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PRINCIPAL INVESTIGATOR: Philip R Troyk, PhD

CONTRACTING ORGANIZATION: Illinois Institute of Technology
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Philip R Troyk, PhD

E-Mail: troyk@iit.edu

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14. ABSTRACT
This project is to perform translational research tasks needed to prepare an intracortical visual prosthesis (ICVP) for testing in a human. No human trial testing of the prosthesis will occur under the funded work. Preparatory tasks include final maturation of the implantable hardware, pre FDA IDE testing of the ICVP in non-human primates, reliability and biocompatibility testing, development of a human testing protocol, development of a human volunteer selection and assessment protocol, preparation of an investigation device exemption application (IDE) to the FDA. Progress to-date has been somewhat hampered by delayed approval of the psychology testing protocols (human subjects), and the animal testing protocols (non-human primates), by the USARMYMC. However, all protocol approvals have now been obtained. This delay has also slowed the spending of funds for these areas within the first year. The work focused on technology maturation has been highly productive. Sample stimulator units have been subjected to brutal environmental testing with 100% survival. Larger numbers of stimulator units are in the process of being constructed to provide statistical power for the environmental testing. Following the human protocol acceptances, work has commenced at both IIT and Johns Hopkins for the development of the testing and assessment protocols. A graduate student from IIT has initiated work within the laboratory of Dr. Dagnelie at JHU. Analysis of interview data from the earlier Dobelle visual prosthesis recipients has already yielded valuable insight about the volunteer recruitment and participation process. Sixteen publications and presentations have resulted from the funded work, and several publications are in preparation. While the project is projected for a 1-year no-cost extension request, due to the slow start-up, it is anticipated that by the end of the project all parts of the SOW will be complete, with the ICVP ready for clinical testing in a human trial.

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INTRODUCTION

The objective of this project is to prepare for clinical feasibility testing of an intracortical visual prosthesis (ICVP) in humans. Our hypothesis is that an ICVP is technically and surgically feasible, has a sufficient likelihood of sensory benefit to warrant human testing, and that our ICVP team is at the point of readiness for proceeding towards a first human clinical trial. While the project will NOT support human testing, per se, it will accomplish all of the necessary steps to prepare the ICVP for testing in a human volunteer. The study uses a well-established project team lead by the Illinois Institute of Technology comprised of: Sigenics, Inc, MicroProbes for Life Science (MLS), University of Chicago (UC), Huntington Medical Research Institutes (HMRI), and Johns Hopkins University (JHU). The project work addresses a military-relevant health problem of compensating for vision loss because over 90% of those individuals with blindness, in the military and civilian population are not gainfully employed and often suffer from depression, social isolation, and a significantly-reduced quality of life.

THE STATEMENT OF WORK (SOW)

Our long-term hypothesis to be tested is that spatial-temporal electrical stimulation of the cortical visual system can provide usable visual sensation and restoration for those individuals with blindness. The objective of this proposed project is to make possible feasibility testing of an intracortical visual prosthesis (ICVP) in humans. While the proposed project will NOT support human testing, per se, it will accomplish all of the necessary steps to prepare the ICVP for testing in a human volunteer. The proposed work addresses a military-relevant health problem of compensating for vision loss because over 90% of those individuals with blindness, in the military and civilian population are not gainfully employed and often suffer from depression, social isolation, and a significantly-reduced quality of life. The potential contribution that the proposed study could make to addressing these issues is that by preparing the ICVP for clinical testing, a potentially ground-breaking alternative could become available to those with blindness.

For the past decade, Illinois Institute of Technology (IIT) has lead a team-based project, consisting of multiple institutions, to advance the ICVP - for which micro-sized wire electrodes provide electrical stimulation directly to the visual cortex. During this time, accomplishments have been achieved for development of electrode materials, electrode array fabrication, implantable wireless hardware design, implantable stimulator fabrication and stress testing, non-human primate psychophysics, normal human psychophysics, surgical feasibility assessment, and psychological assessment of potential and past vision prosthesis recipients. Our hypothesis is that an ICVP is technically and surgically feasible, has a sufficient likelihood of sensory benefit to warrant human testing, and that our ICVP team is at the point of readiness for proceeding towards a first human clinical trial.

The proposed study will use a well-established project team lead by Dr. Troyk of IIT. This team is comprised of six institutions: Illinois Institute of Technology, Sigenics, Inc, MicroProbes for Life Science (MLS), University of Chicago (UC), Huntington Medical Research Institutes (HMRI), and Johns Hopkins University (JHU). Each member of the team brings highly-targeted expertise to address the following six program components. In order to accomplish the ambitious long-term project goal, key steps must be taken to prepare our ICVP system for clinical testing. These comprise the SOW and are (the order of organizations indicates task responsibility):

1. Design evaluation and fabrication of large numbers of implantable electrode array/stimulator modules (ICVP modules) under GLP and GMP conditions with suitable documentation for satisfying regulatory submission needs, within sustainable commercial organizations. (Y1 – IIT, MLS, Sigenics)

2. Testing of, and prediction of long-term biocompatibility and survivability for, (ICVP modules) in animal and laboratory evaluations. (**Y1**/Y2 – IIT, UC, HMRI, Tox Monitor Labs)

3. Design and testing of a real-time psychophysical assessment and testing system for evaluation of an ICVP recipient, and design and fabrication of a first-generation portable image processing system for converting electronic images into cortical stimulation neural coding patterns (Y1/**Y2 –** JHU, IIT, Sigenics)

4. Design and implementation of a volunteer recruitment and evaluation process that preserves subject protection, integrity, and maximizes project scientific significance. (Y1/Y2 – IIT, UC)

5. Constitute a team structure within a clinical setting for preparation of surgical implantation and human subject care. Y1/Y2 – UC, IIT)

6. Preparation and submission of an FDA IDE application for a human trial. (Y2 – IIT, UC, JHU)

PROGRESS FOR SOW TASK 1

TASK 1. Design evaluation and fabrication of large numbers of implantable electrode array/stimulator modules (ICVP modules) under GLP and GMP conditions with suitable documentation for satisfying regulatory submission needs, within sustainable commercial organizations.

The IVCP hardware system is comprised of two key components: the implantable stimulator modules (ISM), and the extracorporeal telemetry controller (TC). Both of these components have undergone extensive design evaluation/refinement during the first-year project period.

The ISM is comprised of an application-specific-integrated circuit (ASIC), fabricated in the XFab CX08 process. The ASIC is being reviewed using a controlled procedure for formal review of ASICs within Sigenics. This is the same process that is used for commercial, and military-grade, ASICs that are manufactured by Sigenics. This process is shown in Figure 1, below, as presented in the project proposal.

Owing to the fact that the ASIC design pre-existed the start of the design control flow process, design review has not followed a linear pathway. Currently the review process is at a combination of the two red-circled steps shown in Figure1. The circuit design has been found to be sound, and absent critical flaws. Certain performance limitations have been identified, and are consistent with the decisions made at the time of initial design process, dating back to 2004. An assessment was made as to whether the ASIC design would notably benefit from revising the circuitry and fabricating within a smaller geometry process: 0.35 micron, rather than the current 0.8 micron technology. Over 75% of the ASIC circuitry is digital in nature. Unquestionably the physical size of this digital circuitry would shrink to approximately 1/3 – 1/4 the current size. Yet the real question to be considered is whether there would be a performance or reliability advantage to the geometry reduction. The assessment is that no performance advantage would be achieved. The current ASIC design has the advantage of historical testing and use over the past five years. Therefore, the assessment result has been to retain the current design. Presently, formal design review, specification, and acceptance test procedure documents are in preparation. These will be used for formal testing of newly procured

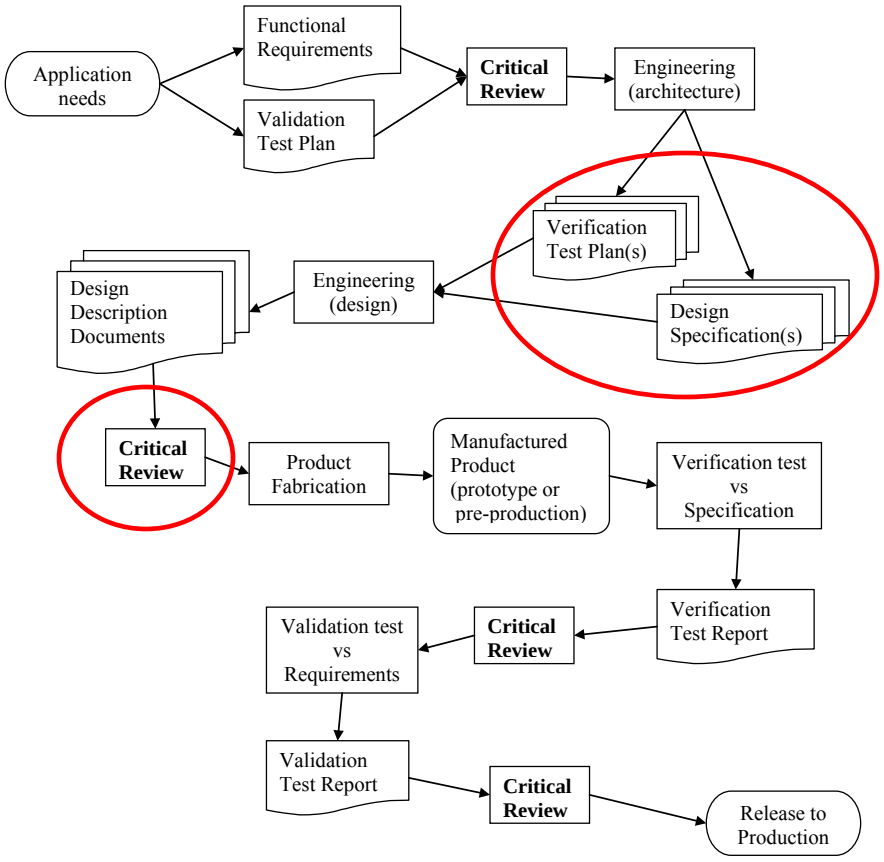
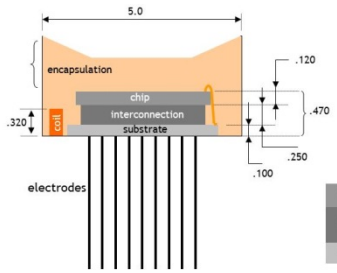
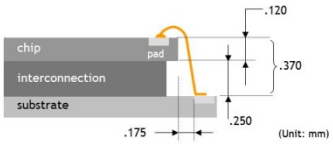


Figure 1 Block diagram of Sigenics design control flow

Module geometry



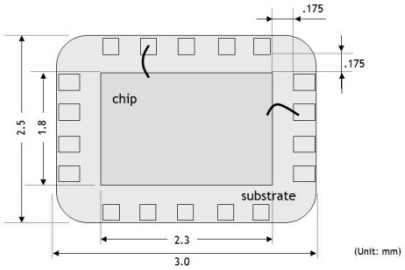
WFMA schematic



Bond details

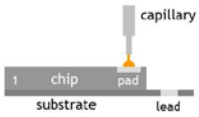
Cont.

Top view of chip on substrate

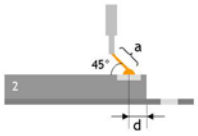


-spacing between die edge and pad on substrate is only 175um.
-chip size may vary depending on sawing.

Bonding procedure

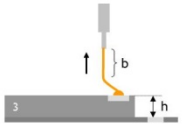


-bond on pad.
-lift up the capillary slightly.

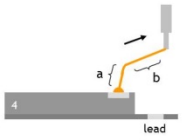


-move it up and left to form angle of 45 degrees.
-pull the wire so that the wire length 'a' is slightly longer than distance 'd' to the die edge from gold ball.

Cont.



-lift the capillary up so that the straight wire length 'b' is approximately same as the height (chip/interconnection), 'h'.



-pull the wire right up until portion 'a' points 1 o'clock.
-length of 'b' will be slightly longer than 'h', passing 2nd bond position.

Cont.

-lower the capillary down.

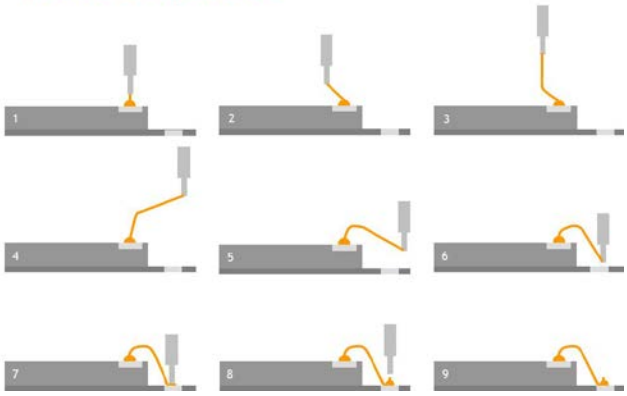
-move the capillary back to the second bond (lead) position.

Cont.

-perform the second bonding on lead (metal trace) on substrate.

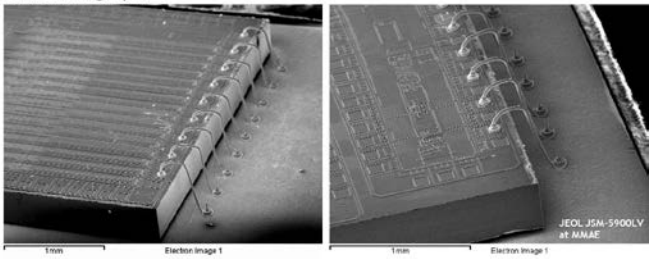
-make the additional bump for secured bond.

Whole sequence



Bonding sample

SEM micrographs



-consistent loop height made manually.
-360um thick device was used to simulate actual WFMA module assembly.

Figure 2 – Illustration of wirebonding assembly flow process

CX08 wafers that contain the ISM ASIC design. In this manner, the necessary traceability and hardware procurement control is being implemented, as needed to support the IDE application.

The telemetry controller (TC) component, used for extracorporeal powering and control of the ICVP stimulator modules, has undergone design revision within Sigenics. This was necessary to provide a testing platform for the highly accelerated stress testing (HAST) evaluation being accomplished within the IIT laboratories. The TC reverse telemetry system, used to wireless monitor the critical system operational parameters (power supply, electrode polarization potentials), was particularly revised to make it more robust. A software platform development has accompanied the hardware refinements, and is being used as the basis for the psychophysical software testing platform being developed within IIT and being tested at JHU.

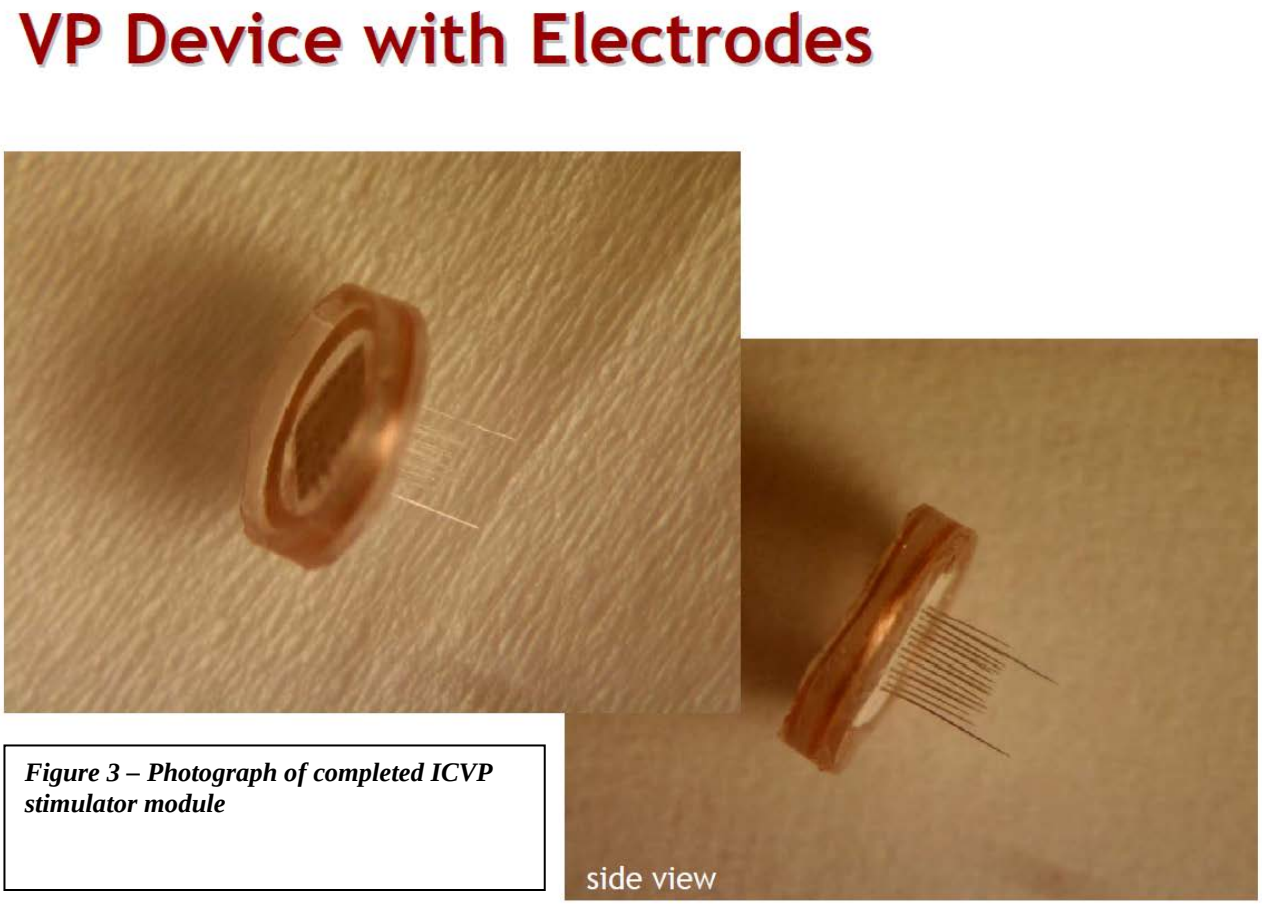


Figure 3 – Photograph of completed ICVP stimulator module

This past year saw the demonstration of the first time that an iridium electrode was activated over a wireless inductive link. Using the ICVP stimulator circuitry, an inductive link, and a modified TC component, iridium electrodes were activated by growing an oxide film – activated iridium oxide film (AIROF). The AIROF film is necessary in order for the electrodes to be capable of enhanced, and safe, charge injection. The wireless activation is needed because the final polymeric packaging process subjects the ICVP module to elevated temperatures that would destroy an AIROF electrode. Therefore, the activation needs to be done following completed assembly – this can only be accomplished through the ICVP module wireless link since no direct connections to the electrodes are possible following final assembly.

Fabrication processes for the ISM have been refined at IIT, facilitating the fabrication of larger numbers of ISM units. A pictorial summary of the wirebonding assembly process is shown in Figure 2, above. Note that a semi-automatic wirebonder has been procured for use in the project. This was necessary in order to allow for the consistent replication of the assemblies without the need for highly skilled personnel to perform the wirebonding.

Coil winding, component integration, and silicone encapsulation have been sophisticated and prepared for transfer to MicroProbes for Life Sciences so that they can fabricate larger numbers of ICVP modules. A completed module is shown in Figure 3, below.

In summary, progress made for SOW Task 1 now allows for fabrication of a large number of modules to be used in toxicology testing, environmental stress testing, and animal implantations.

PROGRESS FOR SOW TASK 2

Task 2. Testing of, and prediction of long-term biocompatibility and survivability for, (ICVP modules) in animal and laboratory evaluations.

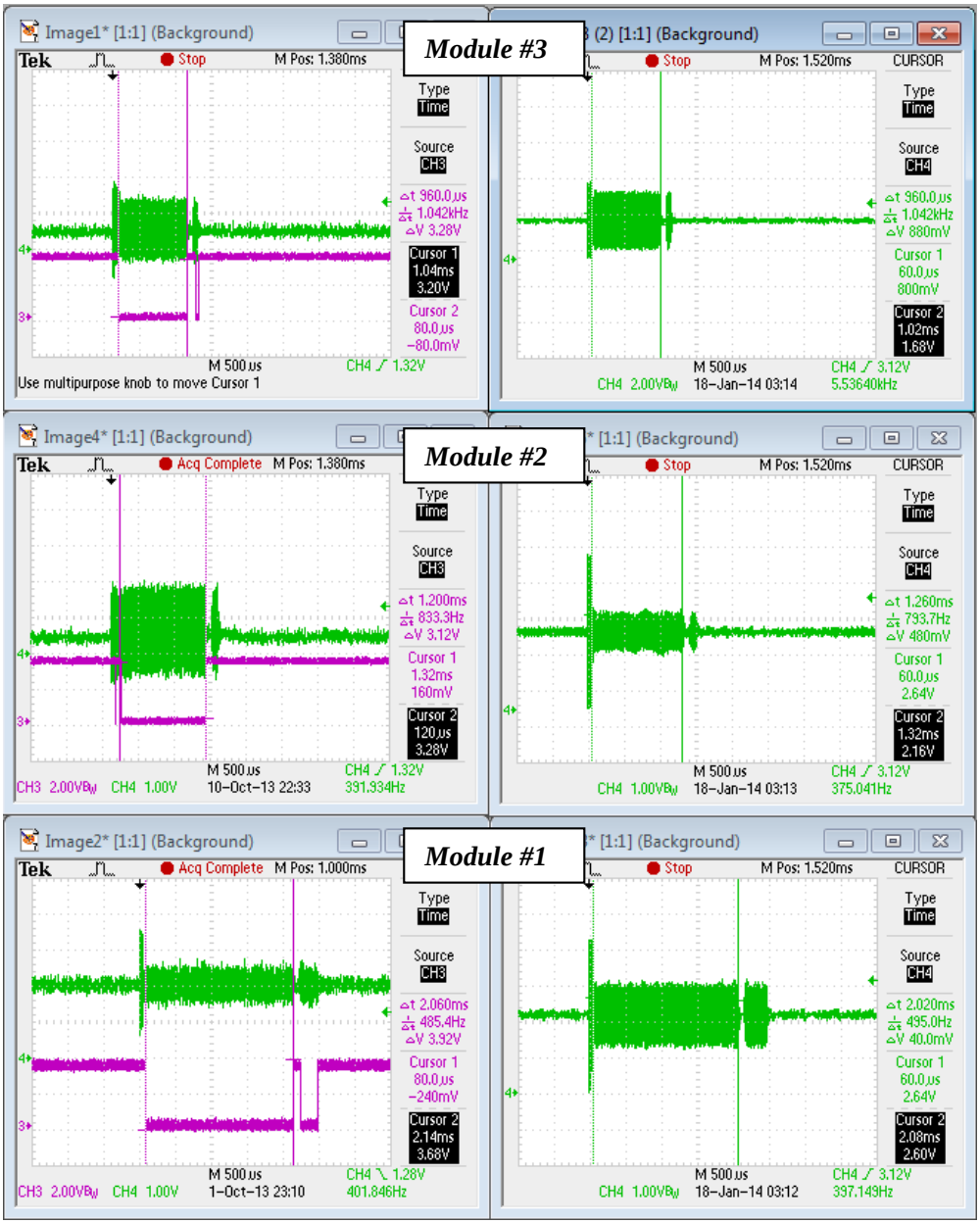


Figure 4 - Oscilloscope photographs of HAST-stressed ICVP stimulator modules #1,#2,#3, during reverse telemetry. Left: initial waveform, Day 1, Right: current waveform, Day (44,39,38) respectively. Note the consistent value of Δt for each module.

For this task, animal testing has been delayed by the final approval of the animal protocol. That approval is scheduled for finalization in January of 2014.

Significant progress has been made on the laboratory environmental testing. We have use "highly accelerated stress test" (HAST), methods for evaluating the integrity of the silicone encapsulant packaging method. Owing to the small size, multiple protrusions of electrodes, and need for magnetic transparency, conventional hermetic packaging methods cannot be applied to the ICVP stimulator module. Therefore, we have used polymeric packaging as a means of protecting the electronic circuitry from deterioration by body fluids. We are using a silicone adhesive that contains an integral silane coupling agent. Once cured at 150 degrees Celsius, the polymer prevents moisture from deteriorating the electronic components by forming bonds to the normally hydrophilic functional groups on the surface of the components, thus preventing the condensation of water.

Three encapsulated modules were placed within a HAST chamber. The chamber is essentially an autoclave that imposes elevated temperature and pressure (120C,

1.5bar) , at 100% RH. This type of stress is commonly used in the semiconductor industry to assess the quality of electronic packaging, and represents a notable acceleration factor over body temperature. After approximately 40 days of storage within the HAST environment, the modules show no variation in the reverse telemetry operation. We are continuing the test until electrical operation shows disruption. If no disruption is seen, after an extended period of time, we will initiate constant electrical powering of the modules.

In summary, progress made for SOW Task 2, provides us with high confidence that the physical ICVP assembly can survive the implanted environment without concern for electrical malfunction. Following fabrication of a larger number of ICVP modules, we will commence toxicology testing, followed by animal testing in non-human primates.

PROGRESS FOR SOW TASK 3

Task 3. Design and testing of a real-time psychophysical assessment and testing system for evaluation of an ICVP recipient, and design and fabrication of a first-generation portable image processing system for converting electronic images into cortical stimulation neural coding patterns.

For this task, work has progressed at IIT, in combination with JHU. Some delay was seen in obtaining updated equipment at JHU to design the psychophysical testing system, however this has now been resolved.

During the past year, work under the proposal at JHU has made major progress in two areas of psychophysics that will be central to the success of the cortical prosthesis program:

Under supervision of subcontract PI Gislin Dagnelie, PhD, Sr. Systems Manager Liancheng Yang and IIT graduate student Gayatri Kaskhedikar have developed phosphene mapping procedures allowing efficient and accurate creation of the spatial representation of each electrode's phosphene in visual space, and conversely of spatial coordinates onto the implanted electrodes. Ms. Kaskhedikar is now prepared for a series of visits to JHU to initiate testing of the hardware/software system at JHU. At IIT, software development for the communication of a portable image processing hardware system, that will command the implanted stimulators, is in development – good progress is being made as part of her doctoral thesis at IIT.

Mr. Yang and Ms. Kaskhedikar have also started development of psychophysical procedures that will allow exploration of phosphene dynamic range; this will provide minimum (threshold) and maximum (comfort or safety limit) stimulation levels for visible phosphene generation at each of the implanted electrodes, including efficient methods to track electrode responsivity over time.

In the 2nd award year, work in these two areas will be completed, and work on the 3rd aspect of the subaward, i.e., phosphene image transformations, will be undertaken.

In summary, the development of a testing system for mapping and evaluation of an implanted volunteer is of crucial importance to a future clinical trial. Similarly, availability of a portable system that the volunteer can take home, out of the laboratory, is, beyond doubt, one of the most important requirements for volunteers (as determined by our work on Task 4). Both of these essential system components have shown good progress during the past year.

PROGRESS FOR SOW TASK 4

4. Design and implementation of a volunteer recruitment and evaluation process that preserves subject protection, integrity, and maximizes project scientific significance.

Although progress on this task has suffered from an unanticipated long approval time for the Human Testing Protocol (psychology testing), preparatory, non-human work, was performed so that once IRB approval was obtained the human testing could proceed with minimal delay. That IRB approval is now in place, and progress for Task 4 is proceeding rapidly.

Task 4 Start-up: The project start-up has consisted of the development of: a recruitment plan, an informed consent document, the research protocol, conducting of interviews of recipients of the Dobelle implant, preparation for focus group interviews, and analysis of data. The specifics of each activity are described below.

Recruitment Plan Development: The co-investigators developed a plan for recruitment of participants for the focus groups. A flyer was developed and project personnel met with representatives at the Chicago Lighthouse for the Blind, the Blind Service Association, the National Association of Blind Veterans, and the U.S. Department of Veterans Affairs. Letters of support were obtained and the investigators included the Division of Rehabilitation Psychology at Illinois Institute of Technology, a top ten program in rehabilitation in the U.S. The plan included use of the IIT radio station to recruit for participants.

Informed Consent Development: The co-investigators developed an informed consent document for the focus groups and individual interviews of the Dobelle implant that meets the criteria set forth by the U.S. Army Medical Research and Materials Command, Office of Research Protection.

Army Research Protocol Approval: The recruitment flyer, informed consent documents and the protocol submission form was submitted to the U.S. Army Medical Research and Material Command, Office of Research Protection and approval was received before any human subjects research was conducted.

Interviews: Interviews of individuals that received a Dobelle implant have begun. One interview has been conducted and two are scheduled for the month of March and the final interview is scheduled for the month of May.

Focus Groups: The first informational session was held at the Chicago Lighthouse for the Blind on Thursday, February 20th. A total of 29 individuals attended the information session and 19 of the participants were screened as meeting the inclusion criteria for participation in a focus group. Three focus groups will be scheduled in the month of March to accommodate the 19 individuals screened to date.

Data Analysis: The preliminary data analysis of 13 transcribed interviews has been conducted. A total of 520 pages of transcribed interview have been coded with themes with an inter-rater reliability of at least 95% across 5 raters. The themes have been operationally defined and the investigators are in the process of reviewing the themes for hierarchical structure.

In summary, progress for Task 4 has been able to leverage work performed under non-TATRC funds. Human subject interview data under that effort has now been imported into this project. Completion of the Dobelle-subject interviews is a landmark event, and we plan to write a publication about the preliminary findings rapidly. Understanding the psychological needs of potential volunteers is crucial to a successful clinical trial. Unless the volunteer is an authentic member of the research team, the likelihood of maximizing knowledge obtained from the trial is substantially reduced. Integration of the psychology component with the technical and medical components of our team is substantial. Students in Dr. Troyk's lab, who are pursuing the technology development, communicate regularly with students from Dr. Lane's lab who are involved with the development of the volunteer selection and evaluation protocols.

PROGRESS FOR SOW TASK 5

Task 5. Constitute a team structure within a clinical setting for preparation of surgical implantation and human subject care.

The progress for this task has been excellent. Following changes in medical personnel at the University of Chicago, a highly qualified surgical and medical group is fully integrated with the technical personnel at IIT, MLS, and Sigenics. Involvement of HMRI has lagged somewhat owing to the delays in the non-human primate animal testing. However, we expect HMRI to be re-integrated into our team structure during Year 2.

The current project team includes:

The ICVP Team

IIT Colleagues:

Philip Troyk, Ph.D. – PI, bioengineer
Frank Lane, Ph.D. – psychologist
Margaret Huyck, Ph.D. – psychologist
Sungjae Suh, Ph.D. – material scientist
Gayatri Kaskhedikar – bioengineer
Sam Bredeson – bioengineer
Michael Davis, Ph.D. – ethicist

U of C Colleagues:

Sozari Chkhenkeli. MD - neurosurgeon
Jack Cowan, Ph.D. - mathematician
David Frim, MD - chief neurosurgeon
Patrik Gabikian, MD - neurosurgeon
Royce Lee, MD - psychiatrist
Ben Roitberg, MD - neurosurgeon
Leo Towle, Ph.D. - neurophysiologist
Wim VanDrongelen, Ph.D. – neurophysiologist
Craig Wardrip, DVM – veterinarian

Other team members:

Marty Bak – (MicroProbes for Life Sciences) bioengineer
Stuart Cogan, DSc – (EIC Labs) bioengineer, material scientist
Gislin Dagnelie, Ph.D. – (Johns Hopkins University) psychophysicist
Conrad Kufka, MD – (NIH - retired) neurosurgeon
Doug McCreery, Ph.D. – (Huntington Medical Research Institutes) bioengineer, neuroanatomist
Ed Schmidt, Ph.D. – (NIH -retired) bioengineer

This team has all of the expertise needed for deployment of the ICVP in a clinical trial. The working relationships are intimate, with publications and conference presentations crossing disciplines.

In summary, progress on Task 5 has been substantial, with the assemblage of an unprecedented team of expert individuals who have working relationships that are active and unified towards the goal of the clinical trial.

PROGRESS FOR SOW TASK 6

Task 6. Preparation and submission of an FDA IDE application for a human trial.

This is the culminating Task for the project work. Preparatory work for accomplishing this task has been performed in the first project year and includes: documentation of the technological status of the implantable hardware, development of a solid medical assessment for safety within a clinical trial, establishment of volunteer recruitment criteria, and an unprecedented understanding of potential volunteer needs, will form a solid ethical basis for presentation to the FDA, and a multi-parametric design of the first clinical trial experimental protocol.

During Year 2, we will engage the services of a consultant to advise us on the mechanics of IDE preparation. With the recent initiation of the "early feasibility program" at the FDA, this project can benefit from a greater recognition that proof-of-concept approaches to device testing is appropriate, provided that safety can be reasonably assured.

A preliminary visit to the FDA in Year 2 will establish the appropriateness of our project plan and form the basis for the IDE application preparation.

In summary, the combination of efforts for Tasks 1-5 have formed a solid basis for the pursuit of the IDE goal for Task 6 in the second project year.

KEY RESEARCH ACCOMPLISHMENTS

- Maturation of the ICVP technology resulting in a reliable implantable system ready for clinical deployment
- Critical laboratory testing of the ICVP stimulator modules to provide supporting evidence for an IDE application
- Design and implementation of novel and advanced psychophysical testing methods
- Design and fabrication of a portable ICVP image processing system
- Establishment of psychological testing and volunteer selection protocols based upon experiences of prior visual prosthesis recipients and focus groups of potential volunteers.
- Formation of a multi-disciplinary ICVP team, with on-going and active participation by all team members.
- Foundation for submission of IDE to the FDA for an ICVP clinical trial.

REPORTABLE OUTCOMES

Publications during the post-award notification/pre-award start date period

1. Samuel D. Bredeson, Philip R. Troyk, Sungjae Suh, and M. Bak, “Investigation of Long-Term Electrical Degradation in Neural Recording and Stimulation Microelectrode Arrays,” 6th Annual International IEEE EMBS Conference on Neural Engineering San Diego, California, 6 - 8 November, 2013 pp. 621 -624
2. Gayatri P. Kaskhedikar, Zhe Hu, Gislin Dagnelie and Philip R.Troyk, “Proposed Intracortical Vision Prosthesis System for Phosphene Mapping and Psychophysical Studies,” 6th Annual International IEEE EMBS Conference on Neural Engineering San Diego, California, 6 - 8 November, 2013 pp. 880-882
3. Samuel D. Bredeson, Philip R. Troyk, Sungjae Suh, and M. Bak, “Investigation of Long-Term Electrical Degradation in Neural Recording and Stimulation Microelectrode Arrays,” 6th Annual International IEEE EMBS Conference on Neural Engineering San Diego, California, 6 - 8 November, 2013 pp. 621 -624
4. Gayatri P. Kaskhedikar, Zhe Hu, Gislin Dagnelie and Philip R.Troyk, “Proposed Intracortical Vision Prosthesis System for Phosphene Mapping and Psychophysical Studies,” 6th Annual International IEEE EMBS Conference on Neural Engineering San Diego, California, 6 - 8 November, 2013 pp. 880-882
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15. F. Lane, P. Troyk, “Intracortical Visual Prosthesis: Assessing Readiness for a Clinical Trial,” 7th World Congress on Visual Prostheses, Detroit MI, September 11, 2012. (invited presentation)
16. Philip R. Troyk, “Intracortical Visual Prosthesis – Assessing Readiness for a Clinical Trial” Proceedings 7th World Congress on Visual Prostheses, Congress on Visual Prostheses: Eye and the Chip, Detroit MI, September 12, 2013

CONCLUSION

Progress towards the clinical trial deployment of the ICVP made possible through the work performed under this project has been good. Examination of the accomplishments, as detailed above, demonstrate that essential steps have been made towards the goal of this project: preparation for the clinical trial.

However, the slow start of the work in year one has hampered the rate progress. In part, the delays have resulted from the unanticipated complications of the animal and human protocol approvals, which delayed onset of critical project components. Therefore the progress in year one, while notable, is accompanied by some disappointments relative to the rate of work accomplished.

While we are now seeing a more rapid ramp up of the project work, we are anticipating a request for a one-year no-cost extension. We feel that for accomplishing the ultimate goal of the project: submission of an IDE to the FDA, it is realistic to plan for the no-cost extension request. The P.I. will be in contact with the TATRC project officer to discuss this plan.

Despite these reservations about the progress, the accomplishments of the first year are notable, particularly with respect to the maturation of the ICVP hardware.