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TITLE: Role of Microglial Activation and Norepinephrine Transporter Abnormalities in Pathogenesis of MS-Related Fatigue

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CONTRACTING ORGANIZATION: Brigham and Women's Hospital, Boston, MA

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13. SUPPLEMENTARY NOTES

14. ABSTRACT This proposal addresses the **Biology and Measurement of MS symptoms** focus area of FY18 MSRP Exploration – Hypothesis Development Award. The **overarching aim** of this proposal is to assess the role of microglial activation and norepinephrine transporter binding in pathogenesis of **MS-related fatigue**, using novel Positron Emission Tomography (PET) radiotracers. [F-18]PBR06 and [C-11]MRB.
The major developments in the progress of this project have been the following:
1. We received permission to resume recruitment of subjects on July 15, 2020.
2. We are pleased to report that we have recruited and obtained informed consent from 10 eligible subjects already (>80% of the target sample size). 3 of these subjects have completed all the study related procedures (25% of the target sample size).
Based on our preliminary data about the role of neuroinflammation in pathogenesis of MS-related fatigue, we had a manuscript published in the journal "Neurology: Neuroimmunology & Neuroinflammation" in September, 2020. The title of the manuscript is "T Singhal, S Cicero, H Pan, K Carter, S Dubey, R Chu, B Glanz, S Hurwitz, S Tauhid, Mi-Ae Park, M Kijewski, E Stern, R Bakshi, D Silbersweig, and HL Weiner. ***Regional Microglial Activation in Substantia Nigra is linked with Fatigue in Multiple Sclerosis.***" (PMID 32769103)

15. SUBJECT TERMS
U.S. Food and Drug Administration (FDA), Institutional review Board (IRB), Investigational new Drug (IND), multiple sclerosis, fatigue, Positron Emission Tomography (PET)

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1. INTRODUCTION:

This proposal addresses the Biology and Measurement of MS symptoms focus area of FY18 MSRP Exploration – Hypothesis Development Award. The overarching aim of this proposal is to assess the role of microglial activation and norepinephrine transporter binding in pathogenesis of MS-related fatigue, using novel Positron Emission Tomography (PET) radiotracers. [F-18]PBR06 and [C-11]MRB.

2. KEYWORDS:

U.S. Food and Drug Administration (FDA), Institutional review Board (IRB), Investigational new Drug (IND), multiple sclerosis, fatigue, Positron Emission Tomography (PET)

3. ACCOMPLISHMENTS:

What were the major goals of the project?

Specific Aim 1: To determine the relationship of cerebral microglial activation, as assessed by [F-18]PBR06 PET, with MS-related fatigue. The hypothesis is that there is a positive correlation between microglial activation with fatigue in MS. We further hypothesize that cognitive and physical aspects of fatigue are mediated by microglial activation in cortical and subcortical grey matter regions, respectively. We'll also perform an exploratory analysis on correlation of [F-18]PBR06 PET and fatigue with serum measurements of IL-1β, TNF-α, IL-6, MCP-1 and MIF-1.
Specific Aim 2: To determine the relationship of norepinephrine transporter (NET) binding, as assessed by [C-11]MRB PET, with MS-related fatigue. The hypothesis is that there is an inverse correlation between NET binding with fatigue in MS. We'll also perform an exploratory analysis on correlation of [C-11]MRB PET and fatigue with measurements of serum norepinephrine.
Specific Aim 3: To determine the relationship of microglial activation and NET binding, with grey matter pathology (lesion load and brain atrophy) assessed using 7T MRI, and evaluate their independent contribution in development of MS-related fatigue. The hypothesis is that microglial activation and NET binding demonstrate positive and inverse correlations respectively, with grey matter pathology (lesion load and atrophy) and are independent predictors of MS-related fatigue.

What was accomplished under these goals?

The major developments in the progress of this project have been the following:
Q1 – 1. Institutional Review Board (IRB) application has been submitted and reviewed. IRB has a major suggestion that that an investigational new drug (IND) application for the novel positron emission tomography (PET) ligand [C-11]MRB (also known as [C-11]MeNer) should be submitted to U.S. Food and Drug Administration (FDA)
2. A U.S. Food and Drug Administration (FDA) investigational new drug (IND) application for the novel positron emission tomography (PET) ligand [C-11]MRB (also known as [C-11]MeNer) was submitted on December 13, 2019.
Q2 – 1. U.S. Food and Drug Administration (FDA) approved the investigational new drug (IND) application for the novel positron emission tomography (PET) ligand [C-11]MRB (also known as [C-11]MeNer) and released the "Study May Proceed" notice for the study on January 6, 2020.
2. Institutional Review Board (IRB) approval was obtained on March 12, 2020.
Q3 – 1. Subject recruitment was placed on hold in mid-March, earlier this year (immediately after we obtained the IRB approval), by our institution (in accordance with local and State government guidelines and advisories) due to the SARS-CoV-2 pandemic situation.
2. We received permission to resume recruitment of subjects on July 15, 2020.
Q4 – 1. We received permission to resume recruitment of subjects on July 15, 2020.
2. We are pleased to report that we have recruited and obtained informed consent from 10 eligible subjects already (>80% of the target sample size). 3 of these subjects have completed all the study related procedures (25% of the target sample size).

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?

We aim to complete recruitment of all 12 subjects and complete the scanning procedures in all subjects. We also aim to begin data analysis.

4. **IMPACT:**

What was the impact on the development of the principal discipline(s) of the project?

Nothing to Report.

What was the impact on other disciplines?

Nothing to Report.

What was the impact on technology transfer?

Nothing to Report.

What was the impact on society beyond science and technology?

Nothing to Report.

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

Nothing to report

Describe problems or delays encountered during the reporting period and actions or plans to resolve them.

Patients recruitment was placed on hold in mid-March by our institution (in accordance with local and State government guidelines and advisories) due to the SARS-CoV-2 pandemic situation. Recruitment was resumed after we got permission from our institution on July 15, 2020. We anticipate that there may be some slowing of study procedures in the winter months due to anticipated potential worsening of pandemic. However, we are diligently continuing our study procedures and patient recruitment for as long as permitted by our parent institution.

Changes that had a significant impact on expenditures

Nothing to Report.

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

Significant changes in use or care of human subjects

Nothing to report.

Significant changes in use or care of vertebrate animals

Nothing to Report.

Significant changes in use of biohazards and/or select agents

Nothing to report.

6. PRODUCTS:

- **Publications, conference papers, and presentations**

Journal publications.

We had a manuscript, "Tarun Singhal, Steven Cicero, Hong Pan, Kelsey Carter, Shipra Dubey, Renxin Chu, Bonnie Glanz, Shelley Hurwitz, Shahamat Tauhid, Mi-Ae Park, Marie Kijewski, Emily Stern, Rohit Bakshi, David Silbersweig, and Howard L Weiner. ***Regional Microglial Activation in Substantia Nigra is linked with Fatigue in Multiple Sclerosis***." published in the journal "Neurology: Neuroimmunology & Neuroinflammation" in September 2020.

Books or other non-periodical, one-time publications.

Nothing to report.

Other publications, conference papers and presentations.

Nothing to report.

- **Website(s) or other Internet site(s)**

Nothing to report.

- **Technologies or techniques**

Nothing to report.

- **Inventions, patent applications, and/or licenses**

Nothing to report.

- **Other Products**

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Unchanged Personnel	Status
Tarun Singhal, MD	No change
Rohit Bakshi, MD	No change
Marie Kijewski, DSc	No change
Removed Personnel	
Steven Cicero	Working per diem and has been replaced by John Ficke as noted below.
Added Personnel	
Name:	John Ficke
Project Role:	Research Assistant
Researcher Identifier (e.g. ORCID ID):	N/A
Nearest person month worked:	1.2 Calendar Months
Contribution to Project:	John assists PI in execution of the study, recruitment of subjects, preparation and submission of regulatory documents, data analysis , data management and manuscript preparation .
Funding Support:	None

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Dr. Singhal has been awarded the following grant since the start of this project which Dr. Bakshi is also a Co-Investigator on:
Research Collaboration (PI Singhal) 06/23/20 - 06/22/25
Novartis Corp.
Open-label, single-blinded, observational, prospective, 9-month study to assess the efficacy of Ofatumumab on microglia in patients with relapsing forms of multiple sclerosis
The *primary* objective of this study is the assessment of the effect of ofatumumab over 9 months on the evolution of microglia pathology in patients with relapsing MS. The *secondary* objectives include the following assessments over 9 months: (a) To determine the time course of effect of Ofatumumab on microglial activation and its relationship with peripheral B-cell depletion, serum neurofilament light chain and glial-fibrillary acid protein levels and other serum biomarkers (IP-10, ITAC, MCP-1 and MIP-3b). (b) To determine the relationship of PET changes following Ofatumumab initiation with 3T MRI changes and clinical parameters.

Dr. Bakshi was awarded the following grant:
RPC1063-MS-13914 (PI Bakshi) 03/10/20 – 03/09/25
Celgene Corporation
CTA: Cortical and meningeal involvement in multiple sclerosis: A 7T MRI study
This is an observational study following MS patients for one year to assess the relationship among cortical lesions, cortical atrophy, and meningeal enhancement using 7T MRI. We will also link these to physical disability and cognition.

Dr. Kijewski has begun working on the following project since the last reporting period:
R01HL150342 (PI Dorbala) 03/01/20 - 01/31/24
NIH
Early Detection of Transthyretin Cardiac Amyloidosis: Defining a Novel Target for HFpEF Treatment and Prevention in Late Life
We plan to identify transthyretin cardiac amyloidosis (ATTR-CA) in late-life by 99mTechnetium pyrophosphate (Tc-99m- PYP) scan in the ARIC longitudinal study cohort (NIH funded longitudinal cohort since 1989) and leverage the rich 30-year longitudinal data from ARIC to compare detailed antecedent alterations in symptoms, cardiac structure and function, cardiac biomarkers, and proteomics, in participants with and without ATTR-CA diagnosed by Tc-99m PYP imaging. The natural history and pathogenesis of age related ATTR-CA defined in this study, we expect, will transform the management of ATTR-CA.

The following project that Dr. Kijewski is on was extended by one year:
R01HL130563 (PI Dorbala) 04/01/16 - 03/31/21
NIH
Molecular Imaging of Primary Amyloid Cardiomyopathy
The major goals of the project are to evaluate myocardial 18F-florbetapir retention as a biomarker for aggressiveness of AL-CMP; and to evaluate if effective chemotherapy will improve systemic oxidative stress, myocardial oxidative metabolism, microvascular function and contractile function, prior to an improvement in myocardial amyloid content.

What other organizations were involved as partners?

Nothing to report.

8. **SPECIAL REPORTING REQUIREMENTS**
   COLLABORATIVE AWARDS:
   QUAD CHARTS:

9. **APPENDICES:**