AWARD NUMBER: W81XWH-17-1-0641

TITLE: Regenerative Peripheral Nerve Interfaces for the Treatment of Painful Neuromas in Major Limb Amputees

PRINCIPAL INVESTIGATORS: Drs. Stephen W.P. Kemp & Theodore A. Kung

CONTRACTING ORGANIZATION: University of Michigan
Ann Arbor, MI 48109

REPORT DATE: OCTOBER 2019

TYPE OF REPORT: Annual Report

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
October 2019	Annual	30Sep2018 - 29Sep2019

4. TITLE AND SUBTITLE

Regenerative Peripheral Nerve Interfaces for the Treatment of Painful Neuromas in Major Limb Amputees

5a. CONTRACT NUMBER
W81XWH-17-1-0641

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)
Drs. Stephen W.P. Kemp & Theodore A. Kung

E-Mail:swpkemp@med.umich.edu; thekung@med.umich.edu

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Regents of the University of
Michigan
Kathryn Dewitt
503 Thompson St.
Ann Arbor, MI, 48109

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT

Approved for Public Release; Distrubution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

There are currently 1.6 million people in the U.S. living with limb loss. More than 185,000 people undergo amputations in the US alone each year, and the total number of amputees is expected to be nearly 3.6 million people by 2050. Moreover, there have been approximately 1,700 combat service-related amputations between 2001 and 2015 resulting from recent U.S. military operations. Almost one-third of these individuals will form painful neuromas as a result of nerve injury that occurs at the time of amputation. This study investigates the novel use of Regenerative Peripheral Nerve Interfaces (RPNIs) to alleviate neuroma pain. Aim 1 of the study will determine the ability of RPNI surgery to treat existing painful neuromas in major lower limb amputees. Aim 2 of the study will assess the efficacy of RPNI surgery to prevent the formation of painful neuromas in patients undergoing major lower limb amputation. Aim 3 will assess both peripheral and central nervous system changes and responses to RPNI treatment. Peripheral changes will be assessed using MR neurography and DTI. Central brain changes in response to neuroma treatment will be analyzed using fMRI. The outcomes of this study will provide much needed insight into the effectiveness of RPNI surgery to treat the debilitating effects of painful neuromas on lower limb amputees. The results will also direct the future surgical standard of care for these individuals, potentially revolutionizing the standard of care for the millions of amputees

15. SUBJECT TERMS

Regenerative Peripheral Nerve Interface (RPNI), neuroma, pain

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified	12	19b. TELEPHONE NUMBER *(include area code)*

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1. INTRODUCTION

There are currently 1.6 million people in the U.S. living with limb loss. More than 185,000 people undergo amputations in the US alone each year, and the total number of amputees is expected to be nearly 3.6 million people by 2050. Moreover, there have been approximately 1,700 combat service-related amputations between 2001 and 2015 resulting from recent U.S. military operations. Almost one-third of these individuals will form painful neuromas as a result of nerve injury that occurs at the time of amputation. This study investigates the novel use of Regenerative Peripheral Nerve Interfaces (RPNIs) to alleviate neuroma pain. Aim 1 of the study will determine the ability of RPNI surgery to treat existing painful neuromas in major lower limb amputees. Aim 2 of the study will assess the efficacy of RPNI surgery to prevent the formation of painful neuromas in patients undergoing major lower limb amputation. Aim 3 will assess both peripheral and central nervous system changes and responses to RPNI treatment. Peripheral changes will be assessed using MR neurography and DTI. Central brain changes in response to neuroma treatment will be analyzed using fMRI. The outcomes of this study will provide much needed insight into the effectiveness of RPNI surgery to treat the debilitating effects of painful neuromas on lower limb amputees. The results will also direct the future surgical standard of care for these individuals, potentially revolutionizing the standard of care for the millions of persons with amputations.

2. KEYWORDS

Regenerative Peripheral Nerve Interface (RPNI)
Neuroma
Pain
Amputation
Peripheral nerve
MRI
MR Neurography
Neural plasticity

3. ACCOMPLISHMENTS

What were the major goals of the project?

The major goals of this project, as approved in the statement of work, are listed below. Italicized text indicates the status of each of these goals.

Major Task 1: Determine the efficacy of <u>treating</u> existing neuromas by implanting RPNIs

Subtask 1a: Submit documents for University of Michigan review. IRB approved - *100% complete*
Subtask 1b: Submit IRB approval and necessary documents to HRPO. HRPO approved – *100% complete*

Subtask 1c: Determine metrics to assess efficacy of RPNI implantation after neuroma excision and directly post-amputation. *100% complete*
Subtask 1d: Recruitment of study participants via telephone, clinic and pre-op visits. Target enrollment: 60 individuals. *20% complete*
Subtask 1e: Complete RPNI surgeries including neuroma excision and implantation of RPNIs. *20% complete*

Major Task 2: Determine the efficacy of <u>preventing</u> neuroma formation by implanting RPNIs

Subtask 2a: Submit documents for University of Michigan review. IRB approved - *100% complete*
Subtask 2b: Submit IRB approval and necessary documents to HRPO. HRPO approved – *100% complete*
Subtask 2c: Determine metrics to assess efficacy of RPNI implantation after neuroma excision and directly post-amputation. *100% complete*
Subtask 2d: Recruitment of study participants via telephone, clinic and pre-op visits. Target enrollment: 160 individuals. *30% complete*
Subtask 2e: Complete RPNI surgery at the time of amputation. *30% complete*

Major Task 3: Assess effects of RPNI surgery on treatment of painful neuromas using MR Imaging

Subtask 3a: Recruitment of subjects via telephone, clinic, and pre-op visits. Target enrollment: 80 individuals, 40 individuals from Aim 1, and 40 healthy controls. *7.5% complete*
Subtask 3b: MR evaluation for candidates of neuroma treatment. *5% complete*
Subtask 3c: MR evaluation for healthy control group. *10% complete*

<u>Milestones:</u>

Milestone #1: We obtained both IRB and HRPO approval for this study. 100% complete
Milestone #2: Program for data management is in place. We are currently using the REDCaP system. *100% complete*
Milestone #3: RPNIs implanted in 10 Aim 1 participants in year 1, 25 participants in year 2, and 25 participants in year 3. *20% complete*
Milestone #4: RPNIs implanted in 10 Aim 2 participants in year 1, 35 in year 2, and 35 in year 3. *30% complete*
Milestone #5: Deliver summary of clinical patient outcomes when performing RPNI surgery to treat or prevent painful neuroma formation. *0% complete*
Milestone #6: Initial data descriptors from MR studies on density of myelinated fibers, number of motor and sensory fascicles, mapping of painful stimuli in the brain, and peripheral nerve regeneration in the RPNI construct group. *0% complete*
Milestone #7: Deliver summary of patient outcomes correlating quantified MR data on RPNI patients. *0% complete*

What was accomplished under these goals?

(1) Major activities:

Recruitment: We have been actively recruiting through patient clinic visits, referrals, and pre-operative visits. We have also successfully added the VA as a site to our study. We have obtained the necessary HRPO approval, and all of our Research Assistants have passed all required VA training. We are confident that we will begin to recruit patients from this site in the near future. In total, we have currently enrolled 63 subjects (Aim 1=12; Aim 2=48; Aim 3=3). The first patients have finished their one-year follow-up, and have therefore completed the study. We are still actively recruiting additional subjects to all three Aims.

Data Collection/Analysis: All participants have completed their pain questionnaire surveys at the appropriate testing times. All patients are serially evaluated for a one year time period.

(2) Specific objectives:

Our initial objectives of obtaining IRB and HRPO approval have been met (both at the University of Michigan University Hospital and the Ann Arbor VA). We have also validated all of our pain questionnaires. We are actively working on finishing each specific objective for each participant.

(3) Significant results:

We have not yet begun to analyze data for this study for either Aims 1 or 2. We have brought on a new faculty member in Radiology, Chelsea Kaplan, who will be able to evaluate all MRIs and MR neurrography after each case is finished.

(4) Other achievement:

NA to our study.

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

Nothing to report.

How were the results disseminated to communities of interest?

Peer-reviewed Publications:

1. Kubiak CA, Kemp SWP, Cederna PS, Kung TA. Prophylactic regenerative peripheral nerve interfaces (RPNIs) to prevent postamputation pain. *Plastic and Reconstructive Surgery*, 144(3), 421e-430e, 2019.

Conference Presentations:

1. Kemp SWP, Kubiak CA, Cederna PS, Kung TA. Regenerative peripheral nerve interfaces for both treatment and prophylactic prevention of postamputation neuroma pain. 2018 Military Health System Research Symposium (MHSRS), Kissimmee, FL, Aug.20-23, 2018.
2. Kung TA, Kubiak CA, Kemp SWP, Cederna PS. Regenerative Peripheral Nerve Interfaces for the Prevention of Postamputation Pain. 64th Plastic Surgery Research Council, Baltimore, MD, May 2-5, 2019.

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

We will continue to recruit subjects into all 3 Aims of our study. We are confident that the inclusion of the Ann Arbor VA will lead to a dramatic increase in patients enrolled in the study. We will also continue data collection and analysis. We also plan to submit abstracts to several conferences to disseminate our study findings once they become available. In addition to the annual CDMRP conference, we also plan to present our findings at The American Society for Peripheral Nerve and the Plastic Surgery Research Council.

4. IMPACT

This was the second calendar year of our experimental studies. We are satisfied with patient recruitment thus far in Aim 2, and hope to increase enrollment substantially in both Aims 1 and 3 during the next calendar year. While initial results seem promising, it is still too early to ascertain the true impact of this work.

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

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

Our recruitment to Aims 1 and 3 have been slower than anticipated. We hope that this will increase next year with the inclusion of the Ann Arbor VA as a site for this study.

Changes that had a significant impact on expenditures
Nothing to report

Significant changes in use or care of human subjects
Nothing to report

Significant changes in use or care of vertebrate animals
Not applicable to our study

Significant changes in use of biohazards and/or select agents
Nothing to report

6. PRODUCTS

Publications, conference papers, and presentations

Peer-reviewed Publications:

1. Kubiak CA, Kemp SWP, Cederna PS, Kung TA. Prophylactic regenerative peripheral nerve interfaces (RPNIs) to prevent postamputation pain. *Plastic and Reconstructive Surgery*, 144(3), 421e-430e, 2019.

Conference Presentations:

2. Kemp SWP, Kubiak CA, Cederna PS, Kung TA. Regenerative peripheral nerve interfaces for both treatment and prophylactic prevention of postamputation neuroma pain. 2018 Military Health System Research Symposium (MHSRS), Kissimmee, FL, Aug.20-23, 2018.
3. Kung TA, Kubiak CA, Kemp SWP, Cederna PS. Regenerative Peripheral Nerve Interfaces for the Prevention of Postamputation Pain. 64th Plastic Surgery Research Council, Baltimore, MD, May 2-5, 2019.

Journal publications
See previous section for reference.

Books or other non-periodical, one-time publications
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

Name:	Stephen Kemp, Ph.D.
Project Role:	Principal Investigator
Researcher Identifier:	
Nearest person month worked:	12
Contribution to project:	Dr. Kemp has completed all of the HRPO requirements, trained students, has been actively involved in data collection and analysis
Funding Support	

Name:	Theodore Kung, M.D.
Project Role:	Principal Investigator
Researcher Identifier:	
Nearest person month worked:	12
Contribution to project:	Dr. Kung has completed all IRB submissions and amendments. He has performed surgery on participants. He has been actively involved in data collection and analysis
Funding Support	

Name:	Paul Cederna, M.D.
Project Role:	Co-Investigator
Researcher Identifier:	
Nearest person month worked:	1
Contribution to project:	Dr. Cederna provides insight into research design and analysis. He also performs RPNI surgery.
Funding Support	

Name:	Carrie Kubiak, M.D.
Project Role:	Post-doctoral Fellow
Researcher Identifier:	
Nearest person month worked:	6
Contribution to project:	Dr. Kubiak is instrumental in designing the patient drug logs, recruiting patients, entering patient data

Funding Support	

Name:	Jenni Hamill
Project Role:	Research Co-ordinator
Researcher Identifier:	
Nearest person month worked:	6
Contribution to project:	Established REDCaP computer based system for online patient questionnaires, high level regulatory support, database management
Funding Support	
Name:	Kelsey White
Project Role:	Research Co-ordinator
Researcher Identifier:	
Nearest person month worked:	6
Contribution to project:	Provided regulatory support, patient follow-ups, administrative duties
Funding Support	

Name:	David Brown, M.D.
Project Role:	Research Staff
Researcher Identifier:	
Nearest person month worked:	1
Contribution to project:	Patient recruitment and performs RPNI surgeries
Funding Support	

Name:	Chandu Vemuri, M.D.
Project Role:	Research Collaborator
Researcher Identifier:	
Nearest person month worked:	1
Contribution to project:	Attending surgeon in vascular surgery. Dr. Vemuri's patients will serve as control patients for Aim 2.
Funding Support	

Name:	Michael Geisser, M.D.
Project Role:	Co-Investigator
Researcher Identifier:	
Nearest person month worked:	3
Contribution to project:	Involved in design and selection of pain questionnaires. IRB support.
Funding Support	

Name:	Jon Jacobson, M.D.
Project Role:	Co-Investigator
Researcher Identifier:	
Nearest person month worked:	1
Contribution to project:	Dr. Jacobson provides ultrasounds and subsequent analysis.
Funding Support	

Name:	Yoav Morag, M.D.
Project Role:	Co-Investigator
Researcher Identifier:	
Nearest person month worked:	1
Contribution to project:	Dr. Morag provides ultrasounds and subsequent analysis
Funding Support	

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?
Nothing to report

What other organizations were involved as partners?
Nothing to report

8. SPECIAL REQUIREMENTS
Our quad chart is attached
9. APPENDICES
Nothing to report

Regenerative Peripheral Nerve Interface for the Treatment of Painful Neuromas in Major Limb Amputees

W81XWH-17-1-0641 OR160164

PI: Drs. Stephen Kemp & Theodore Kung **Org:** University of Michigan **Award Amount:** $1,980,203

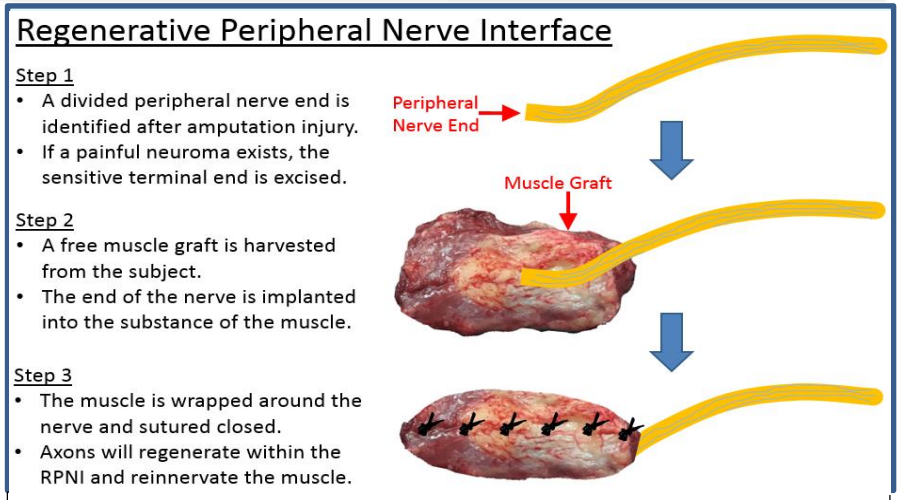
Study/Product Aim(s)

- **SA 1** Determine the efficacy of RPNI surgery to treat existing painful neuromas in major lower limb amputees
- **SA 2** Determine the efficacy of RPNI surgery to prevent the formation of painful neuromas in patients undergoing major lower limb amputess
- **SA 3** Demonstrate changes to the peripheral and central nervous system after RPNI surgery to treat existing painful neuromas in major lower limb amputees

Approach

This study has a prospective cohort study design involving major lower limb amputees drawn from the University of Michigan. We will determine the effectiveness of RPNIs to both treat and prevent neuroma pain, and investigate central mechanisms underlying pain percetion with functional MRI and magnetic resonance neurography techniques.

Regenerative Peripheral Nerve Interface



Accomplishments. Flowchart describing the creation of a regenerative peripheral nerve interface (RPNI)

Timeline and Cost

Activities CY	17	18	19	20
Prospectively enroll patients				
Perform RPNI surgeries				
Prevent painful neuromas				
Evaluate fMRI central mechanisms				
Estimated Budget ($K)	**$20**	**$675**	**$675**	**$630**

Updated: November, 2019

Goals/Milestones

CY17Goal – Enroll subjects
☑Enroll patients (lower limb) who have previously undergone AKA or BKA amputation
CY18 Goals – Treat existing painful neuromas
☑ Analyze RPNIs to treat painful neuromas – *in progress*
☑ Evaluate quality of life parameters – *in progress*
CY19 Goal – Prevent painful neuromas following amputation
☑ Use RPNI as a prophylatic measure for potential neuroma formation – *in progress*
CY20 Goal – Evaluate central mechanisms
☐ fMRI to evaluate central plasticity following RPNI treatment of painful neuromas – *in progress*

Budget Expenditure to Date (Direct cost values)
Projected Expenditure: $3387,016.29
Cost Commitments (Salary): $254,738.20