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TITLE: **Blink Prosthesis for Facial Paralysis Patients**

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14. ABSTRACT

Ripple is developing an implantable stimulator to restore functional eye blink in patients with unilateral facial nerve paralysis. The proposed blink prosthesis is intended for patients with facial nerve damage who suffer long-term disfigurement and dysfunction due to the loss of the ability to convey facial expression and produce eye blink.

15. SUBJECT TERMS
facial paralysis, neuroprosthetics, functional electrical stimulation, medical device, Bell's Palsy

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1. INTRODUCTION

Patients suffering from facial nerve damage experience substantial disfigurement and dysfunction due to the inability to produce eye blink and convey facial expression. The loss of the blink response is very painful and predisposes patients to corneal exposure and dry eye complications that are difficult to effectively treat. The proposed innovation will provide a fundamental improvement in the treatment of ophthalmic manifestations of patients with facial paralysis. These improvements will apply to both the aesthetic and functional use of the paralyzed eyelid by preventing painful dry eye complications and profound facial disfiguration. The goal of this program is to create an implantable blink prosthesis to restore functional eye blink in patients with paralysis on one side of their faces. The system will use electrodes implanted in the eyelid to stimulate the adjacent muscles to close the eye. Another set of electrodes implanted in the healthy eyelid will listen for the onset of a blink and send a timing signal to the electronic system to turn on the stimulator to produce a bilateral symmetric blink in the paralyzed eye.

In this CDMRP project, we will finalize the electronics and develop the hermetic enclosure for the implant, complete the external controller and its software, and verify the system for readiness for clinical testing through:

- Electrode flexural durability verification
- Implant hermeticity verification
- Electrical safety and EM compatibility
- Biocompatibility verification
- Animal study

The proposed device would be the first medical device for restoring blink function to facial paralysis patients. The evoked contractions of the OOM would mitigate ocular complications from long-term dry eye and provide cosmetically pleasing dynamic facial motion to lessen the psychological burden associated with the facial disfiguration resulting from paralysis.

2. KEYWORDS

facial paralysis, neuroprosthetics, functional electrical stimulation, medical device

3. ACCOMPLISHMENTS

Major Goals

Major Task 5: Acute in vivo testing of final device in rabbit study

We have completed the final design of the implanted blink prosthesis in preparation for the upcoming in vivo trial. The implantable system is capable of multichannel stimulation and recording for detecting the onset of blink from EMG signals recorded on the neurally intact side of the face and sending stimulation to the paralyzed eyelid. Long-lead time components for the hermetic package and the feedthroughs have been ordered and assembled, and the test devices pass electrode impedance tests for system performance.

The IACUC protocol is under review at PreClinical Research Services, a contract research organization specializing in animal medical device studies. Upon approval of the IACUC and ACURO, we intend to start the animal study next spring and have it completed by early summer 2019.

Major Task 6: Regulatory submission

We have begun assembling a Master File for IDE submission to the FDA in support of a clinical trial to test the implantable system in human subjects. A pre-submission meeting with the FDA has provided early feedback about the final qualification tests required for the component technologies intended for the clinical trial. Either direct testing results or equivalence data have now been collected to address major FDA issues of biocompatibility, electrical safety, electromagnetic compliance, sterilization, mechanical durability, and essential benchtop performance verifications.

Goals Accomplished

Preparation for in vivo trial

We have submitted an IACUC protocol to PreClinical Research Services, a contract research organization in Ft. Collins, CO that specializes in *in vivo* validation of implantable medical devices. The study is designed to validate the efficacy of the system Ripple has developed to electrically evoke blink for patients with unilateral facial paralysis. The study will evaluate stimulation neuromuscular output response in five animals before and after facial nerve trauma. To evaluate the feasibility of evoking a blink response, an incision will be made at the upper eyelid crease and the thin-film electrode array will be sutured to the superior tarsus adjacent to the palpebral portion of the orbicularis oculi muscle (OOM) approximately 1 mm above the lid margin. Electrical charge will be delivered via these electrodes immediately following electrode implantation. High-speed video will be used to evaluate stimulation thresholds and muscle recruitment of evoked OOM muscle excursion. Following stimulation, the branch of the facial nerve innervating the OOM will be cut. The electrical stimulation protocol will be repeated on the denervated OOM.

In preparation for the study, Ripple has built an implantable system we will use for the upcoming trial. The implantable stimulation and recording device is capable of providing stimulation pulses up to ± 10 mA on each of 8 channels and recording EMG on an additional 16 channels with noise performance of 2 µV on each channel. Wireless data are transmitted from the implant via an infrared telemetry mode to simultaneously transmit all 16 channels of EMG sampled at 12-bits and 2-ksps. The electronics are housed in a hermetic ceramic package that is transparent to IR signals and the inductive powering RF signal transmitted from the external transceiver.

Upon approval from IACUC/ACURO, we are prepared to start the animal study to provide final in vivo validation of the implantable blink prosthesis.

Regulatory Submission

In preparation for submission to the FDA to begin human subject testing, Ripple is working to compile all design documentation and testing reports from preclinical qualification testing of the system. With designs developed within Ripple's Quality control system, we have completed and signed off on Design Input Requirements and a Hazard and Risk Analysis of the blink prosthesis per ISO 13485 requirements. Testing results of the component technology are currently being compiled into a Master File for submission at the FDA. The testing plan for these component technologies has been discussed in a pre-submission meeting with the FDA to confirm these tests are appropriate for this type of implantable device. To date, Ripple has completed the following medical device standards-based testing:

Biocompatibility per ISO 10993

- Cytotoxicity
- Sensitization
- Irritation
- Genotoxicity
- Micronucleus
- Systemic toxicity
- Pyrogenicity
- Subchronic systemic toxicity
- Chronic implantation
- Chemical characterization

Electrical safety and electromagnetic compliance testing

- ISO 60601-1-1
- ISO 60601-1-2
- ISO 14708

Sterilization validation

- Bioburden resistance
- Comparative resistance

Hermeticity

- MIL-STD-883H

Impact testing

- IEC 60068-2-75:2014

Mechanical lead testing

- EN 45502

4. IMPACT

Impact on development of principle disciplines

The goal of this program is to create an implantable stimulator device to restore functional eye blink in patients with unilateral facial nerve paralysis. The system will electrically stimulate the paretic eyelid when EMG electrodes detect normal blink from the contralateral eye to produce a synchronous blink. The implant will consist of a thin, ceramic package placed subcutaneously above the hairline with an EMG electrode pair for detecting contralateral blink and a thin-film stimulating array implanted on the paretic orbicularis oculi muscle (OOM).

We have designed this system to include a novel multichannel stimulation array for selective activation of the paretic OOM. Multiple stimulation sites will allow clinicians the ability to selectively activate all necessary muscle tissue to evoke spontaneous blink via a diffuse injection of low levels of current across the array. The device will be powered by a small, external module worn behind the ear, which activates the implant with a wireless reflected impedance signal and provides a user interface to control stimulation intensity.

The market for these devices is relatively small with annual patient populations on the order of a few thousand per year. For these patients, however, the availability of this technology will provide a profound improvement in quality of life and reduction of total care costs due to complications related to exposure of the affected eye.

Training and Professional Development

Nothing to report

Dissemination of Results

Nothing to report

Year 4 Goals (No-cost extension)

***In vivo* testing**

We will test the implant technology in an *in vivo* study to validate the system performs necessary functions. This animal study will provide confirmation that the system meets requirements for the implantable medical device.

Impact on other disciplines

Nothing to report

Impact on technology transfer

Nothing to report

Impact on broader society

Nothing to report

5. CHANGES/PROBLEMS

Changes in approach

A no-cost extension has been requested and approved to accommodate a prolonged process for initiating the animal study. The study described in the original submission were to take place at the Comparative Medicine Center at the University of Utah, a contract service at the University used by local business to conduct *in vivo* validations. Ripple has had over a decade of experience working at this facility on similar evaluations of implantable system in acute and chronic studies across a range of animal models. However, due to changes in management of the center in 2018, the University has changed their policy to disallow future contract services for outside companies. As a result, our study was delayed as we had to find a new animal testing facility to conduct this CDMRP-funded trial. On-site audits of other testing facilities in Utah deemed these CRO's unsuitable for the work we needed for this study, so we established contact with PreClinical Research Services upon the recommendation of the Intermountain West Medical Device Consortium. After a series of scientific and quality system inspections, we made the decision to move forward with testing at this facility in Colorado. In addition to delays in technology development and testing in Year 2, the process of qualifying this new CRO was a major factor in the causing the delays which led to our request for a no-cost extension on the final year of this project.

In conversation with the IACUC committee administrator on Nov 15, we anticipate having IACUC approval by mid-December and we will submit the protocol immediately after approval to ACURO to start this additional approval process. Based on notifications from federal agencies and feedback from other collaborators in the field, we understand the ACURO approval process is somewhat longer than usual due to the large number of other proposals under review. We hope to have ACURO approval sometime next spring (~April 2019) and we plan to start and finish the animal study by the end of June.

Actual or anticipated problems
Nothing to report

Significant changes of expenditures
Nothing to report

Changes in use of vertebrate animals
Nothing to report

6. PRODUCTS

Publications and presentations

Ripple was invited to present work on this project at the Triological Society meeting in January 2018 in Phoenix. The Triological Society is a professional society of academic and clinical otolaryngologist.

Website

https://rippleneuro.com/about-ripple-neuro/#clinical-projects

Technologies or techniques

Nothing to report

Inventions, patents, and/or licenses

Nothing to report

Other products

Nothing to report

7. PARTICIPANTS AND OTHER COLLABORATING ORGANIZATIONS

Individual contributions

Name:	Brian Crofts		Name:	Ginger Neil
Project Role:	Electrical engineer		Project Role:	Quality specialist
Months:	7.6		Months:	1.5
Contribution:	Electrical engineering design documentation and testing		Contribution:	Quality system documentation and CRO test facility audits
Name:	Steve Barrus		Name:	Tracy Best
Project Role:	Systems engineer		Project Role:	Regulatory specialist
Months:	6		Months:	1
Contribution:	Firmware engineering design documentation and testing		Contribution:	Medical device standards testing documentation; Master File compilation
Name:	Will Talmadge		Name:	
Project Role:	Applications engineer		Project Role:	
Months:	3.75		Months:	
Contribution:	Quality/regulatory documentation and essential performance testing of implant		Contribution:	
Name:	Scott Hiatt		Name:	
Project Role:	Senior Electrical Engineer		Project Role:	
Months:	3.5		Months:	
Contribution:	Directed efforts of engineering development and documentation		Contribution:	
Name:	Nate Srok			
Project Role:	Mechanical engineer			
Months:	2.8			
Contribution:	Mechanical testing for medical device standards			

Change in active other support

Nothing to report

Organizational partners

Nothing to report