

AWARD NUMBER: W81XWH-15-2-0037

TITLE: Harnessing Neuroplasticity to Enhance Functional Recovery in Allogeneic Hand Transplant and Heterotopic Hand Replant Recipients

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1. INTRODUCTION

The overarching hypothesis of this project is that patients recovering from hand transplants, replants and peripheral nerve repairs will exhibit improved hand function resulting from combined transcranial direct current stimulation and behavioral therapies that seek to reverse persistent, amputation-related brain reorganization. This work builds on solid basic findings in neuroscience to develop, implement and evaluate innovative evidence-based rehabilitation in hand transplant, replant and peripheral nerve repair patients. This project will yield effective new therapeutic approaches for improving outcomes of individuals who have undergone hand transplantation, replantation, and peripheral nerve repairs that can be deployed with modest training and minimal cost in a wide variety of settings, including the theatre of engagement. The therapeutic approaches resulting from this work will lead to improved hand function in wounded warriors and civilians, providing them with an improved quality of life through the resumption of meaningful pre-morbid occupational, recreational, familial and social activities.

KEYWORDS: hand transplantation, hand replantation, peripheral nervous system injuries, cortical reorganization, neuroplasticity, functional recovery, rehabilitation.

2. ACCOMPLISHMENTS:

What were the major goals of the project?

The major tasks as listed in the Statement of Work are as follows:

- Major Task 1: Prepare Regulatory Documents and Research Protocol
- Major Task 2: Administrative/Training Procedures
- Major Task 3: Data Collection
- Major Task 4: Data Analysis/Manuscript Preparation
- Major Task 5: Dissemination of Results (not yet applicable)

What was accomplished under these goals?

Major Activities: During this project year, the study team gained full regulatory approval at all study sites. Frey and his colleagues have refined the protocol and randomization procedures. For Aim 1, recruitment activities (i.e. screening the medical record for possible participants) have started at all sites. Frey and team have completed a site initiation visit and training session at the Christine Kleinert Institute for Hand & Microsurgery (CMKI), and have scheduled a site initiation visit in October 2018 for both Washington University (WU) and University of Missouri (MU) to train all members of the team on how to conduct study procedures. The University of Missouri has started data collection for Aim 2 and is more than halfway towards the recruitment goal for Quarter 4 (for Aim 2). Frey hired three critical members of MU's research team: Dr. Carmen Cirstea, MD, PhD, Ms. Sandra Lonergan, MS, OTR/L, and Gregory Petroski, PhD. Dr. Cirstea will supervise and administer study procedures, Ms. Lonergan will administer study procedures, including the rehabilitation therapy, and Dr. Petroski will handle the duties of a biostatistician, including randomization procedures, blinding/unblinding

procedures, and statistical analyses. Progress has been monitored for timely completion of Statement of Work goals at each site, and regular communication between sites has occurred via biweekly coordinator teleconferences, with additional teleconferences that the entire team attends as necessary.

Specific Objectives: Subtasks are defined in the Statement of Work. Below is a summary of subtask status.

Under Major Task 1, the following work on subtasks has been completed:

- 1) Subtask 1: Collaboration with all sites on development of manuals and training documents for Aim 1.
 - a. Status: We have completed refinement of the Aim 1 protocol with input from our collaborating teams from Washington University (WU) and Christine M. Kleinert Institute (CMKI). This work was performed over email, via regular teleconferences between sites, and in-person during site training visits.
- 2) Subtask 2: Preparation and submission of human use materials to local IRB and DoD HRPO.
 - a. Status: The University of Missouri received local IRB approval (1/24/18) and DoD HRPO approval (submitted 3/26/18, approved 5/25/18). Washington University received approval from their local IRB on 6/21/18 and the DoD HRPO on 08/01/18. The Christine Kleinert Institute has received local approval (initial approval: 1/14/17, CRR: 1/11/18) and DoD HRPO approval on 10/08/18.
- 3) Subtask 3: Quarterly/Annual Report Preparation.
 - a. Status: We have submitted all quarterly reports for this year.
- 4) Subtask 4: Coordinate with Sites for annual IRB report for continuing review.
 - a. Status: not yet applicable.
- 5) Subtask 5: Renewal of IRB protocols.
 - a. Status: not yet applicable.
- 6) Subtask 6: Submit amendments, adverse events and protocol deviations.
 - a. Status: No adverse events or protocol deviations to report. We have performed several IRB amendments at the University of Missouri, but nothing that is considered substantive.

Under Major Task 2: Administrative and/or Training Procedures

- 1) Subtask 1: Assistance with troubleshooting for all research sites.
Status: MU continues to provide administrative support to WU & CMKI as needed.
- 2) Subtask 2: Obtain monthly progress reports from each site and coordinate overall project management across sites.
Status: in progress, as scheduled.
- 3) Subtask 3: Subtask 3: Presentation of data at conference.
Status: not yet applicable.
- 4) Subtask 4: Organization, scheduling, and agenda coordination for biweekly teleconference meetings between all research teams.

Status: in progress, as scheduled. We also have teleconferences with site principal investigators as needed.

- 5) Subtask 5: Participate in biweekly teleconference meetings between all research teams.

Status: in progress, as scheduled.

- 6) Subtask 6: Management and organization of all study records.

Status: We have prepared a study data pipeline and RedCAP database for study materials and records.

- 7) Subtask 7: Assess quality of Data across sites and provide corrective feedback.

Status: not yet applicable.

- 8) Subtask 8: Hire/Identify therapists to administer protocol.

Status: complete. At the University of Missouri, Sandra Lonergan will serve as the study's occupational therapist. She is able to dedicate 35% FTE to this project. At WU, Alex Halevi, MD, will perform study procedures. At CMKI, Ms. Ashley Buren-Emrich, MS OTR/L, CHT, and Ms. Laurie Newsome, PT, CHT will perform study procedures.

- 9) Subtask 9: Hire Research Associate at University of Missouri.

Status: Complete. Dr. Frey has hired Dr. Carmen Cirstea, M.D., Ph.D., to contribute 65% FTE to this project. Dr. Cirstea will supervise study procedures including data collection & analysis. Dr. Cirstea will also contribute to manuscript preparation.

- 10) Subtask 10: Travel to CMKI and WU to train research/clinical staff in administration of protocol.

Status: Dr. Frey, Kelli Buchanan, and Dr. Anna Boone traveled to CMKI to train the CMKI team (Dr. Christina Kaufman, Ashely Buren Emrich, Laurie Newsome, and Emily Grantz) in administration of protocol on September 5, 2018. Dr. Boone is proficient in tDCS administration and performed an in-depth seminar on this project's specific tDCS montage. Ms. Buchanan presented on the project's administrative pipeline (including Redcap, the project's electronic data capture system). Dr. Frey oversaw the meeting and provided his expertise in each presentation. During this visit, we also refined the sensory re-education and CIMT tasks to be performed at each study session with guidance from Ms. Buren-Emrich, whom is the director of therapy and orthotics at CMKI, and Ms. Newsome. At the time of writing this report, we have scheduled a study training session/site initiation visit with Washington University School of Medicine on Wednesday, Oct 17, 2018 and an internal training session for Monday, Oct. 15, 2018.

- 11) Subtask 11: Prepare administrative pipeline.

Status- Complete. The research coordinator maintains a regulatory binder and research record for this study to ensure best practices are followed in documentation and compliance.

Major Task 3: Data Collection

Update on Aim 1 data collection: Many of the subtasks related to Aim 1 in this Major Task are not yet applicable. However, MU and WUSM have started to identify potential participants for the study in preparation for recruitment upon completion of training study staff. CMKI received DoD HRPO approval on 10/8/18 has just started recruitment activities as well. MU has prescreened one individual and is working with Dr. Stephen Colbert in Plastic and Reconstructive surgery to obtain information on more potential participants. WU & CMKI are performing the same process: screening the medical record for potential participants.

Update on Aim 2 data collection: The MU team has a productive collaborative relationship with Hanger Prosthetics, a national prosthetic patient care services company that is located in 45 states. Hanger Prosthetics is distributing a recruitment letter to potential Aim 2 participants throughout the United States. At the time of writing this report, Frey's team has:

- prescreened 20 eligible participants
- consented 12 participants from above pool (8 are in the process of being mailed consent forms).
- completed data collection on 4 participants from above pool.
- Are currently collecting data on 3 participants from the above pool.

Additionally, the research team is working on refining the software for data analysis of Aim 2 data and visualization of accelerometry data based on recent developments in the field.

Major Task 4: Data Analysis/Manuscript Script

All subtasks except subtask 1: not yet applicable.

Subtask 1: Communication between research sites and statistical consultant for randomization based on pre-test data.

Status: Dr. Frey has met with Dr. Greg Petroski, the study biostatistician, several times over the past quarter. Dr. Petroski is ready to deploy a randomization procedure for each site. Additionally, Frey and Petroski are developing a strategy to implement during data analysis to optimally balance groups by functional performance at each site.

Major Task 5: Dissemination of Results

All subtasks: not yet applicable.

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

All members of the study team will be provided training in the application of transcranial direct current stimulation (tDCS), constraint induced movement therapy (CIMT), and sensory re-education training. Additionally, we expect the work on this project to foster future inter-institutional collaborative projects related to transplantation science.

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?

In the next reporting period, we plan to complete a large portion of data collection for this project (see statement of work for details) at all study sites. Frey's team will continue to coordinate closely with WU and CMKI to ensure timely completion of study goals and to provide support and feedback.

3. 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.

4. CHANGES/PROBLEMS:

Changes in approach and reasons for change

Nothing to report.

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

Aim 1: Due to the grant transfer process, our originally proposed plan of having three years to collect data has been condensed into a little under two years (Dec 2017-Sept 2019). Our updated Statement of Work (dated 7/20/18) specifies that we expect to complete four Aim 1 participants at each site in Quarter 4 of Year 1 of the award. We now think a reasonable expectation is to pilot 1 to 2 participants per site by the end of Quarter 4. We plan to make up for this delay by increasing enrollment numbers in subsequent quarters.

We also plan to request a no-cost extension (NCE) of the award so data collection can extend beyond the current award end date in September 2019. Although we have taken the necessary steps to expedite and consolidate the data collection process, some participants will not have completed the 6 month follow up process by September 2019: any participant that is enrolled after March 2019 will not complete the entire follow-up process by the award end date. A NCE will allow us to complete the six month follow-up process with all participants that are scheduled in the SOW.

Aim 2: This portion of the study is conducted entirely through the mail, which necessarily creates a lengthy study cycle. We have taken several actions to expedite the process of Aim 2.

- 1) We use USPS Priority Mail Service to mail research materials (including prepaid shipping back to us). Priority Mail is the cheapest specified delivery date service with tracking capabilities and has an approximate 3 day delivery window. Using USPS also mitigates the burden of return shipping for the participant: they can simply drop the prepaid return package in their mailbox, rather than having to travel somewhere to return the package (e.g. Fedex Drop Box, post office).
- 2) However, even with Priority Mail, the absolute minimum amount of time a participant takes to complete the study is 16 days: one day for prescreening on the telephone, 6 days for consent through mail (3 days delivery time to participant, 3 days delivery time back), and 9 days for the data collection research package (3 day delivery, 3 days of accelerometry wear time, 3 days for return shipping). If the participant does not immediately send the materials back via the prepaid envelope, this process is extended: we have found the average time from recruitment to end of data collection is one month. Participation does overlap between subjects.
- 3) A bottleneck occurs during data collection. We only have 4 sets of accelerometers, so we can only run 4 participants concurrently through the data collection. This limitation has resulted in a queue of participants that are consented and ready for data collection, but have to wait for an open set of accelerometers.
- 4) Solution: we plan to further increase our capacity for Aim 2 testing by purchasing 4 more sets of accelerometers. We need these additional sets to be able to efficiently run Aim 2 and concurrently perform pre/post accelerometry testing on Aim 1 participants from all research sites. Having additional sets of accelerometers will decrease the individual study cycle length and also increase our ability to efficiently run more participants at one time.

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

The research team is spending significantly under budget.

Update on MU budget: Data collection for Aim 1 has not yet started at the time of this report. For this reason, we are underspending in several budget categories. In salary/fringe benefits: Dr. Cirstea, our research associate, started on the project on Sept 1 2018, which was a few months later than Dr. Frey expected (due to a lengthy search for a suitable research associate). Ms. Lonergan, our occupational therapist for this study, has not yet expended effort because data collection has not started. Most importantly, we had originally budgeted for two contributing surgeons, Dr. Stephen Colbert and Dr. Jay Bridgeman, to contribute 10% FTE each to this project. Drs. Colbert and Bridgeman will still assist with participant recruitment, but they do not wish to take salary from this award. This unexpected change to the budget leaves approximately \$114,000 unencumbered. We plan to partially re-budget this amount of money by increasing Dr. Frey's FTE with the purchase of an additional course release, reserving more time for Frey to dedicate to the oversight and management of this project. If the expected budget change is greater than 5% in any budget category, we will request permission from our DoD grants team for an official re-budget.

We expect expenditures to increase with the start of data collection for Aim 1 and continuation of data collection under Aim 2.

Update on subaward budgets: similarly to MU, CMKI & WU are underspending due to the delay in data collection. Expenditures will increase as data collection for Aim 1 starts.

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

Human subjects: nothing to report.

Animals: not applicable.

Biohazards/select agents: not applicable.

5. PRODUCTS

Publications, conference papers, and presentations: Nothing to report.

Journal publications: Nothing to report.

Books or other non-periodical, one-time publications: nothing to report.

Other publications, conference papers, and presentations: Nothing to report.

Website(s) or other Internet site(s): Nothing to report.

Technologies or techniques: Nothing to report.

Inventions, patent applications, and/or licenses: Nothing to report.

Other Products: Frey's team has started data collection on Aim 2 of the project. The data collected for this aim is expected to contribute to knowledge on the use of upper extremity prosthetic devices in everyday life.

6. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

University of Missouri

Name: Scott H. Frey, PhD, EdM

Project Role: Principal Investigator

Nearest person month worked: 2

Contribution to project: Dr. Frey has overseen all project activities.

Name: Kelli Buchanan, BA

Project Role: Research Coordinator

Nearest person month worked: 3

Contribution to project: Ms. Buchanan acts as overall program coordinator. She serves as liaison between the University of Missouri and subaward sites, leading communication and biweekly meetings. She has managed the regulatory approval process and leads data collection on Aim 2 of the project, including the recruitment and mailing processes.

Name: Carmen Cirstea, PhD, MD

Project Role: Research Associate

Nearest person month worked: 1

Contribution to the project: Dr. Cirstea started work on this project on September 1, 2018. She lends expertise to the analysis of data in Aim 2. Additionally, she will oversee data collection for Aim 1.

Washington University School of Medicine

Name: Amy Moore, MD

Project Role: Principal Investigator

Nearest person month worked: 1

Contribution to project: Dr. Moore has overseen all project activities at WU and contributed to protocol development and refinement.

Name: Alexandra Halevi

Project Role: Post-Doctoral Research Fellow

Nearest Person month worked: 1.5

Contribution to project: Dr. Halevi is responsible for coordination of IRB submission and study protocol review, patient recruitment, as well as intervention administration, testing, and patient follow-up. Dr. Halevi attends the biweekly coordinators' teleconference to maintain communication, updates and progress reports to Mizzou.

Name: Carie Kennedy, BSN, RN

Project Role: Clinical Research Coordinator

Nearest Person Month Worked: 1

Contribution to Project: Ms. Kennedy has provided work to begin study startup and to obtain local and HRPO approval at WU. Ms. Kennedy attends the biweekly coordinators' teleconference to maintain regular communication, updates and progress reports to Mizzou.

Christine M. Kleinert Institute

Name: Christina Kaufman, PhD

Project Role: Principal Investigator

Nearest person month worked: 1

Contribution to project: Dr. Kaufman has overseen all project activities at CMKI. She has contributed to protocol development and refinement, and submission of regulatory and financial documents. She also participated in the site initiation visit/tDCS training provided by the MU team.

Name: Elkin Galvis, MD

Project Role: Co-Investigator

Nearest person month worked: 1

Contribution to Project: Dr. Galvis runs the University Hand Service located in a Level I trauma center. He participated in protocol refinement and selection of subject inclusion/exclusion criteria. He also participated in the planning of subject screening and recruitment as well as review of procedures for subject outcomes and follow up.

Name: Ashely Buren-Emrich, MS OTR/L, CHT / Laurie Newsome PT/CHT

Project Role: Therapists at CMKI site

Nearest person month worked: 2

Contribution to project: Ms. Emrich and Ms. Newsome share therapist responsibilities on this project, and provide back up for each other. They have worked together to develop the sensory-reeducation protocol that all centers will use, as well participated in protocol development and refinement. In addition they have participated in tDCS training and functional assessment training provided by the MU team.

Name: Emily Goldman, RN

Project Role: Nurse Coordinator

Nearest person month worked: 0.5

Contribution to project: Ms. Goldman acts as liaison for CMKI and assists with tasks as needed. Additionally, Ms. Goldman attends biweekly coordinators' teleconference to maintain regular communication, updates and progress reports to Mizzou.

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

DoD grant W81XWH1310496 ends on October 31, 2018. Dr. Frey plans to take two course releases in Project Year 2 to devote more FTE to the activities of this award.

▪ **What other organizations were involved as partners?**

Washington University School of Medicine and the Christine Kleinert Institute for Hand and Microsurgery are collaborating institutions on this award.

Organization Name: Washington University School of Medicine

Location of Organization: St. Louis, Missouri

Partner's contribution to the project:

- In-kind support:
 - Facilities (*e.g., project staff use the partner's facilities for project activities*);
 - Collaboration (*e.g., partner's staff work with project staff on the project*);

Organization Name: Christine Kleinert Institute for Hand & Microsurgery

Location of Organization: 225 Abraham Flexner Way, Louisville, Kentucky

Partner's contribution to the project

- In-kind support:
 - Facilities (*e.g., project staff use the partner's facilities for project activities*);
 - Collaboration (*e.g., partner's staff work with project staff on the project*);

7. SPECIAL REPORTING REQUIREMENTS

8. COLLABORATIVE AWARDS: N/A

- **QUAD CHARTS:** *N/A*

8. **APPENDICES:** *N/A*