Goals: This Bioengineering Research Partnership project aims to develop and translate new methods for human hyperpolarized carbon-13 MRI of prostate cancer.
Specific Aims: (1) Polarizer Methods; (2) Acquisition Methods; (3) Human Prostate Cancer Studies.

Title: Imaging and Tissue Correlates to Optimize Management of Glioblastoma
Time Commitments: 0.36 calendar
Supporting Agency: NIH/NCI, P01 CA118816 (Chang & Nelson)
Address:
Contracting/Grants Officer: Anne Menkens
Performance Period: 7/01/2013 - 6/30/2018
Level of funding: $1,504,404
Project Goals: The overall goal of the new P01 is to integrate advances in physiologic and metabolic imaging with tissue biomarkers in order to optimize the management of patients with glioblastoma.
Specific Aims: 1) To accurately define tumor burden in the post treated setting. 2) To characterize intratumoral heterogeneity (imaging parameters, histologic characteristics, genetic/epigenetic features) and the effect on treatment response, tumor evolution and clinical outcome. 3) To assess early response to therapy to assist with treatment decisions.

Title: Novel Hyperpolarized MR Markers of Advanced Prostate Cancer Therapy
Time Commitments: 0.36 calendar
Supporting Agency: NIH/NCI, R01 CA166655 (Kurhanewicz & Vigneron)
Address:
Contracting/Grants Officer: Huiming Zhang
Performance Period: 9/30/2012 - 7/31/2018
Level of funding: $394,119
Project Goals: This project is focused on the preclinical development and testing of novel MR techniques approaches for castrate-resistant prostate cancer (CPRC) characterization and treatment monitoring for future translation to the clinic.
Specific Aims: (1) TRAMP mouse model studies; (2) Human Tissue Slice studies; (3) Human Studies

The proposing entity, The Regents of the University of California, San Francisco, must comply with Section 223(a) of the William M. (Mac) Thornberry National Defense Authorization Act for Fiscal Year 2021, which requires that the PI, Partnering PIs (if applicable), and all key personnel:

- Certify that the current and pending support provided on the application is current, accurate, and complete;
- Agree to update such disclosure at the request of the agency prior to the award of support and at any subsequent time the agency determines appropriate during the term of the award; and
- Have been made aware of the requirements under Section 223(a)(1) of this Act.

As the person disclosing previous, current, and pending support in this document, I certify and agree to the above:

Signature: DocuSigned by: 1644A2CD853841E... Date: 8/30/2022

*Name of Individual: Green, A.

Positions/Scientific Appointments

2011-2013 Assistant Professor, Department of Ophthalmology UCSF
2012-present Medical Director, UCSF Mission Bay MS Center
2013-present Associate Professor, Department of Neurology UCSF
2013-present Associate Professor, Department of Ophthalmology UCSF
2017-present Chief of Neuroimmunology and Glial Biology Division

PREVIOUS

Title: Functional validation of SERMs as remyelinating agents

Major Goals: to rigorously test promising candidates from a category of medications called SERMs (selective estrogen receptor modulators). SERMs have been developed to treat a number of medical problems (e.g. osteoporosis or breast cancer).

Specific Aims: Aim 1. Screening and characterization of SERM compounds on OPC differentiation and myelination using human oligodendrocytes. Hypothesis: Many existing SERMs have remyelinating effects that can be detected in vitro and in vivo. Methods: We will analyze the effects of a comprehensive list of candidate SERM compounds on ES¬derived human OPCs cultured in isolation, as well as with purified dorsal root ganglion neurons. We will quantify OPCs, oligodendrocytes, and examine myelin internodes by immunostaining and electron microscopy, using previously validated techniques. Our preliminary findings with one lead compound reveal a strong effect on OPC differentiation and myelination, including on human ES¬derived OPCs. Aim 2. Target validation using previously reported ER¬associated candidate receptors. Hypothesis. The myelinating effects of SERMs are not dependent on estrogen receptors. Methods: To validate the specificity of SERMs for the previously reported candidate receptor targets, we will repeat the studies described in Aim 1 in OPCs from ERalpha, ERbeta, and ER double KO mice. In our preliminary studies, SERMs act independently of ERs to promote differentiation and myelination. Therefore, we will also explore the estrogenic GPR30 as potential receptor target for the effects of SERMs. Aim 3. In vivo preclinical validation for functional remyelination: toxic and inflammatory demyelination combined with electrophysiology (VEPs). Hypothesis: SERMs will promote precocious differentiation and promote remyelination after demyelination. Methods: To perform in vivo validation of the remyelinating properties of target SERMs, we will induce toxic injury with lysolecithin in the corpus callosum, and demyelination in two adult mice models: cuprizone and EAE. We will assess demyelination and remyelination in all models using established approaches and test for functional recovery using VEPs. In our preliminary studies, VEP latency is a more sensitive indicator of demyelination and remyelination than clinical scores in both mouse models, as well as of remyelination in clinical trials. This will allow us to establish a clear clinical path for selected SERMs.

Project Number: RG-1707-28564 (A131194)

Name of PD/PI: Bove, R.

Source of Support: National Multiple Sclerosis Society

Source of Support Address:
National Multiple Sclerosis Society

733 Third Avenue, 3rd Floor
New York, NY 10017

Contracting/Grants Officer: Claude Schofield

Project/Proposal Start and End Date: (MM/YYYY) (if available): 04/2018 – 03/2022 (NCE)

Total Award Amount (including Indirect Costs):

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2019	0.60 calendar
2. 2020	0.60 calendar
3. 2021	0.60 calendar
4. 2022	0.00 calendar

Overlap: None

Title: Transcriptional dynamics of retinal microglia in neuroinflammatory disease: identifying molecular pathways to target for treatment of progressive MS

Major Goals: to validate an innovative, highly sensitive retinal eye-tracking technology, the tracking scanning laser ophthalmoscope (TSLO), as a prognostic and monitoring tool for multiple sclerosis (MS).

Specific Aims: Aim 1a: To identify the timing of microglial activation in EAE. Aim 1b: to characterize the cell composition of retinal innate immunity at each stage of EAE.Aim 1c: To unveil the relationship between the innate autoimmunity, clinical severity and retinal neuronal survival in EAE. Aim 2a: to specifically isolate RNA from retinal microglial cells at each time point during EAE. Aim 2b: to define the changing transcriptomic signature of retinal microglia upon demyelinating neuroinflammation. Aim 2c: to comprehensively analyze the pathways that mediate both the detrimental and the neuroprotective phenotypes of microglia in EAE.

Project Number: 17318

Name of PD/PI: Green, Ari.

Source of Support: Conrad N. Hilton Foundation

Source of Support Address:
Conrad N. Hilton Foundation
30440 Agoura Road
Agoura Hills, CA 91301

Contracting/Grants Officer: Elizabeth Cheung

Project/Proposal Start and End Date: (MM/YYYY) (if available): 07/2017-

06/2019 Total Award Amount (including Indirect Costs):

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2018	0.48 calendar
2. 2019	0.48 calendar

Overlap: None

Title: Retinal eye-tracking for the screening of multiple sclerosis and other neurodegenerative diseases

Major Goals: to validate an innovative, highly sensitive retinal eye-tracking technology, the tracking scanning laser ophthalmoscope (TSLO), as a prognostic and monitoring tool for multiple sclerosis (MS).

Specific Aims: patient/subject recruitment, organizing eye motion data according to disease type and subject de-identifying code, with subsequent secure storage and to compare metrics with classifiers.

Project Number: 1R41NS100222-01A1

Name of PD/PI: Green, A.

Source of Support: C. Light Technologies, Inc

Source of Support Address:
C. Light Technologies, Inc
2070 Allston Way, Suite 102
Berkeley, CA 94704

Contracting/Grants Officer: Christy Sheehy

Project/Proposal Start and End Date: (MM/YYYY) (if available): 03/2018 – 08/2018

Total Award Amount (including Indirect Costs):

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2018	1.74 calendar

Overlap: None

Title: Inception Sciences - rodent efficacy studies at UCSF with 2-3 compound of our Inception compounds 20150421

Major Goals: to provide in vivo validation of novel remyelinating compounds identified by Sponsor using techniques in an animal model for MS (experimental autoimmune encephalomyelitis) analogous to methods that will be used in future human studies.

Specific Aims: AIM1: Assess for improved VEP latency recovery in animals given selected potential remyelinating compounds (from Sponsor) intended to promote oligodendrocyte differentiation and myelination following the induction of EAE. AIM2: Validate electrophysiology findings using histology and targeted immunohistochemistry of the retina and retrobulbar optic nerve.

Project Number: N/A

Name of PD/PI: Green, A.

Source of Support: Inception 5, Inc

Source of Support Address:

Inception 5, Inc
5871 Oberlin Drive, Suite 100
San Diego, CA 92121

Contracting/Grants Officer: Donna Tran

Project/Proposal Start and End Date: (MM/YYYY) (if available): 07/2015 –

06/2018 Total Award Amount (including Indirect Costs):

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2016	0.12 calendar
2. 2017	0.00 calendar
3. 2018	0.00 calendar

Overlap: None

Title: A 3-year, multi-center study to evaluate optical coherence tomography as an outcome measure in patients with multiple sclerosis. This is privately sponsored clinical trials

Major Goals: a clinical trial using multi-center study to evaluate optical coherence tomography.

Specific Aims: N/A

Project Number: FTY72D

Name of PD/PI: Green, A.

Source of Support: Novartis AG

Source of Support Address:
Novartis AG
One Health Plaza
East Hanover, NJ 07936

Contracting/Grants Officer: Debra Sanes

Project/Proposal Start and End Date: (MM/YYYY) (if available): 06/2011 –

06/2018 Total Award Amount (including Indirect Costs):

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2012	0.00 calendar
2. 2013	0.00 calendar
3. 2014	0.25 calendar
4. 2015	1.22 calendar
5. 2016	0.39 calendar
6. 2017	0.46 calendar
7. 2018	0.12 calendar

Overlap: None

Title: R&D Fellowship for Grant ID #FE-13378 - Training opportunities for physician-scientists (biomedical research)

Major Goals: this a fellowship grant is to support postdoctoral Christian Cordano

Specific Aims: N/A

Project Number: FE-13378

Name of PD/PI: Green, A.

Source of Support: Biogen MA, Inc

Source of Support Address:
Biogen MA, Inc
250 Binney Street
Cambridge, MA 02142

Contracting/Grants Officer: Eleane Hardy

Project/Proposal Start and End Date: (MM/YYYY) (if available): 06/2015 –

06/2017 Total Award Amount (including Indirect Costs):

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2016	0.00 calendar
2. 2017	0.00 calendar

Overlap: None

Title: In vivo neuronal imaging after demyelinating injury to the visual pathway

Major Goals: to stop disease progression, restore function, and end MS forever through prevention.

Specific Aims: Aim 1: to determine the timing and morphological changes in ganglion cell degeneration after optic neuritis in the mouse. Aim 2: To define the sequence of morphological changes in dying neurons following demyelinating injury including assessment of the temporal relationship between axonal beading, axon drop out, dendritic beading, dendritic retraction and cell soma loss using the model described in Aim 1. Aim 3: To establish the pathological cellular substrate underlying changes in OCT thickness scores after acute optic neuritis using co-registered OCT and fluorescence- based confocal scanning laser ophthlamoscope images. Aim 4: To a) determine the dynamic relationship between retinal microglial activation and neuronal loss after demyelinating injury, b) investigate the local interactions between activated microglia and dead or degeneratingneuronsand c) characterize the significance of microglial activation for injury observed to deeper unmyelinated retinal neurons and ocular inflammation.

Project Number: JF 2151-A-1

Name of PD/PI: Green, A.

Source of Support: National Multiple Sclerosis Society

Source of Support Address:
National Multiple Sclerosis Society
733 Third Avenue
New York, NY10017-3288

Contracting/Grants Officer: Jennifer Stark

Project/Proposal Start and End Date: (MM/YYYY) (if available): 07/2012 –

06/2017 Total Award Amount (including Indirect Costs):

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2013	4.86 calendar
2. 2014	4.73 calendar
3. 2015	4.52 calendar
4. 2016	3.79 calendar
5. 2017	3.42 calendar

Overlap: None

CURRENT

Title: Establishing VEP as a quantitative biomarker for remyelination using transgenic models for gain and loss of function

Major Goals: This project will establish the underlying cellular basis for latency delay and recovery of latency delay on the visual evoked potential. It will use animal models that specifically enhance remyelination potential as well as other models that eliminate the capacity for remyelination and systems that exhibit demyelination and remyelination without concomitant inflammation. This project will take advantage of newly discovered medicines with remyelinating potential to conclusively resolve if VEP latency can be used as a useful biomarker in both preclinical and early clinical investigations for promising remyelinating therapies.

Specific Aims: Aims 1: Is there a quantitatively meaningful relationship between myelin status and the extent of latency delay on the VEP in rodent models of demyelination? Hypothesis: VEP N1 latency quantitatively correlates to myelin status in the visual pathway of mice with EAE and those exposed to cuprizone. This aim is made possible by combining an adapted VEP technique with histology. Furthermore, remyelination with a validated tool remyelinating compound (clemastine) will be associated with improved latency recovery following demyelination in conjunction with histological evidence of remyelination in the anterior visual pathway. Aim 1a: To perform VEPs in rodents treated with cuprizone and with EAE comparing these data with quantitative IHC and electron microscopy (EM). Aim 1b: To assess the degree of VEP recovery induced by clemastine in these demyelination models in conjunction with similar quantitative IHC and EM. Aim 2: Will genetic cell-specific gain and loss of (re)myelinating capacity be associated with anticipated changes in recovery of latency delay following demyelinating injury? Hypothesis: Genetic ablation of the M1R in OPCs with resultant enhanced remyelinating capacity will be associated with subsequent enhanced restoration of VEP latency as will maintenance of axonal substructure via use of the Sarm 1 KO mouse whereas absence of remyelinating

capacity will be associated with failure to achieve remission of latency delay in EAE even in the presence of clemastine. These approaches will specifically uncouple remyelination from potential off target effects of therapeutics on immune mediated features of MS and allow us to interrogate the isolated effects of remyelination on the VEP signal. Aim 2a: Following MOG EAE induction in an OPC specific M1R conditional knockout mouse we will evaluate the isolated and specific contribution of remyelination to VEP latency delay and recovery – despite the presence of inflammation that is unaffected by the genetic modification. Aim 2b: To perform VEPs and OCT longitudinally in MyRF fl/fl crossed to the PDGFRa-CreER driver mice following induction of demyelination, to demonstrate that absence of remyelinating capacity will lead to persistent VEP latency delay. Aim2c: Following induction of EAE in Sarm1 -/- we will evaluate the specific contribution of axonal preservation to VEP latency and amplitude and assess the enhanced beneficial effects of remyelination when axons are preserved. Aim 3: Does targeted chronic chemical demyelination of the optic nerve in primates show equivalent capacity for remyelination to that seen in rodents? Hypothesis: After chronic myelin injury from direct lysolecithin injection into the optic nerve of macaques, clemastine administration will show capacity to induce remyelination and thereby save axons from loss. Using pattern reversal VEP, histology and quantitative EM, macaques with lysolecithin induced focal myelin loss will be assessed for relative benefit of acute vs. chronic clemastine administration. Aim3: Macaques with unilateral lysolecithin induced optic nerve lesions will be assessed for electrophysiological, histological and ultrastructural recovery from clemastine treatment initiated at 0 and 3 months post-injury.

Project Number: R01NS105741 (A131197)

Name of PD/PI: Green, A.

Source of Support: NIH/NINDS

Source of Support Address:
NiH/NINDS
6001 Executive Boulevard, Suite 3290, MSC 9537.
Rockville, MD 20852

Contracting/Grants Officer: Pamela L. Mayer

Project/Proposal Start and End Date: (MM/YYYY) (if available): 05/2018 –

02/2023 Total Award Amount (including Indirect Costs):

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2019	2.55 calendar
2. 2020	2.32 calendar
3. 2021	2.40 calendar
4. 2022	2.04 calendar
5. 2023	2.14 calendar

Overlap: None

Title: The Four Repeat Tauopathy Neuroimaging Initiative

Major Goals: to develop biomarkers of disease progression in CBD and PSP.

Specific Aims: New treatments that target the protein tau, a neuronal scaffolding protein that accumulates in neurodegenerative diseases including Alzheimer's (AD), are beginning to enter human clinical trials. While tau-related therapies hold great promise for AD, clinical trials focusing on pure tauopathies are appealing because these diseases do not exhibit concurrent amyloid pathology. Pure 4 microtubule binding repeat (4R) tauopathies (4RT) include corticobasal degeneration (CBD), progressive supranuclear palsy (PSP) and some variants of frontotemporal lobar degeneration. There are no approved or effective therapies for CBD or PSP. Aim 1. Determine the natural history of insoluble tau deposition as measured by 18F AV1451 uptake on PET scans in 4RT as compared to age-matched normal elders. Hypotheses: (A) PSP will display baseline AV1451 uptake in basal ganglia, cerebellar dentate and subthalamic nucleus (STN), with increased uptake over one year in these and frontal cortical areas. (B) CBD with low baseline amyloid (assessed by PiB PET), will display AV1451 uptake in frontal cortex, subcortical white matter, and basal ganglia with the greatest longitudinal changes in the same regions. (C) oPSP will display elevated AV1451 uptake at baseline in 4RT associated brain regions, with increased uptake over two years to resemble CBD or PSP. Aim 2. Quantify the longitudinal changes in ocular neuronal injury markers: retinal thickness and vertical saccade gain as measured by optical coherence tomography (OCT) and infrared oculography (IOG). (A) CBD and PSP will display decreased inner plexiform layer and macular volume as compared to normal controls, with decreasing thickness over one year that parallels clinical measures of disease progression. (B) oPSP with baseline OCT or IOG features characteristic of 4RT will have elevated AV1451 uptake and increased likelihood of progression to CBD or PSP after two years. Aim 3. Quantify the longitudinal changes in CSF NfL in 4RT as compared to other fluid biomarkers of neurodegeneration. (A) CSF NfL concentrations will increase over one year in CBD and PSP, in parallel with clinical measures of disease severity, AV1451 uptake and MRI measures of brain structure. (B) Baseline CSF NfL/phosphorylated tau ratio, will predict conversion of oPSP to CBD or PSP after 2 years, and the rate of clinical progression in all syndromes. Aim4. Determine the clinical, MR imaging, and neuronal injury marker correlates of 18F AV1451 uptake. (A) In cross sectional analyses, for all groups, higher regional AV1451 uptake will correlate with: worse motor (PSPRS and UPDRS) and cognitive function (neuropsychological tests); decreased regional brain volume (vMRI), white matter integrity (dMRI) and functional connectivity (ICN fMRI); worse ocular status (OCT and IOG), and higher CSF NfL. (B) Higher baseline AV1415 uptake in tau index regions (globus pallidus, cerebellar dentate nucleus and STN) that are associated with clinically significant tau deposition from autopsy studies will predict a more rapid rate of disease progression measured using clinical scales, vMRI and dMRI, and an increased likelihood of meeting PSP research criteria after 2 years in oPSP.

Project Number: R01AG038791 (A127016)

Name of PD/PI: Boxer, Adam

Source of Support: NIH/NIA

Source of Support Address:
NIH/NIA
6705 Rockledge Drive, Suite 5016, MSC 7986.
Bethesda, MD 20892

Contracting/Grants Officer: Priscilla M. Garner

Project/Proposal Start and End Date: (MM/YYYY) (if available): 03/2016 –

02/2023 Total Award Amount (including Indirect Costs):

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2017	1.20 calendar
2. 2018	1.20 calendar
3. 2019	1.20 calendar
4. 2020	1.20 calendar
5. 2021	1.20 calendar
6. 2022	1.20 calendar
7. 2023	1.20 calendar

Overlap: None

Title: Tracking longitudinal change in presymptomatic genetic prion disease (TLC-Pre-gPrD)

Major Goals: to identify and develop biomarkers for treatment trials in presymptomatic genetic prion disease (PreSx gPrD).

Specific Aims: to identify biomarkers for presymptomatic genetic prion disease (as is already being done in Alzheimer's disease) that will help in the development and design of future treatment trials. Aim 1. Characterize the rates of biomarker change in PreSx Slow-gPrD. We hypothesize that, compared with controls, PreSx Slow-gPrD will show greater rates of: A) cortical MD elevation, B) decline on quantitative motor testing, & C) decline in processing speed. Aim 2. Characterize the rates of biomarker change in PreSx Fast-gPrD. We hypothesize that, compared with controls, PreSx Fast-gPrD will show great rates of: A) deep nuclei (putaminal) MD reduction, B) Greater rates of decline on quantified motor testing, & C) decline in processing speed.

Project Number: R01AG062562 (A133836)

Name of PD/PI: Geschwind, M.

Source of Support: NIH/NIA

Source of Support Address:
NIH/NIA
31 Center Drive, MSC 2292
Bethesda, MD 20892

Contracting/Grants Officer: Mitchell Whitfield

Project/Proposal Start and End Date: (MM/YYYY) (if available): 08/2019 –

05/2024 Total Award Amount (including Indirect Costs):

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2020	0.24 calendar
2. 2021	0.24 calendar
3. 2022	0.24 calendar
4. 2023	0.24 calendar
5. 2024	0.24 calendar

Overlap: None

Title: Establishing Outcome Measures for Remyelination and Defining Myelin-Mediated Neuroprotective Mechanisms

Major Goals: in the treatment of multiple sclerosis (MS) that promises to help with functional recovery and prevention of long-term disability.

Specific Aims: Promoting Remyelination in MS: identifying axonal determinants for repair. This past year we have been extremely productive—we have completed the first aim, and made great progress with the second aim. The major activities of this previous year have been in laboratory research. In this last funding cycle, we published 6 research papers and 1 review (4 of which acknowledge AMRF funding): There are no modifications to Aims 1 and 2. Aim 1: Axonal fiber diameter as a permissive cue for myelination. Hypothesis: A permissive axonal environment in MS lesions is rate-limiting for remyelination. In the absence of dynamic neuronal signaling, we hypothesize that fiber diameter is sufficient to initiate myelination. Aim 2: Determine if neuropeptide release by neurons can promote remyelination. Hypothesis: The neuropeptide dynorphin is released by neurons in an activity dependent manner and modulates OL differentiation and remyelination via activation of ERK1/2 signaling.

Project Number: 04-7023433 (A134345)

Name of PD/PI: Chan, J.

Source of Support: Dr. Miriam & Sheldon G. Adelson Medical Research Foundation

Source of Support Address:
Dr. Miriam & Sheldon G. Adelson Medical Research Foundation
300 1st Avenue.
Needham, MA 02494

Contracting/Grants Officer: Steven Garfinkel

Project/Proposal Start and End Date: (MM/YYYY) (if available): 10/2019 –

09/2022 Total Award Amount (including Indirect Costs):

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2020	1.20 calendar
2. 2021	1.20 calendar
3. 2022	1.20 calendar

Overlap: None

Title: Investigation and Treatment of Undiagnosed Neuroinflammatory Diseases

Major Goals: Neuroinflammatory diseases collectively cause significant morbidity and mortality, and a major roadblock to their effective diagnosis and treatment continues to be poor understanding about the underlying infectious or autoimmune etiologies in a large proportion of cases. This multi-center study combines incredibly deep clinical phenotyping capabilities with the most advanced molecular biology and bioinformatic tools to identify novel infectious and autoimmune causes of neuroinflammatory disease and better understand pathogenesis.

Specific Aims: Aim 1: To comprehensively characterize the immune response in patients with idiopathic neuroinflammatory disease. Aim 2: To perform comprehensive and complementary nucleic acid detection and antibody assays to identify occult pathogens in patients with idiopathic neuroinflammatory disease. Aim 3: To perform B-cell and T-cell antigen discovery to identify autoantigens in patients with idiopathic neuroinflammatory disease.

Project Number: U01NS120836 (A137363)

Name of PD/PI: Wilson, M.

Source of Support: NIH/NINDS

Source of Support Address:
NIH/NINDS
6001 Executive Boulevard, Suite3290, MSC9537
Bethesda, MD20892-9537

Contracting/Grants Officer: James Washington

Project/Proposal Start and End Date: (MM/YYYY) (if available): 05/2021 –

04/2026 Total Award Amount (including Indirect Costs):

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2022	0.24 calendar
2. 2023	0.24 calendar
3. 2024	0.24 calendar
4. 2025	0.24 calendar
5. 2026	0.24 calendar

Overlap: None

Title: Evaluating in vivo retinal imaging as a method of tracking the efficacy of progranulin replacement therapy in Grn KO mice.

Major Goals: The goal is to perform will perform TEM and develop parameters to quantify the number, size, and dimension of ILVs and lysosomes that contain storage materials, such as concentric myelin-like figures [aka multilamellar bodies], electron dense granular aggregates, etc.

Specific Aims: To characterize the effect of Denali's proprietary PGRN replacement therapy (DC0798) in reducing microglial toxicity and mitigating nuclear pore defects, TDP-43 proteinopathy and neuronal death in Grn-/- and GrnR493X/R493X neurons. Aim 2: To determine the effect of Denali's proprietary PGRN replacement therapy, DC0798, can reverse the toxic properties of Grn-/- microglia, including the increased

production of complements C1q and C3b, and transcriptomic changes. Aim 3: To determine whether treatment with Denali's DC0798 restore intraluminal vesicles (ILVs) and mitigate lysosomal defects in Grn-/- microglia and neurons.

Project Number: N/A (A137038)

Name of PD/PI: Green, A.

Source of Support: Denali Therapeutics, Inc

Source of Support Address:
Denali Therapeutics, Inc
161 Oyster Point Blvd
South San Francisco, CA 94080

Contracting/Grants Officer: Joe Lewcock

Project/Proposal Start and End Date: (MM/YYYY) (if available): 06/2021 –

06/2023 Total Award Amount (including Indirect Costs):

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2022	0.60 calendar
2. 2023	0.60 calendar

Overlap: None

Title: Alliance for Therapies in Neuroscience (ATN) Program

Major Goals: The goal of this project is to develop and validate novel radiotracers for synaptic density, neuroinflammation and astrocytosis.

Specific Aims: Aim 1: Qualify SV2A PET imaging as a clinical biomarker for estimating synaptic density and evaluate sensitivity for detecting early neurodegeneration in comparison to existing methods (structural MRI) in AD and MS. This aim includes in vitro/tissue studies and simultaneous in vivo PET methods. Aim 2: Investigate in vitro and in vivo existing radiotracers for gliosis in the context of neuroinflammatory and neurodegenerative disease, including AD, FTLD and MS. Aim 3: Develop novel radiotracers specific for disease associated parameters in microglia and astrocytes in neuroinflammatory and neurodegenerative disorders through the use of large expression data sets and tissue studies.

Project Number: N/A (A137151)

Name of PD/PI: Rabinovici, G.

Source of Support: Genentech, Inc

Source of Support Address:
Genentech, Inc
1 DNA WaySouth
San Francisco, CA 94080

Contracting/Grants Officer: Casper Hoogenraad

Project/Proposal Start and End Date: (MM/YYYY) (if available): 04/2021 – 03/2024

Total Award Amount (including Indirect Costs): Person Months

(Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2022	0.60 calendar
2. 2023	0.60 calendar
3. 2024	0.60 calendar

Overlap: None

Title: UTE MRI: a Novel Biomarker for Remyelination in Multiple Sclerosis Patients

Major Goals: The 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 canmeasure signals from the myelin itself, whereas previous techniques measure signals from nearby water.

Specific Aims: Aim 1: Apply a quantitative UTE-MRI in MS patients undergoing myelin repair therapy. Aim 2: Compare UTE-MRI metrics to electrophysiologyfor assessing remyelination. Aim 3: Evaluate treatment response as measured by UTE-MRI across the brain

Project Number: W81XWH-21-1-0399 (A137540)

Name of PD/PI: Larson, P.

Source of Support: DOD US Army Med. Res. Acq. Activity

Source of Support Address:
DOD US Army
820 Chandler Street.
Fort Detrick, MD 21702- 5014

Contracting/Grants Officer: Linda Taylor Hinson

Project/Proposal Start and End Date: (MM/YYYY) (if available): 08/2021 –

07/2024 Total Award Amount (including Indirect Costs):

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2022	0.60 calendar
2. 2023	0.60 calendar
3. 2024	0.60 calendar

Overlap: None

Title: Dynamic, biomarker-based classification of Multiple Sclerosis

Major Goals: to compare the hazard ratio (HR) of suffering from confirmed disability progression (CDP) in 6, 12, 24 months as well as HR of reaching EDSS milestones

like 4, 6.5, and 7 between the different clusters as well as within cluster (high vs low).

Specific Aims: will compare the hazard ratio (HR) of suffering from confirmed disability progression (CDP) in 6, 12, 24 months as well as HR of reaching EDSS milestones like 4, 6.5, and 7 between the different clusters as well as within cluster (high vs low). Besides the HR, the time needed to reach the milestones mentioned above will be evaluated. Beyond that, the different clusters will be compared based on epidemiological characteristics (age, sex), response to disease-modifying treatments (annualized relapse rate, CDP), and the load of neuroaxonal damage (NfL levels).

Project Number: N/A (A138341)

Name of PD/PI: Green, A.

Source of Support: Hoffmann-LaRoche, Ltd

Source of Support Address:
Hoffmann-LaRoche, Ltd
Grenzacherstrasse 124
4070 Basel, Switzerland

Contracting/Grants Officer: Björn Tackenberg

Project/Proposal Start and End Date: (MM/YYYY) (if available): 01/2022 –

12/2023 Total Award Amount (including Indirect Costs):

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2022	0.60 calendar
2. 2023	0.60 calendar

Overlap: None

Title: Discovery and establishment of novel astrocyte markers in neurological diseases

Major Goals: to develop and validation of highly sensitive assays of neurotoxic astrocyte subpopulations.

Specific Aims: identification of possible novel markers of pathological astrocyte activation and establishing high sensitivity CSF and serum-based assays. Phase 1: Aim: identification of novel candidate protein biomarkers of astrocyte subpopulations. Approach 1: Promising molecules will be identified through literature research for established markers and transcriptomic profiles of astrocyte subpopulations. That approach will be combined with available CSF and plasma proteomic datasets (e.g., CSF Proteome Resource (CSF Proteome Resource (CSF-PR) v2.0 (uib.no)). Numerous markers have been associated with neurotoxic, but not neuroprotective astrocytes3. Phase 2: Aim: Initial assay development and evaluation the following standard approach will be applied: 1) Antibody pair screening and 2) initial ELISA testing: Aim: Identification of the matched capture and detection antibodies against selected protein, identification of assay sensitivity for the lower limit of detection in a standard ELISA. 3) Establishment of a homebrew Simoa assay for a selected protein: Aim: Transfer the selected antibody pairs (for each of the selected

molecules) to the high sensitivity/high-resolution Simoa platform using homebrew starter kit (commercially available) on the Quanterix HD-X analyzer. 4) Internal validation of assay performance: Based on consensus recommendations13,14, and in accordance with the most recent Food and Drug Administration (FDA) guidelines (Bioanalytical Method Validation, 03/2018), as well as the European medical agency (EMA) of 06/2011) the following points will be evaluated for each of the developed assays. Phase 3: The transition to phase 3 will depend on achieving the following go/no-go criteria (in agreement between the involved parties): Development and successful initial evaluation (of criteria 1,2,5, and 6) of at least one homebrew kit for one marker reflecting neurotoxic astrocyte subpopulation.

Aim: Phase 3 will include a series of experiments to provide more extensive proof of concept of the clinical applicability of CSF and/or serum-based marker of neurotoxic astrocytes and define its context of use in MS. The suggested experiments include:

1) Evaluate the correlation between CSF and serum levels of marker XAst: Correlative analysis (spearman's/person's test, linear regression) examining the correlation between levels of XAst in CSF and serum, correcting for covariables like age and sex. Other covariables would be included when appropriate.

2) Explore the association between XAst and neurodegeneration in MS: we postulate a high concentration between XAst correlate with serum levels of neurofilament light chain (NfL), grey matter atrophy metrics (GM volume, GMVOL), and OCT parameters of neurodegeneration (e.g., peripapillary retinal nerve fibre layer). Correlative analysis (linear regression models) between the longitudinal concentration of XAst in correlation with longitudinal NfL concentrations/ GMVOL in serum, correcting for covariables like age and sex. Other covariables would be included when appropriate. Through the process of the clinical validation, we will utilize the samples included in the MS EPIC cohort at UCSF.

Project Number: N/A (A138708)

Name of PD/PI: Green, A.

Source of Support: Hoffmann-LaRoche, Ltd

Source of Support Address:
Hoffmann-LaRoche, Ltd
Grenzacherstrasse 124
4070 Basel, Switzerland

Contracting/Grants Officer: Björn Tackenberg
Project/Proposal Start and End Date: (MM/YYYY) (if available): 01/2022 – 12/2025

Total Award Amount (including Indirect Costs):

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2022	0.60 calendar
2. 2023	0.60 calendar
3. 2024	0.60 calendar
4. 2025	0.60 calendar

Overlap: None

Title: Fixational eye motion as biomarker for mild cognitive impairment

Major Goals: to validate an innovative, highly sensitive retinal eye-tracking technology, the tracking scanning laser ophthalmoscope (TSLO), as an early detection and monitoring tool for MCI.

Specific Aims:
Aim 1: Discretely map fixational eye motion differences between healthy aging controls, controls with amyloid β+, and MCI (amyloid β+) diagnosed patients.
Aim 2: Compare eye motion characteristics with current clinical measures of neurodegenerative disease in MCI.
Aim 3: Apply machine learning architecture to generate clinical scores

Status of Support: Active

Project Number: GDADB-202006-2020512 (A139622)

Name of PD/PI: Green, A.

Source of Support: C. Light Technologies, Inc

Source of Support Address:
C. Light Technologies, Inc
2070 Allston Way, Suite 102
Berkeley, CA 94704

Contracting/Grant Officer: Christy Sheehy

Project/Proposal Start and End Date: (MM/YYYY) (if available): 07/2021 –

01/2023 Total Award Amount (including Indirect Costs):

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2022	0.23 calendar

Overlap: None

PENDING

Title: Evaluating advanced statistical approaches of fixational eye motion as a biomarker for multiple sclerosis

Major Goals: The main goal of this grant is to establish the Retitrack as a prognostic and monitoring tool for MS by developing advanced statistical modeling. Another objective is the creation and validation of machine learning algorithms, to classify patients vs. controls. Also, we plan to implement customized software to convert analytics into clinically actionable metrics. The proposed project will enable us to evaluate the practicality and clinical utility of Retitrack's AI approach.

Specific Aims: Aim 1: Refine and implement advanced statistical modeling to identify the most relevant parameters of fixational eye motion used for the detection and monitoring of MS. Aim 2: Predict and quantify MS disability levels of MS by developing a machine learning model through the refinement of the neural network classification and implementation of explanatory techniques. Aim 3: Create optimized data visualization and reporting for future beta products.

Project Number: P0556787 (Subcontract)

Name of PD/PI: Green, A.

Source of Support: C. Light Technologies, Inc

Source of Support Address:
C. Light Technologies, Inc
2070 Allston Way, Suite 102.
Berkeley, CA 94704

Contracting/Grants Officer: Christy Sheehy

Project/Proposal Start and End Date: (MM/YYYY) (if available): 02/2022 –

02/2023 Total Award Amount (including Indirect Costs):

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2023	0.60 calendar

Overlap: None

Title: A sensitive blood-based biomarker for monitoring myelin injury in neurological disease: preanalytical optimization and defining the clinical context of use

Major Goals: R61 to identification of preanalytical conditions and CSF matrix effects that affect the assay performance. R33 to explore the context of use in demyelinating diseases of the central nervous system, focusing on MS.

Specific Aims:
Aim 1: Technical optimization and determination of the analytical performance in cerebrospinal fluid (CSF).

Aim 2: Defining the dynamics of demyelination (MBP) and neurodegeneration (NfL) following MS activity (clinical or imaging) and under disease-modifying treatments (DMT).
Aim 3: Evaluate peripheral MBP in CIDP and how it can be used to differentiate CIDP from healthy controls and axonal neuropathies.
Aim 4: Explore the evidence for demyelination in cases with AD compared to controls.

Project Number: P0560289

Name of PD/PI: Green, A.

Source of Support: NIH/NINDS

Source of Support Address:
NIH/NINDS
6701 Rockledge Drive
Bethesda, MD 20892

Contracting/Grants Officer: Mary Ann Pelleymounter

Project/ Start and End Date: (MM/YYYY) (if available): 12/2022 – 11/2027

Total Award Amount (including Indirect Costs):

Person Months (Calendar/Academic/Summer) per budget period.

Year (YYYY)	Person Months (##.##)
1. 2023	1.20 calendar
2. 2024	1.20 calendar
3. 2025	1.20 calendar
4. 2026	1.20 calendar
5. 2027	1.20 calendar

Overlap: None

IN-KIND

None

I, PD/PI or other senior/key personnel, certify that the statements herein are true, complete and accurate to the best of my knowledge, agree to update such disclosure at the request of the agency prior to the award of support and at any subsequent time the agency determines appropriate during the term of the award and accept the obligation to comply with Section 223(a) of the William M. (Mac) Thornberry National Defense Authorization Act for Fiscal Year 2021. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

*Signature: DocuSigned by: Ari Green 14EDC3CED4E94F6...

Date: 8/31/2022

Other Support
Name of Individual: Henry, Roland

Positions/Scientific Appointments

Time	Position	Division	Location
6/84 - 1/85	Research Asst.	Particle Physics	Physics Department, Rutgers University
1/85 - 6/91	Teaching Asst.	Physics	Physics Department, Rutgers University
1/87 - 6/88	Research Asst.	Solid State Physics	Physics Department, Rutgers University
6/88 - 6/91	Research Asst.	Nuclear Physics	Physics Department, Rutgers University
1/92 - 5/94	Postdoc. Assoc.	Nuclear Physics	Physics Division, Argonne National Lab
6/94 - 9/97	Postdoc. Assoc.	Biomedical Physics	Radiology Department, UC, San Francisco
10/97 - 6/04	Assistant Prof.	Biomedical Physics	Radiology Department, UC, San Francisco
7/04 - 6/10	Associate Prof.	Biomedical Physics	Radiology Department, UC, San Francisco
7/08 - 6/10	Associate Prof.	Biomedical Physics	Neurology Department, UC, San Francisco
1/00 - pres	Core Faculty	Biomedical Physics	Bioengineering Grad Group, UCSF & UC Berkeley
7/10 - pres	Professor	Biomedical Physics	Radiology Department, UC, San Francisco
7/10 - pres	Professor	Biomedical Physics	Neurology Department, UC, San Francisco

Project/Proposal

PREVIOUS

Title: The role of biological aging on progression in Multiple Sclerosis
Major Goals: To participate in study design, data analysis and interpretation.
Specific Aims: To define the role of biological aging, including sex-specific aging, in the accumulation of clinical disability and central nervous system tissue loss in multiple sclerosis.
Project Number: 00022357-SUB (134989A)
Name of PD/PI: Oksenberg, Jorge
Contracting/Grants Officer: Jackson, Derek
Source of Support: University of California, San Diego / National Multiple Sclerosis Society
Source of Support Address: 9500 Gilman Drive. La Jolla, CA 92093
Project/Proposal Start and End Date: (MM/YYYY) (if available): 07/01/2018-03/31/2021
Total Award Amount (including Indirect Costs):
Time Commitment (Calendar/Academic/Summer): 0.30 calendar months per year
Overlap: None.

Title: Enabling Multisite MRI Studies of Neurodegeneration in Multiple Sclerosis
Major Goals: (i) demonstrate the power of existing real world MRI data across centers worldwide for quantification of MS neurodegeneration, and (ii) to use existing MRI and genetic samples from the International Multiple Sclerosis Genetic Consortium (IMSGC) to execute the first large sample investigation into the role of genes on neurodegeneration in MS.
Specific Aims: The International Multiple Sclerosis Genetics Consortium (IMSGC) led a highly productive global effort to identify the genetic components of MS susceptibility. Addressing the

genetic underpinnings of disease heterogeneity represents the next frontier in the field and, if successful, a true opportunity for gaining important mechanist insights and translation.
Aim 1. Assemble and Centralized Processing of Multicenter Retrospective MRI 1.a Building on our experience with harmonization of volume metrics across these study sites [43], we aim to provide a centralized, secure, user-friendly interface with the Mintlabs data-management system into which we have implemented the UCSF MRI processing pipeline, configured and optimized for MS patients. From the existing large collection of anatomical MRIs across 9 IMSGC sites, MRIs from 1800 female MS subjects with at least 5-years disease duration will undergo centralized processing including our efficient editing platform and correction of lesion and regional volume segmentation (Mindcontrol [56]). 1.b We propose to quantify the upper cervical cord area using a novel analytical procedure. A spinal cord measurement will provide valuable additional metrics that has already been shown to correlate strongly with sensory motor disability and is the clearest imaging marker separating relapsing and progressive MS phenotypes. This measurement is obtained from standard brain 3D T1W volumes [44, 45] and corrected with our recently developed method for gradient non-linearity effects present in most retrospective MRI data.
Aim 2. Genetic risk burden and phenotypic variability Significant variability exists across MS patients in the number and type of disease risk variants each individual carries. A convergent computational analysis of MS genetics will be performed using genome-wide genotypes together with reference transcriptomic and epigenetic information to identify distinct cytotype- and biochemical specific pathways in the composite MS genetic map. We will exploit this information to assess associations between pathways load and CNS tissue degeneration. These analyses will be combined with the already funded independent MultipleMS consortium efforts (from 7 sites not included here) to provide discovery and replication datasets. Scaled hierarchical liner regression models [43] will be constructed with covariates (age, sex, disease duration, without and with treatment status) and a genotype per model to predict each regional volume (cortical and subcortical grey matter, white matter, upper cervical cord areas, and lesion volumes). 2a. The HLA locus and MRI. Our primary analysis will be centered on cumulative burdens from the MHC region to assess the influence of the cumulative (i.e. class I & II risk and protective alleles) HLA genetic burden (HLAGB) and non-HLA MS genetic burdens on the MRI volumes. Our secondary analysis will use individual HLA alleles (e.g. HLA-DRB1*15:01 -susceptibility- and HLA-B*44 -protective-) alone and in extended haplotypic combinations. 2b. Immune and CNS pathways. Our preliminary data suggests that non-MHC cumulative burdens have weak influence on MS degeneration, which further motivates the deconstruction into cellular pathway burdens. Our primary analysis will use immune (Antigen Presenting Cells, Natural Killer Cells) genetics and CNS-genetics of the susceptibility genetic profiles to predict MRI volumes. Secondary analyses will include additional categories to further differentiate Tcells vs. Bcells vs. monocytes genetics, neuronal vs. oligodendrocyte vs. astrocytes genetics, and innate vs. adaptive immunity. 2c. NFkB pathway. Approximately 20% of MS risk loci encode components of the NFκB-mediated transcriptional activation cascade. We will assess the association between the cumulative NFκB pathway genetic burden and the MRI phenotypes.
Project Number: RG-1707-28775 (131101A)
Name of PD/PI: Henry, Roland
Contracting/Grants Officer: Kostich, Walter
Source of Support: National Multiple Sclerosis Society
Source of Support Address: 733 Third Avenue. New York, NY, 10017
Project/Proposal Start and End Date: (MM/YYYY) (if available): 04/01/2018 – 03/31/2022

Total Award Amount (including Indirect Costs):
Time Commitment (Calendar/Academic/Summer): 0.60 calendar month per year
Overlap: None

Title: SUMMIT: An investigation of deeply phenotyped cohorts to understand disease outcomes and the biology of progression in MS
Major Goals: To leverage richly phenotyped cohorts of individuals with MS to understand MS progression.
Specific Aims:
Year 1 Aim(1) Expand and maintain the SUMMIT cohort. Continue the EPIC and CLIMB existing cohorts (N=500 from each site, all followed for 10Y).Enroll new patients (50 per site):
o18+ y/o
o CIS or MS diagnosis (2010 McDonald Criteria, dd3Y or less)
All imaging on the consistent 3T MRI protocol (add on PSIR C2/3 in new patients)
Aim(2): Create a platform resource for use by other investigators.
Data repository infrastructure with clinical and demographic measures available to community
Governance structure ratification
Aim(3): MRI transfers and processing
Complete the transfer of all brain MRIs to single MRI repository
o Storage of MRIs within UCSF summit cloud
Initiate the processing of all MRIs for NEDA 10Y 1K (1,000 individuals followed for 10+ years) and year 2 aims – 500x3 time points for BWH MRIs
Aim(4): Manuscripts
Initial description of SUMMIT.
o In this manuscript that will be submitted during the first year, we will: provide the rationale for the SUMMIT consortium, describe baseline clinical and demographic features of >500 participants in each of the two cohorts, provide an overview of disease progression, report major genetic associations (including genetic risk score), and perform an initial analysis of "NEDA" in a subset of the two cohorts.
MRI-clinical relationships: a multi-site 5-year study.
o In this manuscript that will be prepared in the first year, we will*:* describe MRIclinical relationships at baseline and over 5 years in 100 participants from each of the two SUMMIT cohorts.
Year 2 Aim(1): Integration of the genetics core.
Make available to the repository:
o The 232 risk alleles and MS genetic risk burden on all individuals with available genetic data.
o PCA principal components analysis quantifying genetic ancestry
SNP genotyping of all participants' samples in both cohorts
Aim(2) Joint MRI processing
Ongoing brain MRI single processing of: whole brain and grey matter atrophy, T2 lesions for NEDA 1K 10Y
Complete the transfer of spine (cervical and thoracic) MRIs to single repository
Aim(3) Manuscript preparation(s)
Similarities and Differences in lesion and atrophy progression across cohorts and relationships with genetic burdens.
Baseline Vitamin D levels and 10-year EDSS progression
NEDA 10Y, 1K (1,000 individuals followed for 10+ years) analysis.

o In this manuscript, we will describe the relationship between 2-year NEDA4 and 10-year outcomes in the two cohorts. We will compare the two cohorts and then combine them, and will examine the demographic and clinical (e.g. type of treatment years 2-10) characteristics that may play a role.
Year 3-5
Upon successful completion of the year 1-2 proposed milestones, the Consortium will work the National MS Society to propose appropriate later-stage milestones and make revisions where necessary.
Project Number: RR 2005-A-13(G-1510-06785) (129090A)
Name of PD/PI: Hauser, Stephen
Contracting/Grants Officer: Bebo, Bruce
Source of Support: National Multiple Sclerosis Society
Source of Support Address: 733 Third Avenue. New York, NY, 10017
Project/Proposal Start and End Date: (MM/YYYY) (if available): 10/01/2016 – 09/30/2021
Total Award Amount (including Indirect Costs):
Time Commitment (Calendar/Academic/Summer): 0.60 calendar month per year
Overlap: None

Title: Multiple manifestations of MS disentangled with a multi-omics approach to inform personalized therapy
Major Goals: There is an urgent need for precision management of MS but also because necessary knowledge, methodologies and vast multi-layer data resources are now available.
Specific Aims: For a true personalized medicine approach within the MS domain and to identify stratified patient population using genetic and non-genetic factors of susceptibility, disease severity and progression, and response to disease modifying therapies (DMTs). Publicly available large scale 'multi-omics' data, in combination with omics data from MS patients, will be utilized to identify biological pathways underlying stratified patient populations.
Project Number: EU733161 (128944A)
Name of PD/PI: Baranzini, Sergio
Contracting/Grants Officer: Kockum, Ingrid
Source of Support: European Union/European Commission
Source of Support Address: Nobels vag 15 A. SE – 17177. Stockholm, Sweden
Project/Proposal Start and End Date: (MM/YYYY) (if available): 01/01/2017 – 01/31/2021
Total Award Amount (including Indirect Costs):
Time Commitment (Calendar/Academic/Summer): 1.65 calendar months per year
Overlap: None

Title: Cervical cord areas for SP12
Major Goals: To design and implement the acquisition of upper cervical cord areas using a phase-sensitive inversion recovery (PSIR) sequence.
Specific Aims: All study subjects will provide written, informed consent through the main study informed consent form (for which we will ask to incorporate UCSF compatible language for the spinal cord MRI). The study is 27 months in duration. During the 6 months expected for recruitment protocol manuals, implementation, and site protocol qualification will be undertaken. Data analyses for longitudinal pipelines and study endpoint is expected to require 3 months post the last acquisition. Thus the study will be a minimum of 3 years in duration.
Project Number: N/A (130341A)

Name of PD/PI: Henry, Roland
Contracting/Grants Officer: Lightfoot, Joshua
Source of Support: MedDay
Source of Support Address: 1 DNA Way, South San Francisco, CA, 94080
Project/Proposal Start and End Date: (MM/YYYY) (if available): 03/14/2017 – 12/31/2020
Total Award Amount (including Indirect Costs):
Time Commitment (Calendar/Academic/Summer): 0.16 calendar month per year
Overlap: None

Title: Central Vein Sign in Multiple Sclerosis
Major Goals: Participate in the Central Vein in Multiple Sclerosis (CAVS-MS) Pilot Study as one of the clinical sites.
Specific Aims: A total of 10 patients will be recruited into the study following the inclusion criteria detailed in the study protocol. After informed consent each subject will undergo an MRI of the brain with and without contrast using the approved sequence for the CAVS-Ms study, clinical interview, standardized neurological examination with documentation of the Expanded Disability Status Scale (EDSS), and Multiple Sclerosis functional Composite (MSFC)MSFC measurements. MRI images will be anonymized and uploaded with a study identifier to a cloud based service (MINT Laboratories). Clinical history, EDSS and MSFC will be entered into a RedCap database. The project will combine the efforts of a clinical neurologist (site-PI) and a research coordinator (RC). In addition site PIs will be asked to participate, or delegate participation of reading anonymized central vein images on the MINT web platform.
Project Number: 951-SUB (130895A)
Name of PD/PI: Henry, Roland
Contracting/Grants Officer: Philip, Alexander
Source of Support: Cleveland Clinic Foundation
Source of Support Address: 9500 Euclid Avenue/JJN5-01. Cleveland, OH 44195
Project/Proposal Start and End Date: (MM/YYYY) (if available): 07/01/2017 – 06/30/2019
Total Award Amount (including Indirect Costs):
Time Commitment (Calendar/Academic/Summer): 0.03 calendar month per year
Overlap: None

Title: Neuronal Determinants of Motor Disability in MS
Major Goals: Develop reliable segmentation of motor neurons at the cortex and axons traversing the brain, brainstem and spinal cord appropriate to MS patients.
Specific Aims:
Specific aim: 1. Development of Quantitative Metrics of Motor Injury in Controls and Multiple Sclerosis
Specific aim: 2. Developed and evaluated reliable tissue based measures of motor neuron function and metabolic markers with MR spectroscopic imaging and functional MRI.
Specific aim: 3. Develop reliable segmentation of motor neurons at the cortex and axons traversing the brain, brainstem and spinal cord appropriate to MS patients.
Project Number: W81XWH-14-1-0493 (124525A)
Name of PD/PI: Henry, Roland
Contracting/Grants Officer: Grenier, Kenneth
Source of Support: DOD US Army Med. Res. Acq. Activity

Source of Support Address: 820 Chandler Drive, Building 843-40. MCMR-AAA-AD Assistance Branch 4. Fort Detrick, MD 21702-5014
Project/Proposal Start and End Date: (MM/YYYY) (if available): 09/30/2014 – 09/29/2018
Total Award Amount (including Indirect Costs):
Time Commitment (Calendar/Academic/Summer): 1.78 calendar month per year
Overlap: None

CURRENT

Title: Frontotemporal DementiaTD: Genes, Images and Emotions
Major Goals: To investigate the early changes in FTLD using imaging, and cognitive and behavioral assessment. Dr. Rosen directs the imaging core for the grant.
Specific Aims: To identify patterns of cognitive dysfunction and structural and functional brain abnormalities that discriminate individuals with fronto-temporal dementia from individuals with late life depression.
Project Number: P01AG019724 (129536E)
Name of PD/PI: Miller, Bruce
Contracting/Grants Officer: Laney, Robin
Source of Support: NIH/National Institute on Aging
Source of Support Address**: 31 Center Drive, MSC 2292, Building 31, Room 5C27. Bethesda,** MD, 20892.
Project/Proposal Start and End Date: (MM/YYYY) (if available): 06/01/2017 – 05/31/2023
Total Award Amount (including Indirect Costs):
Time Commitment (Calendar/Academic/Summer): 0.12 calendar month per year through 2022
Overlap: None

Title: Genentech MN39159 MRI Substudy with UCSF Therapy in People with Multiple Sclerosis
Major Goals: This substudy covers work on 40 to 60 patients at 5 time points in the 4-year Consonance study across 10 to 15 sites. MRI outcomes include new and enlarging lesions of the cervical spinal cord (NEL) and areas of the spinal cord.
Specific Aims: None.
Project Number: SOW#MN39159 (132228A)
Name of PD/PI: Henry, Roland
Contracting/Grants Officer: Revirajan, Nisha & Clayton, David
Source of Support: Genentech, Inc.
Source of Support Address: 7070 Mississauga Road. Mississauga, ON L5N5M8. Canada.
Project/Proposal Start and End Date: (MM/YYYY) (if available): 10/25/2018-10/25/2026
Total Award Amount (including Indirect Costs):
Time Commitment (Calendar/Academic/Summer): 1.68 calendar months per year
Overlap: None.

Title: GN41791 Spinal Cord in GN41791 Ocrevus Trial
Major Goals: To measure upper cervical cord areas using phase-sensitive inversion recovery (PSIR) MRI pulse sequences.

Specific Aims: None.
Project Number: WA40404/ GN41791 (135096A)
Name of PD/PI: Henry, Roland
Contracting/Grants Officer: Powell, Geoff & Huang, Jessica
Source of Support: F. Hoffmann-La Roche Ltd
Source of Support Address: Grenzacherstrasse 124. CH-4070 Basel, Switzerland
Project/Proposal Start and End Date: (MM/YYYY) (if available): 04/01/2020-03/31/2027
Total Award Amount (including Indirect Costs):
Time Commitment (Calendar/Academic/Summer): 0.24 calendar months per year
Overlap: None.

Title: Spinal Cord MRI in Ohand - Henry/Hoffmann-LaRoche WA40404
Major Goals: Cervical spinal cord MRI will be implemented in the ORATORIO-HAND phase 3 RCT.
Specific Aims: (1) Upper Cervical cord area measurements using phase-sensitive inversion recovery (PSIR) MRI pulse sequences; (2) Cervical cord lesion metrics obtained for T2-weighted, Short Time Inversion Recovery (STIR), and inversion prepared gradient echo (MPRAGE, IRSPGR) images.
Project Number: WA40404/ OHAND (135114A)
Name of PD/PI: Henry, Roland
Contracting/Grants Officer: Rizan, Nuha & Robichaud, Andrea
Source of Support: F. Hoffmann-La Roche Ltd
Source of Support Address: Grenzacherstrasse 124. CH-4070 Basel, Switzerland
Project/Proposal Start and End Date: (MM/YYYY) (if available): 04/01/2019-04/01/2026
Total Award Amount (including Indirect Costs):
Time Commitment (Calendar/Academic/Summer): 1.8 calendar months per year
Overlap: None.

Title: Atara Spinal Cord atrophy and Lesion Analysis
Major Goals: Implement spinal cord MRI acquisition and process data for Phase 3 study.
Specific Aims: ATA188-MS-101 study Part 2 subjects (approximately 36) spinal cord MRI. This includes spinal cord atrophy analysis.
Project Number: ATA188-MS-101 (135163A)
Name of PD/PI: Henry, Roland
Contracting/Grants Officer: Rohr, Cherilyn & Galgano, Jessica
Source of Support: Atara Biotherapeutics, Inc.
Source of Support Address: 701 Gateway Blvd Suite 200. South San Francisco, CA 94080
Project/Proposal Start and End Date: (MM/YYYY) (if available):
Total Award Amount (including Indirect Costs):
Time Commitment (Calendar/Academic/Summer): 0.36 calendar months per year
Overlap: None.

Title: An open-label, Multicenter Study to assess disease activity and biomarkers of neuronal damage in minority patients with relapsing multiple sclerosis receiving treatment with ocrelizumab
Major Goals: Investigational New Drug Ocrelizumab (RO4964913) (Ocrevus)
Specific Aims: Assessing spinal cord atrophy in African Americans and Latinx patients with MS.

Project Number: ML42071 (135167A)
Name of PD/PI: Henry, Roland
Contracting/Grants Officer: Bell, Derek
Source of Support: F. Hoffmann-La Roche Ltd
Source of Support Address: Grenzacherstrasse 124. CH-4070 Basel, Switzerland
Project/Proposal Start and End Date: (MM/YYYY) (if available): 06/01/2020-05/31/2025
Total Award Amount (including Indirect Costs):
Time Commitment (Calendar/Academic/Summer): 0.6 calendar months per year
Overlap: None.

Title: GN41851 and GN42272
Major Goals: Cervical spinal cord MRI will be implemented in the GN41851 AND GN42272 phase 3 RCT.
Specific Aims: To measure upper cervical cord areas using phase-sensitive inversion recovery (PSIR) MRI pulse sequences.
Project Number: GN41851 and GN42272 (135580A)
Name of PD/PI: Henry, Roland
Contracting/Grants Officer: Cardeal, Daniela & Huang, Jessica
Source of Support: Genentech, Inc.
Source of Support Address: 1 DNA Way. South San Francisco, CA 94080
Project/Proposal Start and End Date: (MM/YYYY) (if available): 08/15/2020-06/14/2024
Total Award Amount (including Indirect Costs):
Time Commitment (Calendar/Academic/Summer): 1.08 calendar months per year
Overlap: None.

Title: BN42083 (CA-0156709)
Major Goals: Cervical spinal cord MRI will be implemented in the BN42083 phase 3 study.
Specific Aims: To measure upper cervical cord areas using phase-sensitive inversion recovery (PSIR) MRI pulse sequences. PSIR imaging for upper cervical spinal cord areas.
A stack of 3 PSIR images will be acquired centered at the C3 vertebral disk level that spans C2 to C4 vertebral disks. For each image, the total cord area and the grey matter areas will be measured. The angle of the PSIR slice to cord axis will be estimated using the T2W sagittal image. The changes in spinal cord areas (total cord area and grey matter area) over time will be computed. The deliverables (see Table 1) will be (a) total cord areas at each timepoint; (b) cord grey matter areas at each time point; (c) cord white matter area defined as total cord areas minus cord grey matter area; (d) change in total cord areas and grey matter areas over time.
Project Number: BN42083/ CW254125 (135962A)
Name of PD/PI: Henry, Roland
Contracting/Grants Officer: Dyrina, Ksenia
Source of Support: F. Hoffmann-La Roche Ltd
Source of Support Address: Grenzacherstrasse 124, 4070 Basel, Switzerland
Project/Proposal Start and End Date: (MM/YYYY) (if available): 09/14/2020-07/01/2028
Total Award Amount (including Indirect Costs):
Time Commitment (Calendar/Academic/Summer): 1.8 calendar months per year
Overlap: None.

Title: BN42082 (CA-0156706)

Major Goals: Cervical spinal cord MRI will be implemented in the BN42082 phase 3 study.
Specific Aims: To measure upper cervical cord areas using phase-sensitive inversion recovery (PSIR) MRI pulse sequences. PSIR imaging for upper cervical spinal cord areas.
A stack of 3 PSIR images will be acquired centered at the C3 vertebral disk level that spans C2 to C4 vertebral disks. For each image, the total cord area and the grey matter areas will be measured. The angle of the PSIR slice to cord axis will be estimated using the T2W sagittal image. The changes in spinal cord areas (total cord area and grey matter area) over time will be computed. The deliverables (see Table 1) will be (a) total cord areas at each timepoint; (b) cord grey matter areas at each time point; (c) cord white matter area defined as total cord areas minus cord grey matter area; (d) change in total cord areas and grey matter areas over time.
Project Number: BN42082/ CW251083 (135979A)
Name of PD/PI: Henry, Roland
Contracting/Grants Officer: Dyrina, Ksenia
Source of Support: F. Hoffmann-La Roche Ltd
Source of Support Address: Grenzacherstrasse 124, 4070 Basel, Switzerland
Project/Proposal Start and End Date: (MM/YYYY) (if available): 06/01/2020-05/31/2027
Total Award Amount (including Indirect Costs):
Time Commitment (Calendar/Academic/Summer): 06/01/2020-05/31/2027
Overlap: None.

Title: Consonance2 - MN39159
Major Goals: Multiple PSIR images and cervical cord in Consonance part 2 (from current MN39159). This study covers 63 substudy subject, 300 new phase at 6 timepoints in 5 year.
Specific Aims: To measure upper cervical cord areas using phase-sensitive inversion recovery (PSIR) MRI pulse sequences. PSIR imaging for upper cervical spinal cord areas.
A stack of 3 PSIR images will be acquired centered at the C3 vertebral disk level that spans C2 to C4 vertebral disks. For each image, the total cord area and the grey matter areas will be measured. The angle of the PSIR slice to cord axis will be estimated using the T2W sagittal image. The changes in spinal cord areas (total cord area and grey matter area) over time will be computed. The deliverables (see Table 1) will be (a) total cord areas at each timepoint; (b) cord grey matter areas at each time point; (c) cord white matter area defined as total cord areas minus cord grey matter area; (d) change in total cord areas and grey matter areas over time.
Project Number: BN42082 (136973A)
Name of PD/PI: Henry, Roland
Contracting/Grants Officer: Gadeyne, Valerie
Source of Support: F. Hoffmann-La Roche Ltd
Source of Support Address: Grenzacherstrasse 124, 4070 Basel, Switzerland
Project/Proposal Start and End Date: (MM/YYYY) (if available): 02/08/2021-10/01/2026
Total Award Amount (including Indirect Costs):
Time Commitment (Calendar/Academic/Summer): 1.2 calendar months per year
Overlap: None.

Title: A randomized controlled trial of N-acetyl cysteine as a neuroprotective agent in progressive MS
Major Goals: To evaluate the safety, tolerability and effect of NAC on progression of brain, thalamic and cervical cord atrophy. Secondary objectives: The main secondary objective is to evaluate if NAC slows down progression of disability. Additional secondary objectives are to

determine if NAC slows down progression on additional imaging metrics and changes captured by a wearable multi-sensor device.
Specific Aims:
Aim 1: To determine whether NAC decreases progression of brain, thalamic and cervical cord atrophy vs.
placebo. Hypothesis: Treatment with NAC has been shown to be safe in various neurological disorders but
it is unknown if it has a benefit in MS. We hypothesize that reducing oxidative stress injury in progressive MS will lessen progression of brain, thalamic and cervical cord atrophy.
Aim 2: To determine whether NAC decreases progression of disability on 9-hole peg test, 25-foot walk and Single Digit Modalities Test vs. placebo. Hypothesis: Treatment with NAC may have neuroprotective properties but its clinical effect in MS is unknown. We hypothesize that targeting oxidative stress injury in progressive MS will lessen clinical worsening.
Exploratory aim 3: To determine whether NAC decreases disease progression measured by a wearable multisensory and algorithm sensitive to single limb disability progression vs. placebo. Hypothesis: Progressive MS trials are limited by the lack of outcome measures that are sensitive to short-term disease progression. Wearable devices may offer new alternatives to capture treatment benefit, especially in progressive MS. We hypothesize that the use of a multi-sensor wearable device will capture differences by treatment group in scores of limb progression.
Project Number: W81XWH2110406 (137745A)
Name of PD/PI: Waubant, Emmanuelle
Contracting/Grants Officer: Lopez, Nathleen
Source of Support: DOD US Army Med. Res. Acq. Activity
Source of Support Address: 820 Chandler Street. Fort Detrick, MD 21702-5014
Project/Proposal Start and End Date: (MM/YYYY) (if available): 09/01/2021-08/31/2025
Total Award Amount (including Indirect Costs):
Time Commitment (Calendar/Academic/Summer): 0.96 calendar months per year
Overlap: None.

Title: UTE MRI: a Novel Biomarker for Remyelination in Multiple Sclerosis Patients
Major Goals: To evaluate Ultashort echo time MRI as a bio marker of Remyelination
Specific Aims: Implement and acquire UTE MRI in patients with MS undergoing treatment to promote remyelination.
Project Number: W81XWH-21-1-0399 (137540A)
Name of PD/PI: Larson, Peder
Contracting/Grants Officer: Hinson, Linda
Source of Support: DOD US Army Med. Res. Acq. Activity
Source of Support Address: 820 Chandler Street. Fort Detrick, MD 21702-5014
Project/Proposal Start and End Date: (MM/YYYY) (if available): 08/01/2021-07/31/2024
Total Award Amount (including Indirect Costs):
Time Commitment (Calendar/Academic/Summer): 0.6 calendar months per year
Overlap: None.

Title: CELLO (protocol ML42790)
Major Goals: MRI in RIS patients treated with Ocrevus.
Specific Aims: Spinal cord atrophy and lesion changes in RIS patients treated with Ocrevus.
Project Number: ML42790 (138858A)

Name of PD/PI: Henry, Roland
Contracting/Grants Officer: Mastracchio, Joseph & Cadena, Lynn
Source of Support: Yale University
Source of Support Address: 150 Munson Street, 5th Floor. New Haven, CT 06511
Project/Proposal Start and End Date: (MM/YYYY) (if available): 02/01/2022-01/31/2028
Total Award Amount (including Indirect Costs):
Time Commitment (Calendar/Academic/Summer): 0.24 calendar months per year
Overlap: None.

PENDING

Title: Assessment of myelin content and tissue microstructure in multiple sclerosis: a repeated MRI study
Major Goals: Multicenter feasibility of MRI techniques sensitive to myelin.
Specific Aims: MRI Measures of myelin in MS patients across multiple centers to determine feasibility for clinical trials.
Project Number: P0563941
Name of PD/PI: Henry, Roland
Contracting/Grants Officer: Magon, Stefano
Source of Support: F. Hoffmann-La Roche Ltd
Source of Support Address: 340 Kingsland Street, Nutley, NJ 07110-1199
Project/Proposal Start and End Date: (MM/YYYY) (if available): 09/01/2022-08/28/2027
Total Award Amount (including Indirect Costs):
Time Commitment (Calendar/Academic/Summer): 0.9 calendar months per year
Overlap: None.

IN-KIND

None

I, PD/PI or other senior/key personnel, certify that the statements herein are true, complete and accurate to the best of my knowledge, agree to update such disclosure at the request of the agency prior to the award of support and at any subsequent time the agency determines appropriate during the term of the award and accept the obligation to comply with Section 223(a) of the William M. (Mac) Thornberry National Defense Authorization Act for Fiscal Year 2021. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties.

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Date: 8/31/2022

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