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TITLE: Imaging of Glial Activation and Risk for Post-Traumatic Epilepsy

PRINCIPAL INVESTIGATOR: Ryan Martin, MD

CONTRACTING ORGANIZATION: University of California, Davis

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None

14. ABSTRACT

The development of post-traumatic epilepsy (PTE) is associated with significant disability. Despite our keen awareness of this significant public health issue, little is known regarding the biological mechanism leading to PTE. One plausible mechanism is that unchecked neuroinflammation, a process that occurs in animal and human models of both traumatic brain injury (TBI) and epilepsy, leads to altered synaptic transmission and neuronal excitability. Positron emission tomography (PET) can be used to measure the degree of *in vivo* neuroinflammation in the central nervous system through radiotracer binding of the translocator protein (TSPO), which co-localizes to neuro-inflammatory cells. Currently, no pre-clinical or clinical study has analyzed the relationship between neuroinflammation, as measured by TSPO PET, and the risk for developing PTE. **We hypothesize that persistent neuroinflammation following moderate-to severe TBI will be associated with an increased risk for developing PTE, and with this current proposal, set out to discover a mechanistic link between persistent trauma-induced glial activation and epilepsy.** To investigate this hypothesis, we are enrolling patients with moderate-to-severe TBI to undergo two TSPO PET scans at 2 weeks and 2 months following injury to determine the degree of *in vivo* neuroinflammation and its relationship with the risk for PTE. These patients will be followed longitudinally for up to one -year with regular assessments for the develop of PTE and assessment for cognitive outcome.

15. SUBJECT TERMS					
Post-traumatic epilepsy, traumatic brain injury, PET, neuroinflammation, TSPO, TBI, microglia					
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1. Introduction

The development of post-traumatic epilepsy (PTE) is associated with significant disability. Despite our keen awareness of this significant public health issue, little is known regarding the biological mechanism leading to PTE. One plausible mechanism is that unchecked neuroinflammation, a process that occurs in animal and human models of both traumatic brain injury (TBI) and epilepsy, leads to altered synaptic transmission and neuronal excitability. Positron emission tomography (PET) can be used to measure the degree of *in vivo* neuroinflammation in the central nervous system through radiotracer binding of the translocator protein (TSPO), which co-localizes to neuro-inflammatory cells. Currently, no pre-clinical or clinical study has analyzed the relationship between neuroinflammation, as measured by TSPO PET, and the risk for developing PTE. **We hypothesize that persistent neuroinflammation following moderate-to severe TBI will be associated with an increased risk for developing PTE, and with this current proposal, set out to discover a mechanistic link between persistent trauma-induced glial activation and epilepsy.** To investigate this hypothesis, we are enrolling patients with moderate-to-severe TBI to undergo two TSPO PET scans at 2 weeks and 2 months following injury to determine the degree of *in vivo* neuroinflammation and its relationship with the risk for PTE. These patients will be followed longitudinally for up to one -year with regular assessments for the develop of PTE and assessment for cognitive outcome.

2. Keywords

Post-traumatic epilepsy
traumatic brain injury
TBI
PET
Neuroinflammation
TSPO
Microglial

3. Accomplishments

a. What are the major goals of the project?

Major tasks for the first quarter are listed below. Included is an update on the status of each task

	Timeline	**Site 1**
Major Task 1: To identify and enroll patients with moderate and severe TBI into the research project	Months	Status
Subtask 1: Finalize IRB protocol and consent form; this process will commence before receiving the award and will be completed prior to or shortly after receiving the award	1	UC Davis IRB Approval was obtained on 10/24/2019 Final HRPO approval was obtained on 01/30/2020
Subtask 2: Complete IRB approval process	1	Final HRPO approval was obtained on 01/30/2020
Subtask 3: Identify and enroll participants into the study	2-24	Initially open to Enrollment on 2/1/2020; suspension of enrollment since 3/19/20 secondary to COVID-19
Subtask 3: Complete longitudinal follow-up for patient outcomes and diagnosis of post-traumatic epilepsy	5-36	Not applicable as no patients enrolled yet
Major Task 2: To image subjects longitudinally with TSPO PET		
Subtask 1: Obtain Investigational New Drug approval from	1	IND 145061 for DPA-714 was obtained

the FDA for the DPA-714 radioligand; this process has already commenced and will be completed prior to or shortly after receiving the award		from the FDA on 08/30/2019
Subtask 2: Identify whether patients have appropriate genotype for TSPO PET imaging with ^{18}F-DPA-714	2-24	Initially open to Enrollment on 2/1/2020; suspension of enrollment since 3/19/20 secondary to COVID-19
Subtask 3: Acquire MRI scans	2-24	Initially open to Enrollment on 2/1/2020; suspension of enrollment since 3/19/20 secondary to COVID-19
Subtask 4: Acquire baseline and follow-up TSPO PET scans	2-26	Initially open to Enrollment on 2/1/2020; suspension of enrollment since 3/19/20 secondary to COVID-19
Subtask 5: Register MRI and PET scans, define regions of interest and quantify TSPO binding	2-36	Initially open to Enrollment on 2/1/2020; suspension of enrollment since 3/19/20 secondary to COVID-19
Major Task 3: Statistical Analysis		
Subtask 1: Determine the relationship between TSPO binding in peri-contusional brain, thalamus, and hippocampus and incidence of early seizures, epileptiform discharges and PTE using logistic regression and survival analysis techniques	33-36	Not applicable
Subtask 2: Determine the relationship between TSPO binding and functional outcomes using repeated measures, random effects models	33-36	Not applicable
Subtask 3: Determine the relationship between TSPO binding and identified serum biomarkers from the EpiBios4Rx study	33-36	Not applicable
Milestone: Submit abstract or paper for presentation or publication	36	Not applicable

b. What was accomplished under these goals?

Progress was made over the first 6 months of the study, having obtained the necessary IND (145061) for the radiotracer used in the study on 08/30/2019. Institutional IRB approval was obtained on 10/24/2019, followed by final HRPO approval on 01/30/2020. All research personal are trained and all research processes are in place to begin enrolling patients.

In addition, I have met with the FITBIR liaison (Rakib Zaman) twice. The first session was on 10/1/2019 as an introduction to FITBIR. I then met with Evan McCreedy and Rakib Zaman on 3/18/2020 to discuss requirements with regards to uploading imaging studies. I plan to meet with them again after several PET studies are performed to troubleshoot any difficulties with uploading the images to FITBIR.

c. What opportunities for training and professional development has the project provided?

I have learned a significant amount regarding grant fund management, the IRB process, and interactions with the funding agency. It has also been an invaluable process to better understand the research process, organizing and leading a diverse collection of individuals and

implementing a plan. I have also worked through several delays, including the delays in the initial HRPO approval, as well as suspension in enrollment secondary to the COVID-19 pandemic.

d. How were the results disseminated to communities of interest?

Nothing to Report

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

The suspension of patient enrollment by the University of California, Davis was lifted on 7/14/2020. We were the able to obtain approval from the Nuclear Medicine Department at UC Davis to resume research activity on 07/30/2020. As of 08/01/2020, we are now actively enrolling and anticipate enrolling the first patient shortly. The goals over the next quarter include enrolling the first several patients into the study.

4. Impact

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

Nothing to Report

b. What was the impact on other disciplines?

Nothing to Report

c. What was the impact on technology transfer?

Nothing to Report

d. What was the impact on society beyond science and technology?

Nothing to Report

5. Changes/Problems

a. Changes in approach and reason for change?

Nothing to Report

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

Final HRPO approval was not obtained until 01/30/2020. In addition, subject enrollment was suspended on 3/19/2020 secondary to the COVID-19 pandemic. This suspension was lifted by the University of California, Davis on 7/14/2020. We were the able to obtain approval from the Nuclear Medicine Department at UC Davis to resume research activity using the institutional PET scanner on 07/30/2020. As of now, we are open for enrollment. Given the delay in obtaining HRPO approval and the subsequent enrollment suspension secondary to COVID-19, we anticipate needing a 12-month no-cost extension.

c. Changes that has significant impact on expenditures

Nothing to Report

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

Nothing to Report

6. Products

Nothing to Report

7. Participants & Other Collaborating Organizations

a. What individuals have worked on the project?

Name: Ryan Martin, MD
Project Role: PI
ORCID ID: https://orcid.org/0000-0003-2765-2845
Nearest Person Month Work: 0.5
Contribution to Project: I have completed all tasks necessary to obtain the IND, IRB and HRPO approval, and the necessary steps to re-initiate active enrollment after the COVID-19 suspension of research activities.

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

Nothing to Report

c. What organizations are involved as partners?

Organizational Name: Optimal Tracers
Location of Organization: Sacramento, CA, USA
Contribution to the Project: As the radiotracer manufacturer for the project, Optimal tracers developed the CMC and QA portions of the IND application. They have also completed all the analytical qualifications and a test run to verify that all the materials and equipment are in right condition.

8. Special Reporting Requirements

Please see attached Quad Chart

9. Appendices

Nothing to Report