AWARD NUMBER: W81XWH-21-1-0771

TITLE: Regenerative Peripheral Nerve Interfaces (RPNIs) for Surface Myoelectric Control of a Novel Powered Finger Partial Hand Prosthesis

PRINCIPAL INVESTIGATORS: Dr. Stephen W.P. Kemp

CONTRACTING ORGANIZATION: University of Michigan

REPORT DATE: OCTOBER 2022

TYPE OF REPORT: Annual Report

PREPARED FOR: U.S. Army Medical Research and Development 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 2022	Annual	30SEPT2021 - 29SEPT2022

4. TITLE AND SUBTITLE

Regenerative Peripheral Nerve Interfaces (RPNIs) for Surface Myoelectric Control of a Novel Powered Finger Partial Hand Prosthesis

5a. CONTRACT NUMBER
W81XWH-21-1-0771

5b. GRANT NUMBER

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Drs. Stephen W.P. Kemp
Dr. Richard Weir (co-PI – University of Colorado Site).

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 Development 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; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT

This proposal aligns with the specific **PRORP Focus Area of Retention Strategies**, with a specific focus on ***Return to Duty***. The proposed research will facilitate return to duty for combat-related musculoskeletal injuries through development of a novel powered prosthetic Finger (PPF) control strategy and PPF system for persons with partial hand amputations. Partial hand loss comprises the largest population of individuals with upper limb loss in the United States[1,2]. Traumatic finger amputations represent more than 90% of all amputations in the US, with an incidence of 45,000/year[3,4]. Reductions in function secondary to amputation negatively impacts a person's independence in performing normal activities of daily living (ADLs), and is often associated with debilitating neuroma and/or phantom limb pain (PLP), depression, anxiety, and an overall decreased quality of life[5-7]. Existing powered-prosthetic finger options for persons with partial hand amputations are few and prone to breakdown. Limitations of these devices include: (1) a lack of robustness including frequent breakage of the prosthetic device; (2) poor fit resulting in prosthetic devices that are too long; (3) a limited selection of sizes that are non-anthropomorphic, and; (4) poor control options with too few myoelectric control (EMG) sites in the residual limb to provide individual digit control. To overcome these limitations in the control interface, signal recording ability and the general lack of robustness of current prosthetic devices, we propose to use subcutaneous superficially located Regenerative Peripheral Nerve Interfaces (RPNIs) to create multiple myoelectric control sites to allow us to use standard-of-care surface electromyography (sEMG) methods to measure muscle activity from multiple control sites simultaneously. In addition, we will explore the use of novel surgical techniques to move innervated residual muscles close to the skin to enable the use surface myoelectric control techniques.

15. SUBJECT TERMS

Regenerative Peripheral Nerve Interface (RPNI), neuroma, pain, surface electrodes

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRDC
U	U	U	UU	13	19b. TELEPHONE NUMBER *(include area code)*

Table of Contents

Page

1. INTRODUCTION

The proposed research will facilitate return to duty for combat-related musculoskeletal injuries through development of a novel powered prosthetic Finger (PPF) control strategy and PPF system for persons with partial hand amputations. Partial hand loss comprises the largest population of individuals with upper limb loss in the United States[1,2]. Traumatic finger amputations represent more than 90% of all amputations in the US, with an incidence of 45,000/year[3,4]. Reductions in function secondary to amputation negatively impacts a person's independence in performing normal activities of daily living (ADLs), and is often associated with debilitating neuroma and/or phantom limb pain (PLP), depression, anxiety, and an overall decreased quality of life[5-7]. Existing powered-prosthetic finger options for persons with partial hand amputations are few and prone to breakdown. Limitations of these devices include: (1) a lack of robustness including frequent breakage of the prosthetic device; (2) poor fit resulting in prosthetic devices that are too long; (3) a limited selection of sizes that are non-anthropomorphic, and; (4) poor control options with too few myoelectric control (EMG) sites in the residual limb to provide individual digit control. To overcome these limitations in the control interface, signal recording ability and the general lack of robustness of current prosthetic devices, we propose to use subcutaneous superficially located Regenerative Peripheral Nerve Interfaces (RPNIs) to create multiple myoelectric control sites to allow us to use standard-of-care surface electromyography (sEMG) methods to measure muscle activity from multiple control sites simultaneously. In addition, we will explore the use of novel surgical techniques to move innervated residual muscles close to the skin to enable the use surface myoelectric control techniques.

Objective/Hypothesis: The *long-term goal* of this research is to develop a high-fidelity prosthesis control interface capable of providing independent, simultaneous control of four advanced finger prostheses, thereby restoring natural finger control to persons with partial hand amputations. Our *overall objective*, which is the next logical step in achieving this goal, is to utilize superficially placed, subcutaneous RPNIs to create multiple surface myoelectric control (EMG) sites. The *central hypothesis* is that subcutaneously placed RPNIs will be healthy, revascularize, remain electrophysiologically stable over time, and provide robust surface EMG sites with which to control our novel motorized powered finger prostheses.

Specific Aims and Study Design: This project contains two *Specific Aims:*

1. Determine the viability and signaling capabilities of subcutaneous RPNIs for sEMG prosthetic control. A key characteristic of the RPNI is the ability to amplify efferent motor action potentials from peripheral nerves. The ability to record superficial RPNI signals using sEMG will permit control of our novel powered-finger prosthesis system. Although both sEMG and intramuscular EMG can be used to detect motor intention, there are many situations in partial hand amputations where functional motor units are scarce, scattered, or even completely non-existent. These include situations where the muscle has been avulsed, or are non-functional as typically seen in blast injuries, advanced sarcoma resection, or volumetric muscle loss (VML). In these situations, surgical placement of an RPNI is warranted for prosthetic control. In Aim 1A, subcutaneous RPNIs will be created on both the common peroneal and tibial nerve, creating agonist/antagonist RPNI sites. Although sEMG remains one of the foundational approaches for prosthetic control, it often has difficulties extracting appropriate neural control signals due to cross-talk from deep muscles (e.g., if two muscles are contracting simultaneously but controlling two different functions such as thumb flexion and index finger flexion). In Aim 1B, we will surgically dissect out residual innervated muscles that are deep to one another and move them to a superficial location in order to use sEMG to record compound muscle action potentials (CMAPs) from them. These muscles would not normally be able to be evaluated with sEMG due to their deep position within the limb. Here, we will assess sEMG from both subcutaneous innervated residual muscles and RPNIs simultaneously for multiple control sites.

2. Complete development of the novel powered-finger prosthesis system. We will complete the mechatronic design of the current powered prosthetic finger (PPF) under development in our laboratory and integrate it with an EMG control interface. We will optimize our system for use with RPNIs. We will fabricate and assemble eight powered finger prototypes and their controllers, and then verify the function and robustness of the 3D metal printed powered finger prostheses through a battery of mechanical and electrical tests. Finally, we will utilize sEMG signals from RPNIs to control the novel system.

2. KEYWORDS

Surface Regenerative Peripheral Nerve Interface (S-RPNI)
Peripheral nerve
Regeneration
Nerve Injury
Prosthetic

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. See the Appendix for a summary of results so far.

Specific Aim 1: Determine the viability and signaling capabilities of subcutaneous RPNIs for sEMG prosthetic control.

Subtask 1: Local IACUC protocol approvals – *100% complete*

Subtask 2: Submit documents for DoD Animal Care and Use Review Office (ACURO) – *100% complete*

Major Task 1: Determine sEMG amplitude from RPNIs surgically placed subcutaneously

Subtask 1: Surgery for all experimental groups (subcutaneous and traditional RPNIs; neuroma [negative control]; sham surgery [positive control]– *60% complete*

Subtask 2: Endpoint electrophysiological assessment of all experimental groups in Aim 1A. Harvest tissue for analysis – *80% complete*

Subtask 3: Immunohistochemical and histomorphometrical analysis, including iDISCO, H&E staining, muscle histology, nerve histomorphometry – *30% complete*

Major Task 2: Determine sEMG amplitude from both subcutaneously placed RPNIs and residual innervated muscles.

Subtask 4: Surgery for all experimental groups (subcutaneous RPNIs; subcutaneous residual innervated muscles; neuroma [negative control]; sham surgery [positive control] – *10% complete*

Subtask 5: Endpoint electrophysiological assessment of all experimental groups in Aim 1B. Harvest tissue for analysis – *10% complete*

Subtask 6: Immunohistochemical and histomorphometrical analysis, including iDISCO, H&E staining, muscle histology, nerve histomorphometry – *5% complete*

Specific Aim 2: Complete the development of the powered-Prosthetic finger system.

Major Task 3: Stabilize the Design of the Novel Powered-Finger Prototype – 40%

Subtask 7: Focus group review of current Powered Prosthetic Finger prototype – 40%

Subtask 8: Powered Prosthetic Finger is updated – 40%

Subtask 9: Manufacturing of 8 Powered Prosthetic Fingers for testing – 0%

Major Task 4: Verify Robustness of the Powered Finger by Performing Mechanical Tests – not started. This Major Task will be started during the second year of the grant.

Subtask 10: Geometric requirements are tested

Subtask 11: Strength and speed specifications are tested

Subtask 12: Static and cycle specifications are tested

Subtask 13: Firmware specifications are tested

Subtask 14: Revision of mechanical, electrical, and software as indicated by testing

Major Task 5: Utilize sEMG from sRPNIs to Drive our Novel Powered Finger Prosthesis – not started. This Major Task will be started during the second year of the grant.

Subtask 15: Place surface myoelectrodes over each RPNI/residual innervated muscle in the rat and set them up as control inputs to our prosthetic finger. Perform surface myoelectric recordings during the *in vivo* EMG recording sessions and compare these surface recordings with the intramuscular recordings to quantify signal attenuation.

Milestones:

Milestone #1: ACURO approval received – *100% complete*
Milestone #2 (M1A.2): Surgically place subcutaneous RPNIS on both the common peroneal (CP) and tibial (TIB) nerve, creating agonist/antagonist RPNI sites **–** *60% complete*
Milestone #3 (M1A.3): Chronic assessment of potential pain behavior over time **–** *60% complete*

Milestone #4 (M1A.2, M1A.4): Record sEMG from these subcutaneous agonist/antagonist RPNIs and compare them to EMG recorded *in situ* from traditional placed RPNIs deep to the biceps femoris muscle – 40% complete

Milestone #5 (M1B.1): Surgically place multiple residual innervated muscles in a subcutaneous plane with RPNI constructs **-** *10% complete*
Milestone #6 (M1B.3): Assessment of a battery of behavioral pain tests serially over a three-month period including: (1) mechanical allodynia; (2) cold allodynia, and; (3) thermal allodynia – *10% complete*

Milestone # 7 (M1B.2, M1B.4): Record sEMG from both residual innervated muscles and subcutaneous RPNI constructs – *0% complete*

Milestone #8 (M2A.1): Iterate the existing PPF prototype into a robust powered finger prosthesis and mounting system – 40% complete

Milestone # 9 (M2A.2): Develop motor controller boards to meet the specifications defined in our User Needs document – 40% complete

Milestone #10 (M2A.3): Fabricate and assemble eight powered prototypes using 3D metal printing technology – will start in second year of grant.

Milestone #11 (M2A.4): Make eight motor controller boards for verification – will start in second year of grant.

Milestone #12 (M2B.1): Verify digital control of the finger position using custom motor controller boards – will start in second year of grant.

Milestone #13 (M2B.2): Perform geometric and kinetic testing of the powered finger – will start in second year of grant.

Milestone #14 (M2B.3): Perform life cycle testing by performing 250,000 unloaded cycles – will start in second year of grant.

Milestone #15 (M2B.4): Perform fatigue lifetime testing by performing 10,000 loaded cycles to test fatigue lifetime and load the finger to failure to test strength (spec: >66 N) – will start in second year of grant.

Milestone #16: Establish control of the prosthetic finger utilizing sEMG signals from both subcutaneous RPNIs and residual innervated muscle – will start in second year of grant.

What was accomplished under these goals?

(1) Major activities:

We have begun multiple studies for the grant. More specifically, we first tested multiple variations of the S-RPNI surgery. Unfortunately, our first studies resulted in the grafts either significantly

decreasing or dying altogether. We have since optimized our surgical procedure and have now had a 100% S-RPNI survival rate. We have also optimized how to surgically place side-by-side S-RPNIs in the same animal, without signal or noise interference. We have assessed pain in all animals studied.

We have leveraged work in another project and have a stable design concept established for a powered finger concept. We have yet to fabricate a full prototype but have both a controller and actuator identified as we perform extensive modeling to improve device and system robustness. We are in a design, fabricate, build cycle for the gearbox and have been iterating our transmission concept to get to a stable design. We have been having issues identifying ball bearing that are small enough yet strong enough to meet our needs.

Much of our initial work on the EMG side of things has been looking at using a Double Differential EMG recording approach to allow us to obtain more focal recording consistent with the pick-up volume associated with the RPNIs – we have developed working prototypes capable of recording from the small slips of the forearm and are at present working to characterize and quantify the overall performance associated with this type of recoding over more conventional differential approaches. We believe the double differential approach we are exploring will allow us to achieve a focal recording with a high Common Mode Rejection Ratio.

Data Collection/Analysis: We are actively collecting data and analyzing our results.

(2) Specific objectives:

Our initial ULAM and ACURO objectives have been accomplished. We are actively working on finishing each specific objective for the grant.

(3) Significant results:

See attached Appendix for data completed thus far.

(4) Other achievement:

NA to our study.

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

We have had the opportunity to work with several colleagues in both Surgery and Biomedical Engineering to try and optimize the surgical process and to limit signal/noise interferences from electrodes in adjacent S-RPNIs. Colleagues in PM&R have consulted on all electrophysiological data from the project.

This project has afforded the opputnity

How were the results disseminated to communities of interest?

We have submitted an abstract to the American Society for Peripheral Nerve (ASPN) and the Plastic Surgery Research Council (PSRC). These annual meetings will be held in Miami, FL, and Cleveland, OH, respectively. We will also submit for this years DoD conference in Orlando at the Gaylord Palms Hotel.

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

We are continuing to work on all Project Specific Tasks and Milestones. We are on target to achieve our goals laid out in the SOW.

4. IMPACT

This was the first year of our grant, and we have not yet had the chance to publish any results or present our work at an international conference. Our goal is to start doing this during Year 2 of the grant.

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
Nothing to report

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

We have submitted an abstract to the American Society for Peripheral Nerve (ASPN) and the Plastic Surgery Research Council (PSRC). These annual meetings will be held in Miami, FL, and Cleveland, OH, respectively. We will also submit for this years DoD conference in Orlando at the Gaylord Palms Hotel.

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
Nearest person month worked:	12
Contribution to project:	Dr. Kemp has completed all of the U of M ULAM and DoD ACURO requirements. He has worked on all projects in the grant, and mentors the trainees involved.

Name:	Richard Weir, Ph.D.
Project Role:	Co-Investigator, Denver site lead
Nearest person month worked:	12
Contribution to project:	Dr. Weir lead the Colorado team, which is a sub-contract of the primary grant to Dr. Kemp's team at The University of Michigan.

Name:	Paul Cederna, M.D.

Project Role:	Co-Investigator
Nearest person month worked:	1
Contribution to project:	Dr. Cederna provides insight into research design and analysis.

Name:	Myra Kim
Project Role:	Statistician
Nearest person month worked:	2
Contribution to project:	Dr. Kim is responsible for all the statistical analysis resulting from this project.

Name:	Gabriela Cinotto, M.D.
Project Role:	Post-doctoral Fellow
Nearest person month worked:	6
Contribution to project:	Dr. Cinotto has been optimizing histology, EMG, and histomorphometry parameters for the study.
Name:	Jana Moon
Project Role:	Technician
Nearest person month worked:	12
Contribution to project:	Jana provides all of the animal care and technical support to the trainees involved in the grant.

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
None to report

9. APPENDICES

See attached data document.

DEPARTMENT OF SURGERY
PLASTIC SURGERY
UNIVERSITY OF MICHIGAN HEALTH SYSTEM

UM Neuromuscular Lab
Uniting Biology and Technology

Surface myoelectric control of sensorimotor function using Superficial Regenerative Peripheral Nerve Interfaces (S-RPNIs)

Amir Dehdashtian MD, MPH; Shelby R Svientek MD; Daniel C Ursu PhD; Theodore A Kung MD; Paul S Cederna MD; Stephen WP Kemp PhD.

Background:

- Modern prosthetic devices share functional and cosmetic similarities with the natural limb.

The problem:

Lack of a reliable human-machine interface to provide:

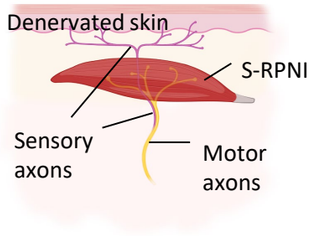
1. Intuitive motor control.
2. Sensory feedback.

Possible solution:

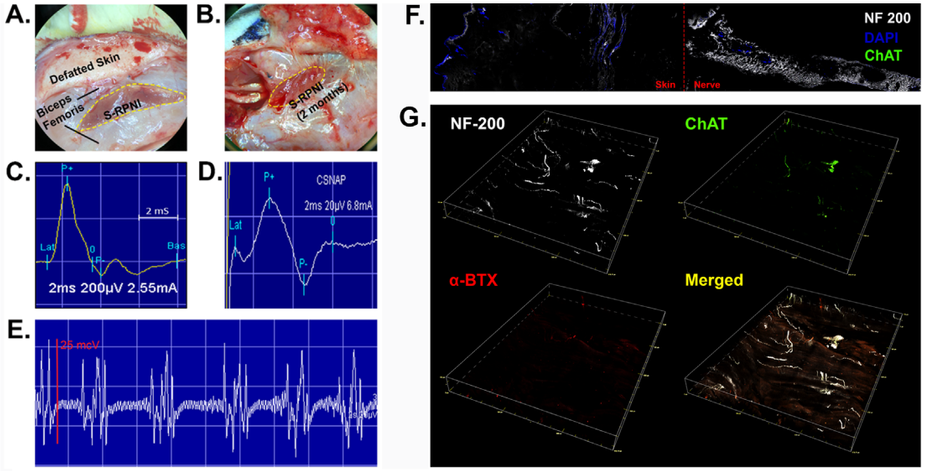
- Regenerative peripheral nerve interface (RPNI) is fabricated by neurotizing an autologous free muscle graft using a residual nerve that can amplify neuronal signals.
- Superficially placed RPNI (S-RPNI) underneath the denervated skin physiologically segregates sensory axons to the skin and motor axons to the muscle component of S-RPNI.

Methods:

- RPNIs were fabricated using contralateral extensor digitorum longus (EDL) muscles and tibial nerve and allowed to mature for 2 months.



Results:



(A) S-RPNI construct fabrication. **(B)** The same construct after 2 months. **(C)** Electrical stimulation of the tibial nerve generated robust compound muscle action potentials recordable from the skin. **(D)** Electrical stimulation of the skin resulted in tri-phasic compound sensory nerve action potentials. **(E)** Brushing the overlying skin using a cotton swap generated synchronous and monomorphic afferent sensory signals. **(F)** Staining for neurofilament 200 (NF200, general nerve marker) and choline acetyl transferase (ChAT, specific for motor fibers) shows regeneration of ChAT negative sensory fibers toward the skin. **(G)** Whole mount immune staining of the muscle component adjacent to the skin for the same antigens, as well as α bungarotoxin (specific for neuromuscular junctions, NMJ) confirmed the viability of S-RPNI construct with motor fibers creating new NMJ and sensory fibers travelling toward the skin.

Summary and conclusion:

- S-RPNI constructs remained viable in the subcutaneous space.
- Motor signal transduction through surface electrodes was robust and feasible.
- Motor axons preferentially reinnervate the muscle AND sensory axons reinnervate the skin by traveling through the muscle.
- Sensory afferent signals were possible to generate using both electrical and mechanical stimuli.
- S-RPNI facilitated bidirectional and simultaneous sensory and motor signal transduction, establishing the basis for a closed-loop neural control system.

Contact:

amird@med.umich.edu

This work was supported by THE PLASTIC SURGERY FOUNDATION.

CDMRP Congressionally Directed Medical Research Programs Department of Defense

Regenerative Peripheral Nerve Interfaces for Surface Myoelectric Control of a Novel Powered Finger Partial Hand Prostheses.

Application #: W81XWH-21-1-0771 OR200173

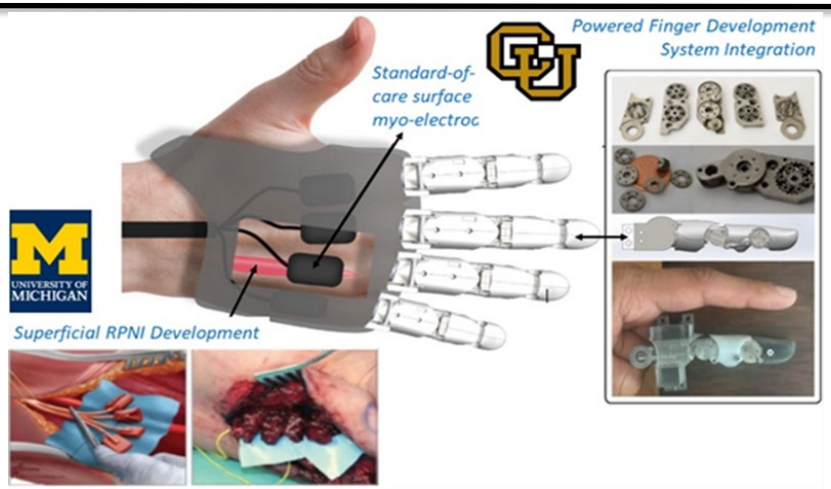
PI: Kemp, Stephen W.P. **Org:** University of Michigan **Award Amount:** $725,000

Study/Product Aim(s)

1. Determine viability & signaling ability of superficial RPNIs and residual innervated muscles for surface EMG (sEMG).
2. Completion of Powered Prosthetic Finger (PPF) system development.
3. sEMG control of the Powered Finger Prosthesis from Superficial RPNI and residual innervated muscles.

Approach

We seek to demonstrate that multiple superficially located RPNIs and residual innervated muscles can be used to create multiple independent surface myoelectric control sites which in turn will provide independent parallel myoelectric control sites for each finger in our Powered Prosthetic Finger system, while still addressing both neuroma and phantom limb pain (PLP). Our goal for the University of Colorado Denver (UCD) is to develop the PPF system to a point where it is stable enough to be tested experimentally with superficial Regenerative Peripheral Nerve Interfaces (sRPNI) and for University of Michigan (UM) to optimize the RPNI surgical procedure to create multiple independent surface myoelectric control sites while still providing relief from chronic neuroma and phantom limb pain.



Accomplishment: Initial 3D metal printed Powered Finger Prototypes exist and are undergoing testing and design iteration. Regenerative Peripheral Nerve Interfaces (RPNI) have been shown to be effective at mitigating phantom limb pain and control.

Timeline and Cost

Activities CY	21	22
Aim 1: Animal Model Experiments		
Aim 2: Development of the novel Powered Prosthetic Finger RPNI/residual muscle control of the novel Powered Prosthetic Finger		
Estimated Budget ($K)	**$362k**	**$363k**

Updated: 12/02/2022

Goals/Milestones

CY21 Goal – Completion of Powered Prosthetic Finger System

- ❑ Freeze design for Powered Prosthetic Finger
- ❑ Functional and engineering specifications are met

CY21 Goal – Pre-clinical animal model determines viability

- Show no enhanced pain response with subcutaneous RPNI
- Produce robust and reliable electrophysiological recordings
- Determine that subcutaneous RPNI constructs are healthy

CY22 Goal – Drive the Powered Prosthetic Finger System in an experimental rat model

- ❑ Utilize sEMG

Budget Expenditure to Date

Projected Expenditure: $725,000
Actual Expenditure: $102,779.75
Cost Commitments: $370,389.74