SUMMARY STATEMENT

PROGRAM CONTACT:
Dr. Margaret Grabb
301-443-3563
mgrabb@mail.nih.gov

(Privileged Communication)

Release Date: **12/13/2018**
Revised Date:

Application Number: **1 R43 MH119880-01**

Principal Investigator

COLLINS, MICHAEL

Applicant Organization: OPEN SOURCE INSTRUMENTS, INC.

Review Group: **ZRG1 ETTN-C (10)**
Center for Scientific Review Special Emphasis Panel
Small Business: Clinical Neurophysiology, Devices, Neuroprosthetics, and Biosensors

Meeting Date: **11/29/2018**
Council: **JAN 2019**
Requested Start: **04/01/2019**

RFA/PA: **PA18-871**
PCC: **7T-SB**
Dual PCC: **FERTISTR**
Dual IC(s): **NS**

Project Title: **An optogenetic brain implant with EEG monitoring and response for mice**

SRG Action: **++**
Next Steps: **Visit https://grants.nih.gov/grants/next_steps.htm**
Human Subjects: **10-No human subjects involved**
Animal Subjects: **30-Vertebrate animals involved - no SRG concerns noted**

Project Year	Direct Costs Requested
1	206,469
TOTAL	206,469

++NOTE TO APPLICANT: Members of the Scientific Review Group (SRG) were asked to identify those applications with the highest scientific merit, generally the top half. Written comments, criterion scores, and preliminary impact scores were submitted by the assigned reviewers prior to the SRG meeting. At the meeting, the more meritorious applications were discussed and given final impact scores; by concurrence of the full SRG, the remaining applications, including this application, were not discussed or scored. The reviewers' comments (largely unedited by NIH staff) and criterion scores for this application are provided below. Because applications deemed by the SRG to have the highest scientific merit generally are considered for funding first, it is highly unlikely that an application with an ND recommendation will be funded. Each applicant should read the written critiques carefully and, if there are questions about the review or future options for the project, discuss them with the Program Contact listed above.

1R43MH119880-01 COLLINS, MICHAEL

DESCRIPTION (provided by applicant): Optogenetics can be used to selectively stimulate or suppress the firing of genetically targeted and spatially targeted mammalian neurons. It is used to study neuropsychiatric diseases in vivo with mouse models of conditions including epilepsy, schizophrenia, and Parkinson's. Optogenetics may be used as functional neurosurgical intervention for correcting disease states in the brain. It has been previously shown that seizures have the ability to be halted or reduced by optogenetic activation of inhibitory neurons with the use of Channelrhodopsin-2. It has also been shown that expressing Halorhodopsin (HR) in cortical pyramidal neurons can also reduce seizure propagation. By monitoring EEG data in real time, seizures can be identified at their onset and correcting pulses of optogenetic stimulation may be applied. This line of research is currently limited by the lack of suitable instruments. This project proposes the development of a fully implantable, wireless EEG monitor capable of autonomously detecting EEG events in real-time and applying correcting pulses of closed-loop optogenetic stimulation. The proposed instrument will be compatible with mouse biology, thus permitting chronic experiments in the enormous pool of transgenic mouse strains available with photosensitive proteins and validated as models of human disease. Aim 1 will develop the necessary hardware by combining core technologies demonstrated in existing products. Aim 2 will enable autonomous EEG event detection in the instrument's micropower logic chip by adapting a computationally efficient algorithm that has been proven capable of classifying EEG events including normal activity, seizures, ictal spikes, inter-ictal spikes, and polyspikes. Aim 3 will test the device's ability to detect seizures, apply correcting optogenetic stimulation, and reduce the duration of focal seizures induced in mice by the nanoinjection of iron chloride. Phase I of this project will make the mouse-compatible instrument available for sale to researchers studying circuit theory of the brain and diseases/disorders characterized by aberrant EEG states such as epilepsy, schizophrenia, Alzheimer's, and obsessive compulsive disorder. Potential follow-on Phase II would develop the technology into a medical instrument that aborts focal seizures in humans who suffer from pharmaceutical-resistant partial epilepsy (approximately 15 million people).

PUBLIC HEALTH RELEVANCE: A wireless instrument capable of simultaneous EEG recording and optogenetic stimulation in mice will enable a new class of experiments of epilepsy, schizophrenia, Alzheimer's, obsessive compulsive disorder, and other conditions characterized by aberrant electrophysiology. In addition to aiding basic research and the identification of pharmacological treatments, the instrument will enable a new class of functional neurosurgical intervention. The instrument will demonstrate a new treatment of focal seizures in patients suffering from pharmaceutical-resistant partial epilepsy.

CRITIQUE 1

Significance: 3
Investigator(s): 2
Innovation: 2
Approach: 4
Environment: 3

Overall Impact: Open Source Instruments Inc propose to develop a neural interface capable of detecting EEG events and applying corrective optogenetic stimulation in real-time. The proposed instrument targets investigators employing mouse models to study mental disease states providing entry to a potentially large market. Aim 1 exploits the company’s core technologies to develop the hardware. Aim 2 will implement autonomous EEG event detection in the instrument’s micropower logic chip. Aim 3 seeks to test the device’s ability to detect seizures and apply corrective optogenetic

stimulation in a mouse model of epilepsy. The company was founded in 2004 and its telemetry products have been profitable since 2009.

1. Significance:

Strengths

- The need for interfaces that can read neural activity, interpret it and trigger stimulation has scientific merit thus this proposal has a solid scientific premise
- Some very strong letters of support for the proposed product development are included with the application.
- The projected price of units ($350 & $700) and of a system ($12.5k) seems very reasonable, making the product attractive.
- The goal of greater than one week of data recording and periodic optogenetic stimulation or less hours of recording per day over more days should meet many investigators needs

Weaknesses

- Motivation for the design was clearly informed by the needs of researchers in the field of epilepsy. It was not made sufficiently clear how wide is the investigator need for a device that couples EEG signals with optogenetic stimulation. More evidence of a wide market need would have made for a stronger proposal.

2. Investigator(s):

Strengths

- The company was founded in 2004 and its telemetry products have been profitable since 2009, so there is no reason to question the competence of the investigators for the work proposed.

Weaknesses

- Animal testing is proposed to take place at Professor Nishimura and Schaffer's laboratories at Cornell University. No biosketch was provided for Professor Nishimura and Professor Schaffer does not seem to have much experience with epilepsy research. He refers to a paper in press in Cerebral Cortex where a rodent seizure model has been developed – one intended to be used for the work contained in this proposal – although he is not a co-author on the paper. Professor Nishimura is and the relationship between the two laboratories seems extremely close. More clarification in this area would have tightened the proposal somewhat.

3. Innovation:

Strengths

- A device that combines EEG recording with autonomous event detection to trigger optogenetic stimulation of targeted neural populations in mice would be a novel product.

Weaknesses

- While the application of the device to studies of epilepsy is clear, whether such a product would find more general application was not well described.

4. Approach:

Strengths

- The three aims complement one another well and, if completed successfully, will provide evidence supporting the device's potential as a new research tool.
- Table 1 which compares their proposed device to competitors was useful and demonstrated significant advantages of the proposed new technology.

Weaknesses

- Aim 2 is focused on embedded software that will detect seizure-related EEG events. Evidence that other embedded software (e.g., to detect different sleep states) might offer a wider potential market. Consideration of other potential uses for the core technology would have made for a stronger proposal.
- Some discussion of the limitations resulting from restricting neural signals to EEG alone should have been included.
- Exactly what is expected from the animal experiments could have been described better. The number of mice and their genders needed for a reliable result was not detailed.

5. Environment:

Strengths

- The facilities at Open Source Instruments and their record of successful product development promote high confidence that the environment is well suited to the work proposed.

Weaknesses

- The incomplete description of the relationship between the Nishimura and Schaffer laboratories at Cornell University and the apparent minimal experience in epilepsy research by these investigators weakens one's feeling about the suitability of the environment for the work proposed marginally.

Vertebrate Animals:

YES, all criteria addressed

- No consideration of gender is made but with an N=3 this would be impossible

Biohazards:

Not Applicable

CRITIQUE 2

Significance: 4
Investigator(s): 4
Innovation: 3
Approach: 6
Environment: 3

Overall Impact: This Phase 1 SBIR project proposes the development of an implantable, wireless, mouse-sized device for detecting EEG events and applying optogenetic stimulation. The EEG monitor will be capable to detect and classify a variety of epileptiform activity. The device would be suitable for long-term mouse studies. If successful, this work would make the mouse-compatible instrument available for sale to researchers studying neurological disorders. Lack of details on the computationally efficient EEG event classification algorithm and its performance metrics has diminished the enthusiasm for the project. As a result, the proposal, as described in this application, was expected to have a medium impact.

1. Significance:

Strengths

- The proposed miniaturization would result in unique technology for combined optogenetics and EEG in freely behaving mice.
- The long-term objective is to develop a closed-loop device to detect and abort seizures.

Weaknesses

- Porting existing technology for mouse models is not that significant.

2. Investigator(s):

Strengths

- The PI has experience in optical fiber technology,

Weaknesses

- The PI does not appear to have significant prior education or experience in EEG analysis.

3. Innovation:

Strengths

- Miniaturized device for combined EEG analysis and optogenetic stimulation in mice is novel.

Weaknesses

- The proposed product is a miniaturization of an existing rat model.
- Automatic seizure detection is not new and has been around for several decades.

4. Approach:

Strengths

- The proposed set of aims are well described.
- The device will be based on technology previously developed by the team.

Weaknesses

- Lack of details on the computationally efficient EEG event classification algorithm and its performance metrics such as specificity, sensitivity and false alarm rate.
- Early seizure onset detection is a challenging task. It is not clear if the investigators already have the algorithm. No specifics are given on how seizure onset is detected.
- It would be beneficial for the application to compare the anticipated device with existing close-loop devices such as responsive neurostimulator developed by NeuroPace.

5. Environment:

Strengths

- Open Source Instruments and Cornell University facilities appear to be adequate.

Weaknesses

- None noted.

Vertebrate Animals:

YES, all criteria addressed

- Animal studies will be conducted at Cornell University

Biohazards:

Not Applicable (No Biohazards)

Authentication of Key Biological and/or Chemical Resources:

Not Applicable (No Relevant Resources)

Budget and Period of Support:

Recommend as Requested

CRITIQUE 3

Significance: 5
Investigator(s): 5
Innovation: 5
Approach: 1
Environment: 1

Overall Impact: This is a phase I SBIR submission. In this work, the development of an optogenetic brain implant that also includes EEG monitoring system for the mice is going to be fabricated. The proposed device would be a combination of existing technologies that are currently being used. The size of the proof-of-concept device is very large. Although it's been proposed that there's a need for mouse size device, the new size and design aspects of the device has not been discussed. The proposed device is a combination of existing technologies and also other research groups have already proposed on the development and modifications of it. The significance of this application for the fabrications of the device might be below average.

1. Significance:

Strengths

Weaknesses

- The size of the proof of the concept device is very large. Not clear what would be the new size and weight of the proposed device in this study.
- There are many research groups that are already investigating a device with the same properties.

2. Investigator(s):

Strengths

Weaknesses

- The PI is non-PhD, with an academic background and research focus that might not be very relevant to the proposed work, as well as one of the Co-PIs (Kevan Hashemi), also non-PhD, has only one publication.

3. Innovation:

Strengths

Weaknesses

- The proposed work is a combination of existing technologies.

4. Approach:

Strengths

- Well written proposal.

Weaknesses

- None noted.

5. Environment:

Strengths

- No concerns about the environment of the proposed study.

Weaknesses

- None noted.

Vertebrate Animals:

3 out of 4 points were addressed. □□□□□

Biohazards:

Not Applicable

Budget and Period of Support:

Recommended budget modifications or possible overlap identified:

- Recommend as Requested. □□□□□

Footnotes for 1 R43 MH119880-01; PI Name: Collins, Michael

NIH has modified its policy regarding the receipt of resubmissions (amended applications). See Guide Notice NOT-OD-14-074 at http://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-074.html. The impact/priority score is calculated after discussion of an application by averaging the overall scores (1-9) given by all voting reviewers on the committee and multiplying by 10. The criterion scores are submitted prior to the meeting by the individual reviewers assigned to an application, and are not discussed specifically at the review meeting or calculated into the overall impact score. Some applications also receive a percentile ranking. For details on the review process, see http://grants.nih.gov/grants/peer_review_process.htm#scoring.

MEETING ROSTER

Center for Scientific Review Special Emphasis Panel
CENTER FOR SCIENTIFIC REVIEW
Small Business: Clinical Neurophysiology, Devices, Neuroprosthetics, and Biosensors
ZRG1 ETTN-C (10)
11/29/2018 - 11/30/2018

Notice of NIH Policy to All Applicants: Meeting rosters are provided for information purposes only. Applicant investigators and institutional officials must not communicate directly with study section members about an application before or after the review. Failure to observe this policy will create a serious breach of integrity in the peer review process, and may lead to actions outlined in NOT-OD-14-073 at https://grants.nih.gov/grants/guide/notice-files/NOT-OD-14-073.html and NOT-OD-15-106 at https://grants.nih.gov/grants/guide/notice-files/NOT-OD-15-106.html, including removal of the application from immediate review.

CHAIRPERSON(S)

HETTS, STEVEN W, MD
PROFESSOR
NEUROINTERVENTIONAL RADIOLOGY
MEDICAL CENTER
UNIVERSITY OF CALIFORNIA SAN FRANCISCO,
SAN FRANCISCO, CA 94143

MEMBERS

CLEMENTS, ISAAC P, PHD
PRINCIPAL ENGINEER
AXION BIOSYSTEMS, LLC
ATLANTA, GA 30309

CRAWFORD, FIONA C, PHD
RESEARCH CAREER SCIENTIST
JAMES A. HALEY VETERANS' HOSPITAL
PRESIDENT AND CHIEF EXECUTIVE OFFICER
ROSKAMP INSTITUTE
SARASOTA, FL 34243

DAS GUPTA, ABHIJIT, PHD
CO-FOUNDER & CHIEF DATA SCIENCE OFFICER
ZANSORS, LLC
ARLINGTON, VA 22201

DECOSTER, MARK A, PHD
PROFESSOR
DEPARTMENT OF BIOMEDICAL ENGINEERING
INSTITUTE FOR MICROMANUFACTURING
LOUISIANA TECH UNIVERSITY
RUSTON, LA 71272

DU, CONGWU, PHD
PROFESSOR
DEPARTMENT OF BIOMEDICAL ENGINEERING
STATE UNIVERSITY OF NEW YORK AT STONY BROOK
STONY BROOK, NY 11794

ELM, JORDAN J, PHD
ASSOCIATE PROFESSOR
DIVISION OF BIOSTATISTICS AND EPIDEMIOLOGY
MEDICAL UNIVERSITY OF SOUTH CAROLINA
CHARLESTON, SC 29425

ETTENHOFER, MARK, PHD
ASSISTANT PROFESSOR
DEPARTMENT OF MEDICAL AND CLINICAL PSYCHOLOGY
UNIFORMED SERVICES UNIVERSITY
BETHSDA , MD 20814

FECTEAU, SHIRLEY, PHD
ASSOCIATE PROFESSOR
DEPARTMENT OF REHABILITATION
SCHOOL OF MEDICINE
UNIVERSITE LAVAL
QUEBEC CITY, QUEBEC G1V 0A6
CANADA

GERMAIN, ANNE, PHD
PROFESSOR
DEPARTMENT OF PSYCHIATRY
UNIVERSITY OF PITTSBURGH SCHOOL OF MEDICINE
PITTSBURGH , PA 15213

GOOD, CAMERON H, PHD
PHYSICAL SCIENTIST
U.S. ARMY RESEARCH LABORATORY (ARL)
ABERDEEN PROVING GROUND, MD 21005

GOODMAN, MARK M, PHD
PROFESSOR
DEPARTMENT OF RADIOLOGY
EMORY UNIVERSITY SCHOOL OF MEDICINE
ATLANTA, GA 30322

GRATTON, GABRIELE, MD, PHD
PROFESSOR
DEPARTMENT OF PSYCHOLOGY
UNIVERSITY OF ILLINOIS
URBANA, IL 61801

KIANI, MEHDI, PHD
ASSISTANT PROFESSOR
DEPARTMENT OF ELECTRICAL ENGINEERING
THE PENNSYLVANIA STATE UNIVERSITY
UNIVERSITY PARK, PA 16802

LAM, CORNELIUS H, MD, PHD
PROFESSOR
DEPARTMENT OF NEUROSURGERY
UNIVERSITY OF MINNESOTA
MINNEAPOLIS, MN 55455

LANE, COURTNEY C, PHD
PRINCIPAL SCIENTIST
ANACAPA CLINICAL RESEARCH
VENTURA, CA 93001

LIEBER, BARUCH B, PHD
PROFESSOR
DEPARTMENT OF NEUROLOGICAL SURGERY,
SCHOOL OF MEDICINE
STONY BROOK UNIVERSITY MEDICAL CENTER
STONY BROOK, NY 11794

LINNENBERGER, ANNA, PHD
SENIOR SCIENTIST
MEADOWLARK OPTICS
FREDERICK, CO 80530

MINASYAN, GEORGIY R, PHD
SENIOR SCIENTIST
SOFTWARE ARCHITECT
TELEFACTOR ROBOTICS
WEST CONSHOHOCKEN, PA 19428

NOLL, DOUGLAS C, PHD
PROFESSOR
DEPARTMENT OF BIOMEDICAL ENGINEERING
DEPARTMENT OF RADIOLOGY
UNIVERSITY OF MICHIGAN
ANN ARBOR, MI 48109

PETROSSIANS, ARTIN, PHD
CO-FOUNDER
PLATINUM GROUP COATINGS
UNIVERSITY OF SOUTHERN CALIFORNIA
LOS ANGELES, CA 90033

RAGHAVAN, SURESH M, PHD
PROFESSOR
DEPARTMENT OF BIOMEDICAL ENGINEERING
UNIVERSITY OF IOWA
IOWA CITY, IA 52242

RODE, CATRIN, PHD
PROFESSOR
DEPARTMENT OF PSYCHOLOGY
UNIVERSITY OF OREGON
CENTER ON BRAIN INJURY
EUGENE, OR 97403

SCLABASSI, ROBERT J, MD, PHD
CHIEF EXECUTIVE OFFICER
COMPUTATIONAL DIAGNOSTICS, INCORPORATED
CLINICAL NEUROPHYSIOLOGICAL SERVICES, LLC
PITTSBURGH, PA 15213

STEPHEN, JULIA M, PHD
DIRECTOR MEG CORE
THE MIND RESEARCH NETWORK
ALBUQUERQUE, NM 87106

TORBEY, MICHEL T, MD
PROFESSOR OF NEUROLOGY AND NEUROSURGERY
CHAIRMAN, NEUROLOGY DEPARTMENT
UNIVERSITY OF NEW MEXICO
ALBUQUERQUE, NM 87131

TROY, JOHN B, PHD
PROFESSOR
DEPARMENT OF BIOMEDICAL ENGINEERING
NORTHWESTERN UNIVERSITY
EVANSTON, IL 60208-3107

WEBER, DOUGLAS J, PHD
ASSOCIATE PROFESSOR
DEPARTMENT OF BIOENGINEERING
UNIVERSITY OF PITTSBURGH
PITTSBURGH, PA 19104

WEIR, RICHARD F, PHD
RESEARCH CAREER SCIENTIST
EASTERN COLORADO VA HEALTH CARE SYSTEM
DIRECTOR, BIOMECHATRONICS DEVELOPMENT
LABORATORY
UNIVERSITY OF COLORADO, DENVER
AURORA, CO 80045

WEISS, CRAIG, PHD
RESEARCH ASSOCIATE PROFESSOR
DEPARTMENT OF PHYSIOLOGY
FEINBERG SCHOOL OF MEDICINE
NORTHWESTERN UNIVERSITY
CHICAGO, IL 60611

ZENHAUSERN, FREDERIC, PHD
PROFESSOR
APPLIED NANOBIOSCIENCE
THE BIODESIGN INSTITUTE
ARIZONA STATE UNIVERSITY
TEMPE, AZ 85287

ZHU, LIANG, PHD
PROFESSOR
DEPARTMENT OF MECHANICAL ENGINEERING
UNIVERSITY OF MARYLAND BALTIMORE COUNTY
BALTIMORE, MD 21250

ZOLA, STUART, PHD
CO-FOUNDER
MAPHABIT
ATLANTA, GA 30030

MAIL REVIEWER(S)

PHILLIPS, JAMES O, PHD
RESEARCH ASSOCIATE PROFESSOR
DEPARTMENT OF OTOLARYNGOLOGY
HEAD AND NECK SURGERY
UNIVERSITY OF WASHINGTON
SEATTLE, WA 98195

SCIENTIFIC REVIEW OFFICER

BACKMAN, CRISTINA, PHD
SCIENTIFIC REVIEW OFFICER
CENTER FOR SCIENTIFIC REVIEW
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MD 20892

EXTRAMURAL SUPPORT ASSISTANT

DEMBOWSKI, JULIA K
ADMINISTRATIVE ASSISTANT
CENTER FOR SCIENTIFIC REVIEW
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MD 20892

WAITERS, WYKENA B
EXTRAMURAL SUPPORT ASSISTANT
CENTER FOR SCIENTIFIC REVIEW
NATIONAL INSTITUTES OF HEALTH
BETHESDA, MD 20814

Consultants are required to absent themselves from the room during the review of any application if their presence would constitute or appear to constitute a conflict of interest.