

AWARD NUMBER: W81XWH-15-C-0066

TITLE: Development of an Implantable Pudendal Nerve Stimulator To Restore Bladder Function in Humans After SCI

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<b>13. SUPPLEMENTARY NOTES</b>					
<b>14. ABSTRACT</b> The goal of this contract is to develop an implantable pudendal nerve stimulator to obtain the FDA approval for a future clinical trial to restore bladder function in human after SCI. During the first year of the contract, we have achieved the following: <ol style="list-style-type: none"> <li>1. InCube Labs (subcontractor) has developed the pre-application material for FDA approval of Humanitarian Use Designation (HUD) of the device.</li> <li>2. InCube labs has designed and manufactured the first prototype of the stimulator, including both software and hardware.</li> <li>3. University of Pittsburgh has tested the first prototype of the stimulator in animal studies. Additional improvements on the first prototype were determined during the animal experiments.</li> </ol> We have made significant progress on every items listed in the statement of work (SOW). More details about this year's progress can be found in this annual report.					
<b>15. SUBJECT TERMS</b> Spinal Cord Injury, Bladder, Pudendal Nerve, Electrical Stimulation, Neuroprosthesis					
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## **1. INTRODUCTION**

After spinal cord injury (SCI) the bladder contracts frequently during urine storage - termed detrusor hyperreflexia (DH) which results in frequent incontinence (urine leakage). Meanwhile, during micturition the external urethral sphincter (EUS) contracts simultaneously with the bladder - termed detrusor sphincter dyssynergia (DSD) which prevents the bladder from emptying completely.

Currently, there is no medication that can treat both DH and DSD to normalize bladder functions after SCI. Daily urethral catheterization is the most common treatment, which can result in frequent infections of the lower urinary tract. The daily life of SCI people is burdened tremendously by these urinary problems. In the 1970s, Brindley and his team developed an implantable sacral anterior root stimulator to restore bladder functions after SCI. This stimulator is now commercially available (Finetech Medical Limited, UK) and has been implanted in approximately 2000 people around the world during the last 40+ years. Its usage has been limited due to it requiring sacral posterior root rhizotomy (i.e. cutting the sensory spinal roots) that is destructive and irreversible. Sacral posterior root rhizotomy also results in the loss of reflex sexual and defecation functions that are very important residual reflexes for SCI people.

The long-term goal of our project is to develop a novel neuroprosthetic device (PSTIM device) to restore the functions of the urinary bladder for SCI people without causing associated damage to the nervous system. Based on our previous studies, we propose in this project to use pudendal nerve stimulation and blockade to restore both continence and micturition after SCI.

Our strategy does not require sacral posterior root rhizotomy, is expected to preserve the spinal reflex functions of the bowel and sexual organs, and more importantly provides the opportunity for SCI people to benefit from any advance in neural regeneration and repair techniques in the future. Our novel implantable stimulator is designed to greatly improve the quality of life for thousands of veterans suffering from SCI. It is also designed to significantly reduce the burden for the veteran's family members who are currently the primary care-givers in the management of the lower urinary tract problems.

## **2. KEYWORDS**

Spinal Cord Injury, Bladder, Pudendal Nerve, Electrical Stimulation, Neuroprosthesis

### 3. ACCOMPLISHMENTS

#### **What were the major goals of the project?**

The major tasks and sub-tasks listed in the statement of work (SOW) over 48 months are as follows. The Yr1 SOW was refined and approved by DOD:

Task 1. Design and develop an implantable pudendal nerve stimulation system for FDA (Investigational Device Exemption) IDE approval (months 1-48).

- 1a. Schedule a pre-application FDA meeting (months 1-2)-DONE.
- 1b. First design of the implantable stimulator (months 1-6)-DONE.
- 1c. Manufacture first stimulator for animal studies (months 6-12)-DONE.
- 1d. Improve the design based on acute animal studies (months 12-24).
- 1e. Improve the design based on chronic animal studies (months 24-42).
- 1f. File FDA IDE application (months 40-42).
- 1g. FDA IDE approval (months 42-48).

Task 2. Test the safety and efficacy of the implantable stimulator in chronic SCI cats (months 13-48).

- 2a. Test the stimulator acutely in normal cats (months 13-24)-STARTED EARLY.
- 2b. Test the stimulator chronically in SCI cats (months 24-48).
- 2c. Test the stimulator for FDA IDE approval (months 36-48).
- 2d. Data analysis and publishing the results (months 42-48).

#### **What was accomplished under these goals?**

During the first year of the project, we have made significant progress on Tasks 1a and completed Tasks 1b and 1c. We have even made an earlier than expected start on Task 2a as listed in the SOW (see above).

Task 1a. Schedule a pre-application FDA meeting (months 1-2).

Mr. Mike Billig, Vice President, Regulatory and Quality Affairs at InCube Labs, has had an informal conversation with an FDA representative from the Division of Orphan Devices at a recent MDMA (Medical Device Manufacturer's Association) conference in the San Francisco Bay Area that they both attended and participated in as panelists and obtained the FDA representative's informal input to entertain a formal communication re: a regulatory path for implantable pudendal nerve stimulator. Based on this informal communication with FDA, InCube Labs has developed pre-application materials to the FDA requesting a Humanitarian Use Designation (HUD) of the implantable stimulator. InCube Labs has submitted a completed draft of a request for FDA HUD to its regulatory consultant (Experien Group) and received initial feedback that is being addressed in a revised draft. InCube Labs is planning to submit the

completed HUD request to FDA in October-November 2016. If FDA approves this HUD request, we will pursue the Humanitarian Device Exemption (HDE) pathway instead of a FDA IDE as planned initially. The HDE is a unique approval pathway for medical products intended for very small patient populations. FDA requires that a company provide data to show that the product is safe-"will not expose patients to an unreasonable or significant risk of illness or injury"-for its intended patient population. The device also needs to illustrate a benefit to health. In this case, a subset of spinal cord injury patients with DSD and meeting specific conditions required for reasonable efficacy of the device have been identified. The outline of the FDA HUD request is included with this report as Appendix 1. If however FDA does not approve the HUD request, we will pursue the IDE/PMA regulator pathway.

Task 1b. First design of the implantable stimulator (months 1-6).

InCube Labs has designed the first prototype of the implantable pudendal nerve stimulator that can provide 3 output channels for stimulation and/or blockade of the pudendal nerves. The block diagram of the implantable electronics design for the PSTIM is shown in Figure 1.

## P-Stim Block Diagram

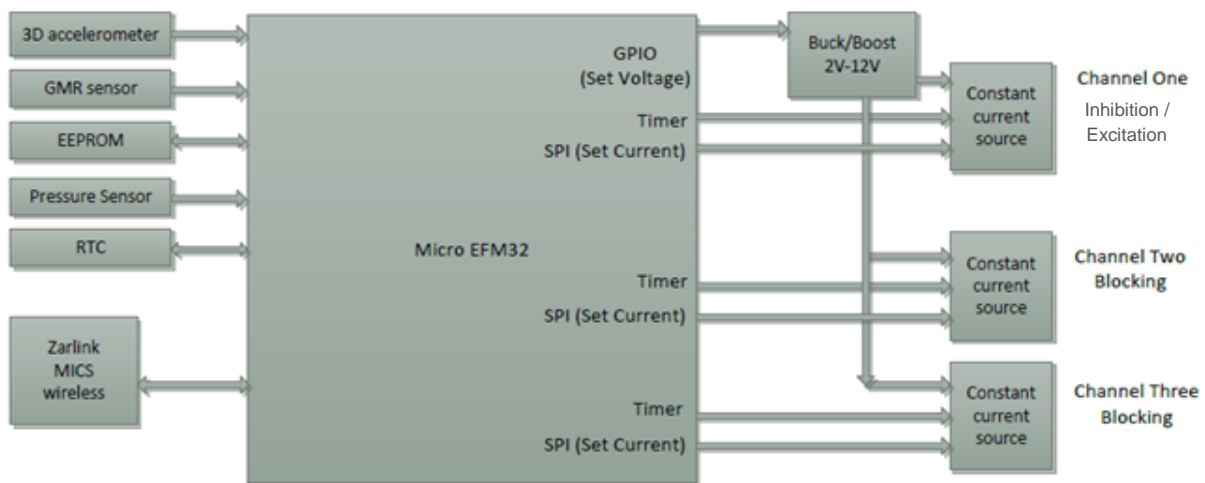


Figure 1. Block Diagram

The 3 output channels are designed to provide constant current outputs that are driven by a 12 V power supply. Channel #1 is designed to have a maximal output of 10 mA and channels #2 and

#3 are designed to have maximal outputs of 20 mA. This first design does not include wireless charging and wireless communication functions. These wireless functions will be added as the design and development circles progress. The main purpose of the first design is to determine if the 12 V power supply is strong enough to provide the maximal constant current outputs, which will also be dependent on the impedance of the electrode-nerve interface. Therefore, this first design was tested in animal studies using the newly developed stimulation cuff electrode (described below) to determine the electrode impedance and the maximal current output. Electrical circuits of this design are attached with this report as Appendix 2.

In addition to the hardware, InCube Labs has also developed software to control / program the stimulator via a USB port interface. The software can program the stimulation parameters for each output channel. The graphical user interface (GUI) is shown in Figure 2.

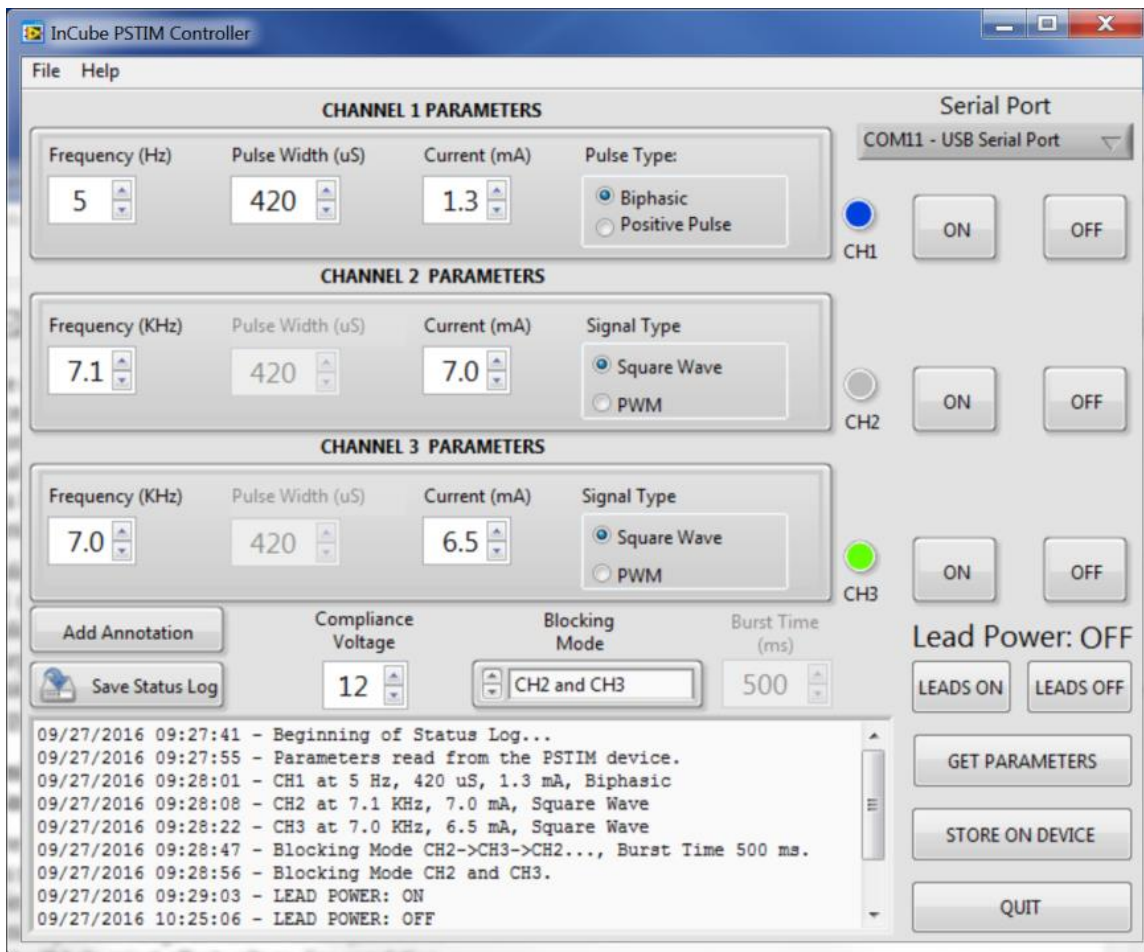


Figure 2. Graphical User Interface

InCube Labs has also designed and tested methods to make the cuff electrodes for animal studies. Methods of manufacturing nerve cuff electrodes were evaluated and tested. This includes methods for flattening platinum wire and die cut or molded silicone components for construction

of leads. One of the molds for manufacturing the silicone cuff and an example of a developed tripolar cuff electrodes are shown in Figure 3.

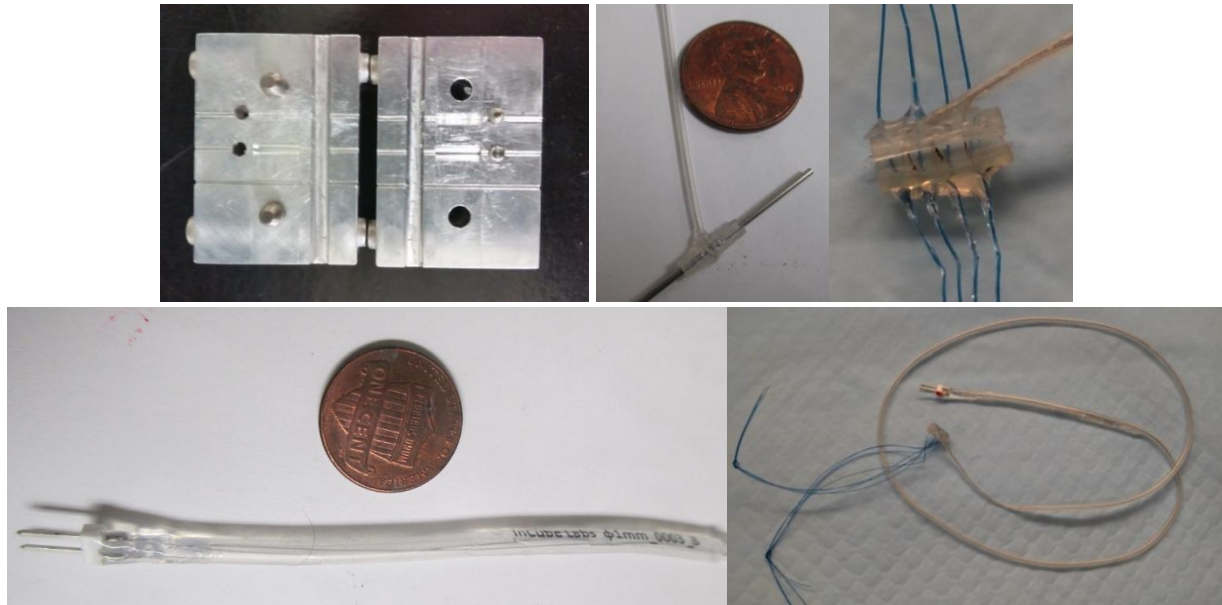


Figure 3. Prototype Nerve Cuff Electrode. Clockwise from top left: nerve cuff mold; distal nerve cuff electrode with pin representing pudendal nerve; close up tripolar electrode with anchoring suture; whole nerve cuff electrode; proximal connector.

#### Task 1c. Manufacture first stimulator for animal studies (months 6-12).

Based on the above design, InCube Labs has manufactured ten (10) functional stimulators and numerous cuff electrodes (bipolar or tripolar) of variable sizes (1-2 mm inner cuff diameters) for testing in animal and bench-top studies. The final version of the first prototype of the stimulator is shown in Figure 4:

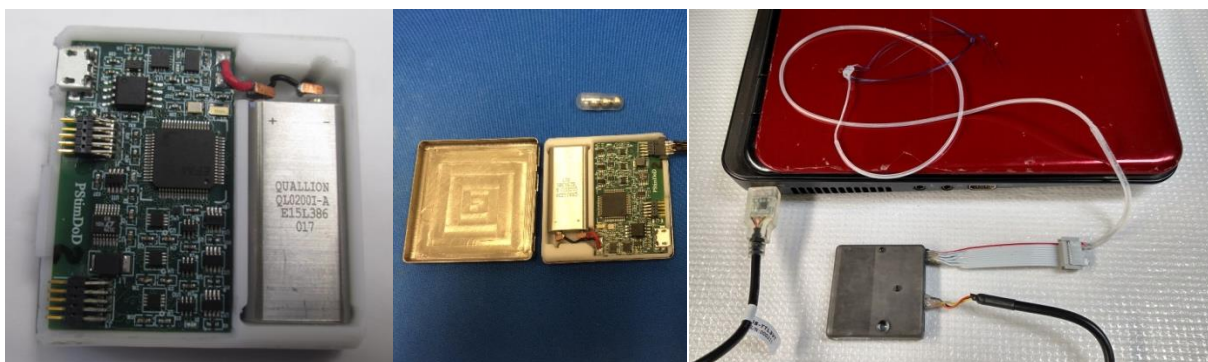


Figure 4. Prototype Implantable Pulse Generator. From left to right: circuit board and battery; pulse generator and open housing with size 00 capsule for comparison; pulse generator with programming cable, laptop, and nerve cuff electrode.

This first prototype has been tested in two anesthetized cats to determine if the stimulator can provide the required stimulation parameters/waveforms to stimulate or block the pudendal nerves. The protocols for animal studies have been approved by the IACUC at the University of Pittsburgh and by the USAMRMC Animal Care and Use Review Office (ACURO). The experiment setup is shown in Figure 5.

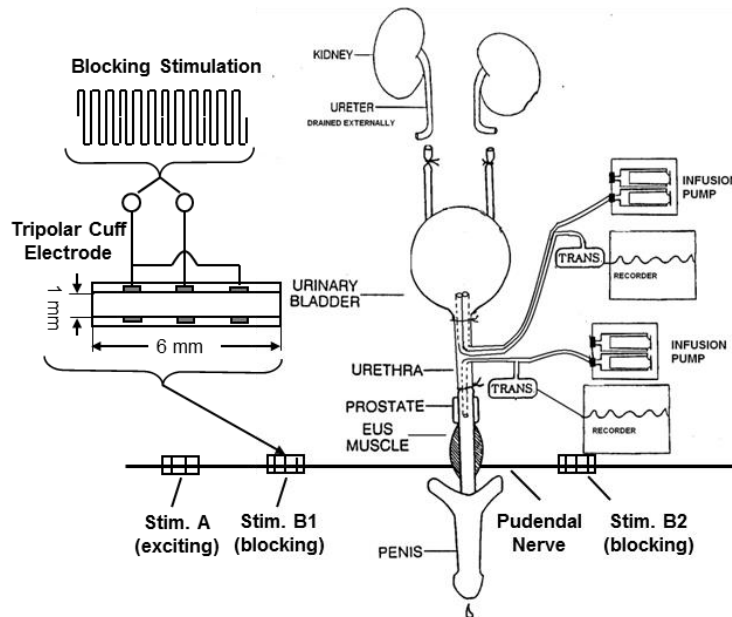


Figure 5. Experimental Setup

The temperature of the animal was maintained at 35 °C to 37 °C using a heating pad. The ureters were cut and drained externally. A double lumen catheter (5F) was inserted into the bladder through a small incision in the proximal urethra and secured by a ligature. One lumen of the catheter was attached to a pump to infuse the bladder with saline, and the other lumen was connected to a pressure transducer to monitor the bladder activity. Another catheter (5F) was also inserted at the same site in the proximal urethra but directed toward the distal urethra and secured by a ligature. This catheter was attached to an infusion pump and to a pressure transducer via a T connector. The pudendal nerves were accessed posteriorly in the sciatic notch lateral to the tail. The three cuff electrodes (Stim. A – bipolar cuff, Stim. B1/B2 – tripolar cuff) were placed around the left and right pudendal nerves as shown in the figure above. After implanting the electrodes, the muscle and skin were closed by sutures. The three cuff electrodes were connected to the prototype stimulator that was external to the animal (not implanted). Stimulation current generated by the stimulator was delivered to each cuff electrode as needed during the experiment.

The prototype stimulator generated stimulation current strong enough to stimulate the pudendal nerve to inhibit reflex bladder activity. The stimulator output channel #1 provided pudendal nerve stimulation (PNS) at 5 Hz, 0.2 ms, and 1 mA to the Stim.A cuff electrode, which completely inhibited micturition reflex contraction during a slow infusion of the bladder (Figure

6). This result indicates that the maximal output 10 mA as designed is large enough for producing bladder inhibition.

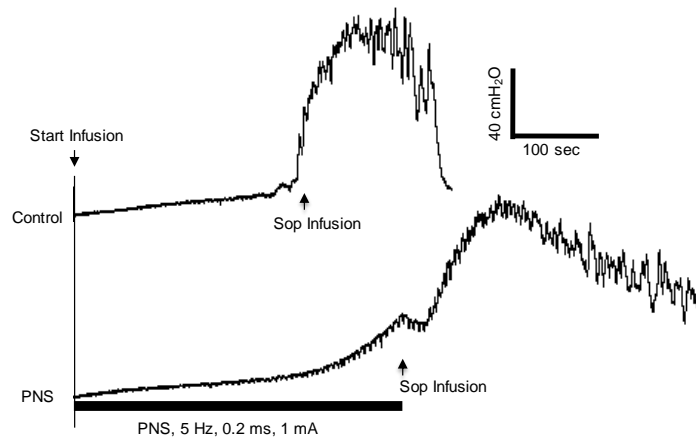


Figure 6. Bladder Inhibition

The prototype stimulator also generated strong enough current output to stimulate the pudendal nerve to excite the bladder and induce a strong bladder contraction. PNS (1 mA, 0.2 ms) at 20 Hz produced the maximal bladder contraction while PNS at 5 Hz had no effect (Figure 7) when the bladder was maintained at isovolumetric conditions with its volume at about 80-90% bladder capacity. This result indicates that the maximal output of 10 mA at channel #1 is also large enough for producing bladder excitation.

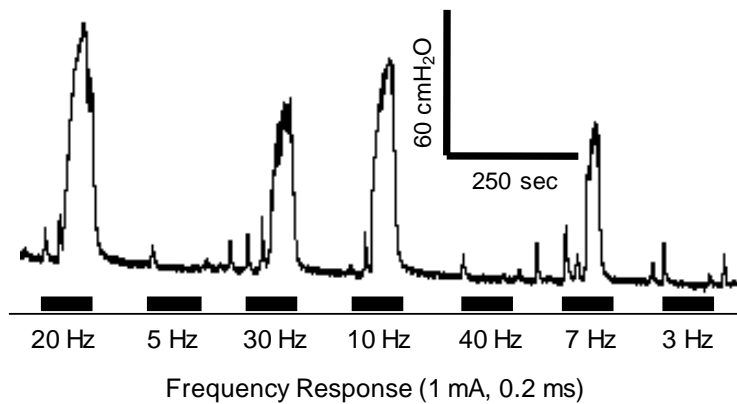
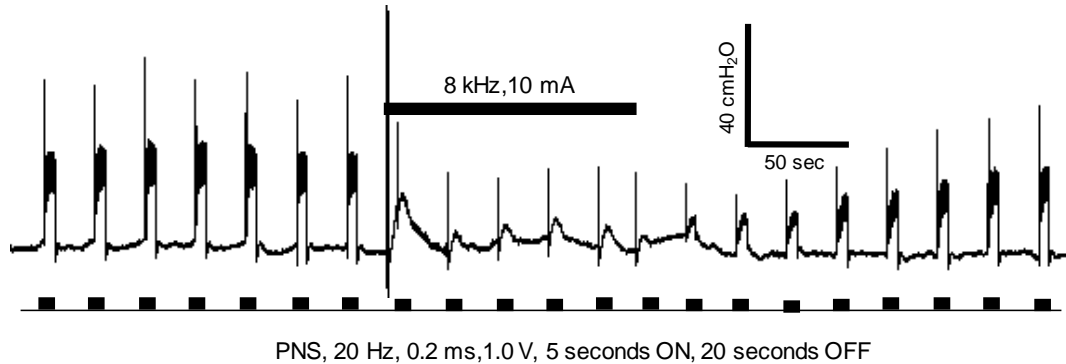


Figure 7. Bladder Contraction

We further tested the stimulator to block the pudendal nerve using the 2 electrodes implanted on the same side of the pudendal nerve (Stim. A and Stim. B1, see Figure 5). PNS at Stim. A was 20 Hz, 0.2 ms, 1.0 V (5 seconds ON and 20 seconds OFF) that was provided by our lab stimulator (S88, Grass Medical Instruments, Quincy, MA), while the PNS at Stim. B1 was 8 kHz biphasic square waveform (see Figure 5) that was provided by the prototype stimulator. As shown in the Figure 8, the 8 kHz PNS significantly reduced the urethral sphincter contractions but did not

completely block the contractions. This result indicates a partial block (Figure 8) of the pudendal nerve. After measuring the impedance of the electrode-nerve interface, we found that the impedance could be as high as 2 k $\Omega$ . Therefore, the 12 V power supply could only produce 6 mA maximal current output (not 10 mA as requested), which is not strong enough to induce a complete block of the pudendal nerve. Similar results were also obtained when the kHz blocking stimulation was applied on both sides of the pudendal nerves.



*Figure 8. Pudendal Nerve Block (partial)*

Based on the results of our animal experiments, we learned that: (1) the voltage of the power supply may need to be increased in order to provide strong enough constant current for nerve block; (2) the impedance of the electrode-nerve interface may need to be reduced so that the voltage of the power supply will not have to be very high. We will re-design the electrodes to increase the contact surface between the electrode and nerve in order to reduce the impedance. We may also re-design the stimulator to provide a higher voltage power supply to generate the required maximal current output.

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

Nothing to Report.

**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?**

Based on our SOW, we are planning to do the following during the next year:

Task 1. Design and develop an implantable pudendal nerve stimulation system for FDA IDE approval (months 1-48).

1a. Schedule a pre-application FDA meeting (months 1-2).

InCube Labs will submit the completed HUD request to FDA in October / November 2016. If FDA approves this HUD request, we will pursue this regulatory pathway instead of a FDA IDE as planned initially. Otherwise, InCube Labs will continue the original plan to obtain FDA IDE approval and get that process started by planning for a pre-submission meeting with FDA in later Yr2 or early Yr3.

1d. Improve the design based on acute animal studies (months 12-24).

InCube Labs will further improve the design based on the learnings from the acute in-vivo animal studies that have already been started in Yr1. Then, a new version of the stimulator will be manufactured and tested again. This design-build-test cycle will be repeated multiple times during the second year of this project to converge on a robust and efficacious implantable system.

Task 2. Test the safety and efficacy of the implantable stimulator in chronic SCI cats (months 13-48).

2a. Test the stimulator acutely in normal cats (months 13-24).

At University of Pittsburgh, the investigators will test the implantable stimulator in anesthetized normal animals (N= 10 cats) to determine its functionality or identify problems to further improve the design. These experiments are non-GLP studies for the purpose of device design and development.

## **4. IMPACT**

### **What was the impact on the development of the principal discipline of the project?**

After spinal cord injury (SCI) the bladder contracts frequently during urine storage - termed detrusor hyperreflexia (DH) which results in frequent incontinence (urine leakage). Meanwhile, during micturition the external urethral sphincter (EUS) contracts simultaneously with the bladder - termed detrusor sphincter dyssynergia (DSD) which prevents bladder from emptying completely. Currently, there is no medication that can treat both DH and DSD to normalize the bladder functions after SCI. Daily urethral catheterization is the most common treatment, which can result in frequent infections of the lower urinary tract and hospitalization. The daily life of SCI people is burdened tremendously by these urinary problems. Our project will develop a wirelessly charged, wirelessly controlled, small implantable pudendal nerve stimulator to restore bladder function after SCI. The success of our project will create a novel implantable neuroprosthesis to restore both continence and micturition functions for SCI people. It will fundamentally change the current medical treatments for the lower urinary tract dysfunctions

after SCI. Daily urethral catheterization will not be the norm for SCI. Frequent infection of the lower urinary tract will be eliminated. The quality of life will be improved greatly for both SCI people and their family.

**What was the impact on the other disciplines?**

Nothing to Report.

**What was the impact on technology transfer?**

InCube Labs is the subcontractor of this DOD-Pitt contract and is collaborating with the University of Pittsburgh (Pitt) to develop this technology for clinical application. During this contract period, InCube Labs will develop the implantable stimulator as a Class III medical device for FDA HDE/IDE approval. After this DOD contract ends, InCube Labs expects to further commercialize this technology by conducting the clinical trial and applying for FDA PMA approval. After FDA PMA approval, InCube Labs will aim to market this technology for clinical application or will transfer it to an established medical device company for commercialization. Therefore, the success of our current effort will significantly impact the technology transfer to benefit those people suffering from SCI. Towards this commercialization objective, InCube had optioned the existing issued patent and related intellectual property and know-how from the University of Pittsburgh. If results and progress are promising, InCube will convert this option into a license and start a company to commercialize this technology.

InCube has developed intellectual property (IP) in the area of closed loop treatment of neurogenic bladder, which will be very relevant to the PSTIM project. InCube Labs has also developed, over the past several years, IP relating to wireless communications for implantable devices, ceramic to metal feed-through for implants as well as hermetic sealing processes for implantable devices. Many of these technologies will also be utilized in the development and manufacture of the PSTIM devices. Details of this technology are included in Exhibit G2 (Subcontractor Background IP) of the contract.

**What was the impact on society beyond science and technology?**

The success of our project will significantly impact the quality of life of SCI people and their family members who are currently the primary care-givers in the management of the lower urinary tract problems. Our technology will fundamentally change the current medical treatments for the lower urinary tract dysfunctions after SCI. Daily urethral catheterization will not be the norm for SCI. Frequent infection of the lower urinary tract will be eliminated.

## **5. CHANGES/PROBLEMS**

### **Changes in approach and reasons for change**

InCube Labs is planning to submit the completed HUD request to FDA in October / November 2016. If FDA approves this HUD request, we will pursue the Humanitarian Device Exemption (HDE) pathway instead of a FDA IDE as planned initially. The HDE is a unique approval pathway for medical products intended for very small patient populations. FDA requires that a company provide data to show that the product is safe-"will not expose patients to an unreasonable or significant risk of illness or injury"-for its intended patient population. The device also needs to illustrate a benefit to health. In this case, a subset of spinal cord injury patients with DSD and meeting specific conditions required for reasonable efficacy of the device have been identified. The outline of the FDA HUD request is included with this report as Appendix 1. If however FDA does not approve the HUD request, we will pursue the IDE/PMA regulator pathway.

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

The DOD-Pitt contract became effective on September 23, 2015. However, the subcontract between InCube Labs and Pitt was delayed and it was signed on February 29, 2016. The investigators at the University of Pittsburgh (Pitt) and the InCube Labs have worked diligently during the first year of the contract and have managed to successfully accomplish the tasks as listed in the SOW despite a 5 month delay in the signing of the subcontract between Pitt and InCube Labs.

The challenges that we anticipate going forward and their mitigation plans are:

- a. Translation of results in acute and chronic cat model to the human: The risk is not knowing whether and how well results in cats will translate to safety and efficacy in humans. Towards this end, we are developing a design optimization tool in Yr2 which is catheter based and could enable us to test stimulation parameters in humans (outside the scope of the DOD project) sooner than later in order to inform the final design of the implantable system.
- b. Anatomic fit in proposed SCI patients: Surgical implantation of the IPG (implantable pulse generator) and reliable implantation and placement of the cuffs and connecting to the IPG, as well as related surgical implant and explant tools is a challenge that has been identified, and will be resolved by consulting with well-recognized urological surgeons performing cadaveric anatomic fit trials using models and prototypes developed. These will be performed in Yr2.

### **Changes that have a significant impact on expenditures**

Due to the delay of the subcontract signing process, InCube Labs requested re-budgeting and DOD has approved the re-budgeting. The total amount of the re-budget is same as the original budget.

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

Nothing to Report.

## **6. PRODUCTS**

### **Publications, conference papers, and presentations**

Nothing to Report.

### **Websites or other Internet sites**

Nothing to Report.

### **Technologies or techniques**

During the first year of the contract, InCube Labs has designed and manufactured the first prototype of the implantable pudendal nerve stimulator and cuff electrodes suitable for animal studies. These developments have been reported in previous sections of this report.

### **Inventions, patent applications, and/or licenses**

Nothing to Report.

## **Other products**

InCube Labs is investigating methods of determining bladder “full” and “empty” status in an effort to develop a “closed loop” implantable device whereas the patient can be made aware of their bladder status and respond accordingly. Efforts to date have focused on bladder wall impedance, direct and indirect pressure measurements, and infrared (IR) sensing of bladder distention. IR sensing has shown the most promise. InCube is making accommodations for this sensing technology in the electro-mechanical design of the implant and will pursue studies to validate this technology in Year 2.

A catheter-based system is being developed to optimize the stimulation parameters by getting human data sooner. This technology could eventually be commercialized in its own right or it could be commercialized in conjunction with the implantable PSTIM system as a way to screen for potential responders using an external device prior to deciding to implant the PSTIM device.

## **7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS**

### **What individuals have worked on the project?**

Name:	Changfeng Tai
Project Role:	PI
Nearest Person Month Worked:	4
Contribution to Project:	Manage the project, develop the specifications of the implantable stimulator, and test the prototype stimulator in animal experiments.
Funding Support:	This DOD contract

Name:	James Roppolo
Project Role:	Co-Investigator
Nearest Person Month Worked:	2
Contribution to Project:	Develop the specifications of the implantable stimulator, and test the prototype stimulator in animal experiments.
Funding Support:	This DOD contract

Name:	Bing Shen
Project Role:	Research Associate
Nearest Person Month Worked:	3

Contribution to Project: Test the prototype stimulator in animal experiments and analyze the data.

Funding Support: This DOD contract

Name: Pratap Khanwilkar

Project Role: Co-PI

Nearest Person Month Worked: 3

Contribution to Project: VP Product Development – provide project management and oversight of engineering efforts.

Funding Support: This DOD contract

Name: Phil Morgan

Project Role: Co-PI

Nearest Person Month Worked: 1

Contribution to Project: VP and General Manager – provide project management and contribute to regulatory package.

Funding Support: This DOD contract

Name: Mir Imran

Project Role: Co-PI

Nearest Person Month Worked: 1

Contribution to Project: President – direct overall design efforts

Funding Support: This DOD contract

Name: Kyle Horlen

Project Role: Program Manager

Nearest Person Month Worked: 3

Contribution to Project: Program management, preclinical and regulatory package development.

Funding Support: This DOD contract

Name: Elmar Fischer

Project Role: Mechanical Engineer

Nearest Person Month Worked: 1

Contribution to Project: Design and prototyping of housing, header, connector, and catheter.

Funding Support: This DOD contract

Name: Kevin Honeager  
Project Role: Firmware Engineer  
Nearest Person Month Worked: 3  
Contribution to Project: Firmware / software design and development.  
Funding Support: This DOD contract

Name: Paul Spehr  
Project Role: Leads Engineer  
Nearest Person Month Worked: 6  
Contribution to Project: Design and production of nerve cuff electrodes, catheter design and prototyping.  
Funding Support: This DOD contract

Name: Carl Santora  
Project Role: Mechanical Engineer  
Nearest Person Month Worked: 1  
Contribution to Project: Equipment procurement and set up for prototyping and manufacturing.  
Funding Support: This DOD contract

Name: Lu Zheng  
Project Role: Electrical Engineer  
Nearest Person Month Worked: 6  
Contribution to Project: Hardware design and circuit board development.  
Funding Support: This DOD contract

Name: Ralph Peterson  
Project Role: Biomedical Engineer  
Nearest Person Month Worked: 1  
Contribution to Project: Design and testing of bladder sensing methodology.  
Funding Support: This DOD contract

Name: Ryan Young  
Project Role: Quality Engineer  
Nearest Person Month Worked: 1  
Contribution to Project: Set-up of Arena quality assurance program.  
Funding Support: This DOD contract

Name: Varghese George  
Project Role: Research Scientist  
Nearest Person Month Worked: 2  
Contribution to Project: Nerve cuff electrode production, bladder sensor testing, contribute to regulatory package  
Funding Support: This DOD contract

Name: Katherine Pitts  
Project Role: Intern  
Nearest Person Month Worked: 3  
Contribution to Project: Nerve cuff lead production.  
Funding Support: This DOD contract

Name: Isabel Pina  
Project Role: Intern  
Nearest Person Month Worked: 3  
Contribution to Project: Nerve cuff electrode production.  
Funding Support: This DOD contract

Name: Celeste Rayon  
Project Role: Consulting Quality Engineer  
Nearest Person Month Worked: 1  
Contribution to Project: Establish quality assurance program.  
Funding Support: This DOD contract

Name: Tim Cox  
Project Role: Consulting Electrical Engineer  
Nearest Person Month Worked: 1  
Contribution to Project: Wireless charger design.  
Funding Support: This DOD contract

Name: Steve Kraus  
Project Role: Consulting Physician  
Nearest Person Month Worked: 1  
Contribution to Project: Provide clinical feedback of prototypes.  
Funding Support: This DOD contract

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

InCube PI and key personnel efforts were substantially increased as a result of the reported delay in executing the InCube-Pitt subcontract in Yr1, in order to complete Yr1 deliverables in six months, which was originally planned to take the entire Yr1. These changes have been pre-approved by DOD.

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

Organization Name:	InCube Labs, LLC.
Location of Organization:	2051 Ringwood Ave, San Jose CA 95131 12500 Network Blvd. #112, San Antonio, TX 78249
Partner's contribution to the project:	Subcontracted to design and develop the implantable stimulator for FDA IDE approval.

**8. SPECIAL REPORTING REQUIREMENTS**

The Quad Chart is attached as Appendix 3.

**9. APPENDICES**

# **An Implantable Pudendal Nerve Stimulator (P-Stim Device) for Treatment of Detrusor Sphincter Dyssynergia (DSD)**

## **Request for Humanitarian Use Device (HUD) Designation.**

*Request for a Specifically Identified Subset of a Non-Rare Condition*

### EXECUTIVE OUTLINE

#### **1.0 NAME AND ADDRESS OF THE APPLICANT AND PRIMARY CONTACT PERSON**

InCube Labs, LLC – Mir Imran

#### **2.0 DESCRIPTION OF THE RARE DISEASE OR CONDITION**

The innervations for sympathetic and parasympathetic systems that control bladder storage and micturition, respectively, are described here. This section also explains how these two systems are in sync with each other to help the bladder function in a coordinated fashion. Detrusor-sphincter dyssynergia (DSD) is defined as the impaired coordination between detrusor and sphincter during voiding due to a neurologic abnormality and is commonly characterized by involuntary contractions of the external urethral sphincter during an involuntary detrusor contraction. Sequelae of DSD include hydronephrosis, recurrent pyelonephritis, and renal failure. Current treatments involving physical intervention and pharmacological therapies and their inconveniences, lack of efficacy, etc. are discussed, enabling the discussion of how the PSTIM device would be an appropriate alternative treatment. Etiological reasons to the development of DSD are described, which include: traumatic spinal cord injury, multiple sclerosis, spinal dysraphism, and transverse myelitis. A detailed description of each of these conditions associated with DSD is provided.

#### **3.0 PROPOSED INDICATION FOR USE OF THE DEVICE**

The P-Stim Device seeks to provide effective, long-term, treatment of DSD thereby increasing functional bladder capacity, continence and evacuation of urine along with reduction in urinary tract infections and improvement in upper tract function.

#### **4.0 DESCRIPTION OF THE DEVICE AND SCIENTIFIC RATIONALE FOR ITS USE AS PROPOSED**

In this section, the P-stim device is described in detail. The housing of the generator can as well as the anticipated life span of the battery of up to 5 years and how it will be wirelessly charged across the skin by an external coil is briefly described. The implantable pulse generator (IPG) will provide outputs to 3 channels by energizing 3 electrodes. Channel 1 is connected via a bipolar cuff electrode, while Channel 2 and 3 are connected to a tripolar cuff electrode. The detailed frequencies that each channel will be set to are also given followed by an explanation of which combinations of these stimulated channels will result in certain expected outcomes that are seen in vivo. Peer reviewed research is cited to support these claims.

## **5.0 POPULATION DETERMINATION**

This section describes the idea behind selecting populations with DSD along with its 4 etiological reasons: 1) traumatic spinal cord injury, 2) multiple sclerosis, 3) spinal dysraphism, and 4) transverse myelitis. Reasons as to why a specific subset or the entire population of each of these four conditions were or were not considered is provided.

For example, incidences of traumatic spinal cord injury that are associated with DSD from T7-L5 were considered. Cervical injuries (C1-C6) are excluded from the discussion, as individuals with these types of injuries are unable to complete a self-care program. Injuries that are above T6 are also excluded due to autonomic dysreflexia. Autonomic dysreflexia is associated with large sympathetic surges that result in peripheral vasoconstriction, and as a result uncontrolled hypertension. If left unchecked, it could lead to other detrimental conditions, including death. Since sensory input is being modulated by the actions of the device, the likelihood of a sequential surge of a sympathetic response makes pudendal nerve stimulation a safety concern for patients with injuries above T6. Since sacral innervations preserve the parasympathetic reflex, an attribute that is important in order for the P-Stim device to be successful, injuries here can lead to detrusor areflexia also known as a flaccid bladder. The P-Stim device is incompatible with such a condition.

On a different note, the progressivity of conditions such as multiple sclerosis and spinal dysraphism entails its exclusion from the discussion. Individuals with transverse myelitis, on the other hand, are included in this discussion due to the very fact that the nature of this condition is not progressive despite this condition being similar to multiple sclerosis with regards to demyelination.

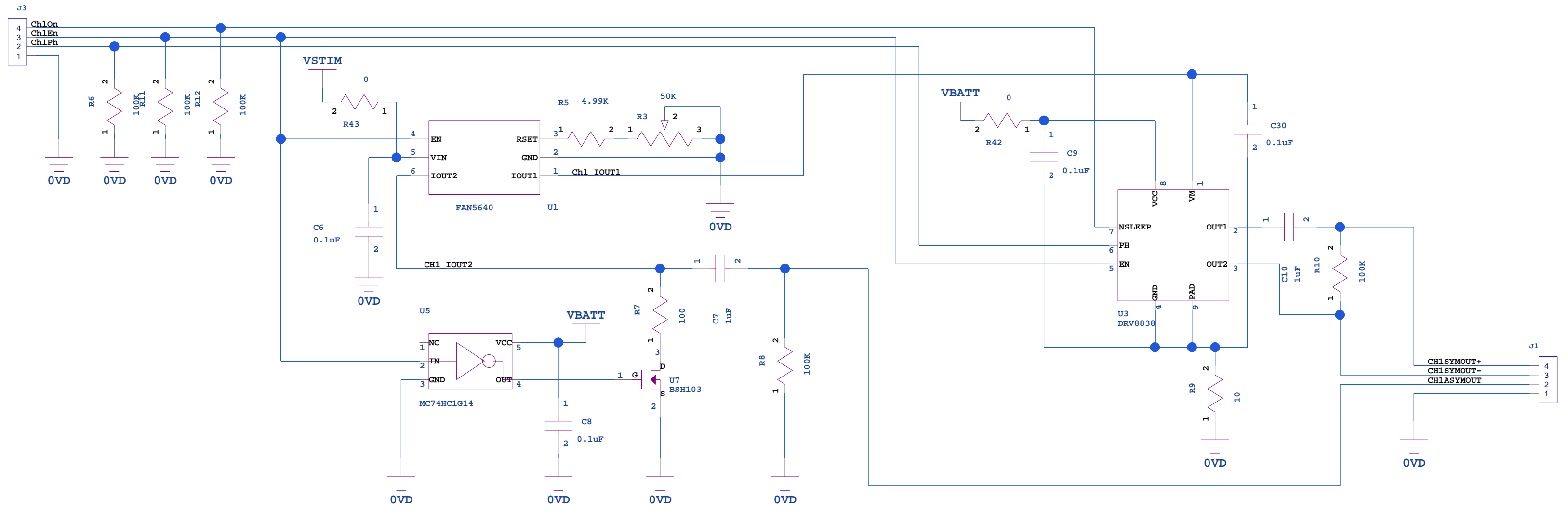
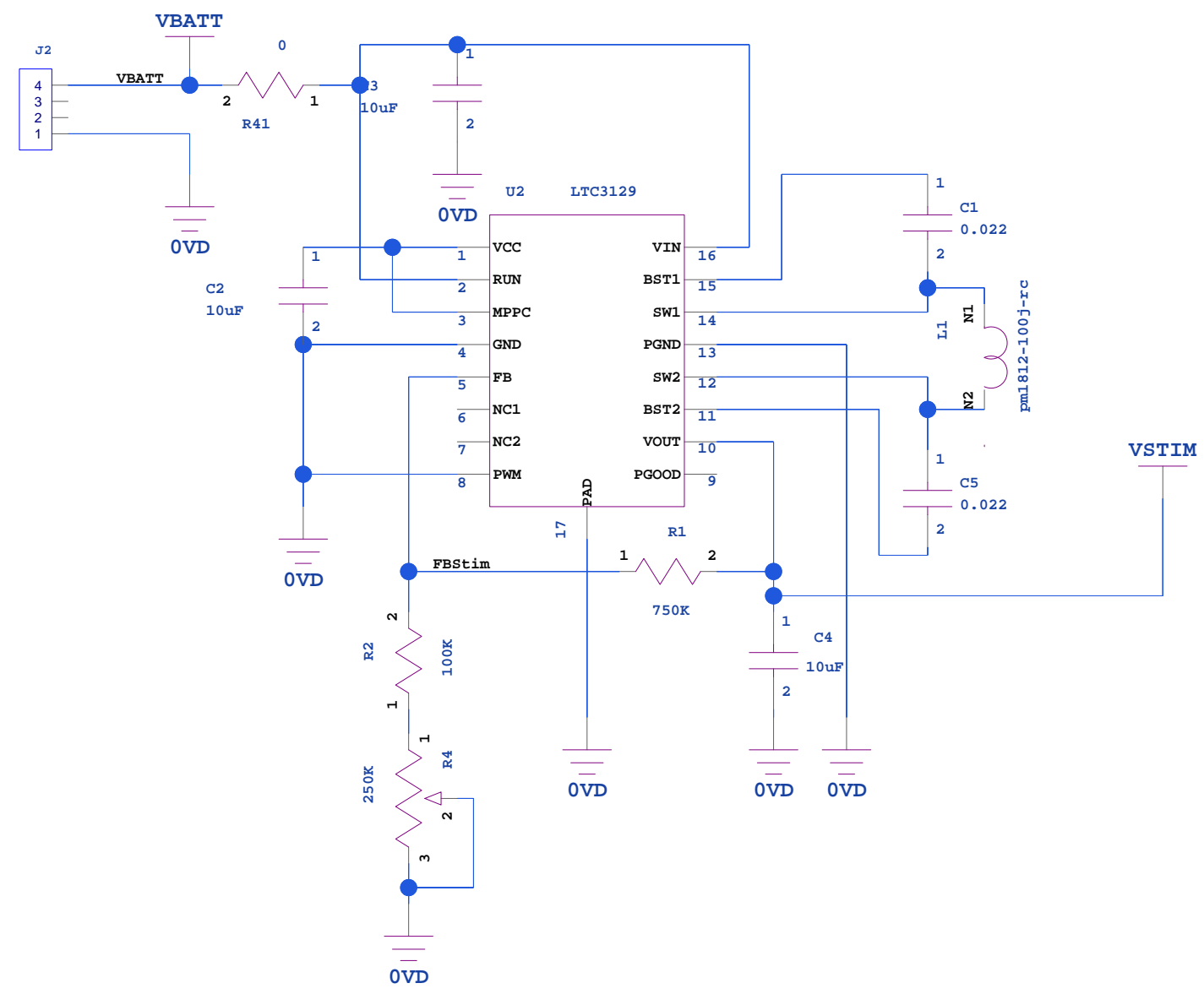
The population in consideration are those that have DSD with a traumatic spinal cord injury from T7 to L5 and transverse myelitis. The average incidence of traumatic spinal cord injury is around 13,000. 31.2% of these patients have an injury from T7-L5, and 33.3% of those patients will exhibit symptoms of DSD. This comes out to about 1,351 patients. The average incidence of transverse myelitis is around 1400, and 48% of these patients will exhibit DSD. Hence, the grand total of patients that are considered appropriate for the P-stim device is around 2023, well below the 4000 cases needed to help make the case for HUD.

## **6.0 CONCLUSIONS TO SUPPORT HUD OF THE PSTIM DEVICE**

The P-Stim device is a neural prosthetic implant intended to treat symptoms of DSD. DSD is associated with 4 distinct disease processes: spinal cord injury, multiple sclerosis, spinal dysraphism, and transverse myelitis. Of these patient populations, multiple sclerosis and spinal dysraphism are excluded due to the progressive nature of the disease. As the P-Stim device utilizes a combination of afferent pudendal nerve stimulation and efferent pudendal nerve blocking to achieve therapeutic effect, risk of autonomic dysreflexia secondary to afferent pudendal nerve stimulation, requirement for patients to complete a self-care bladder management program, and requirement that patients have an intact sacral micturition center

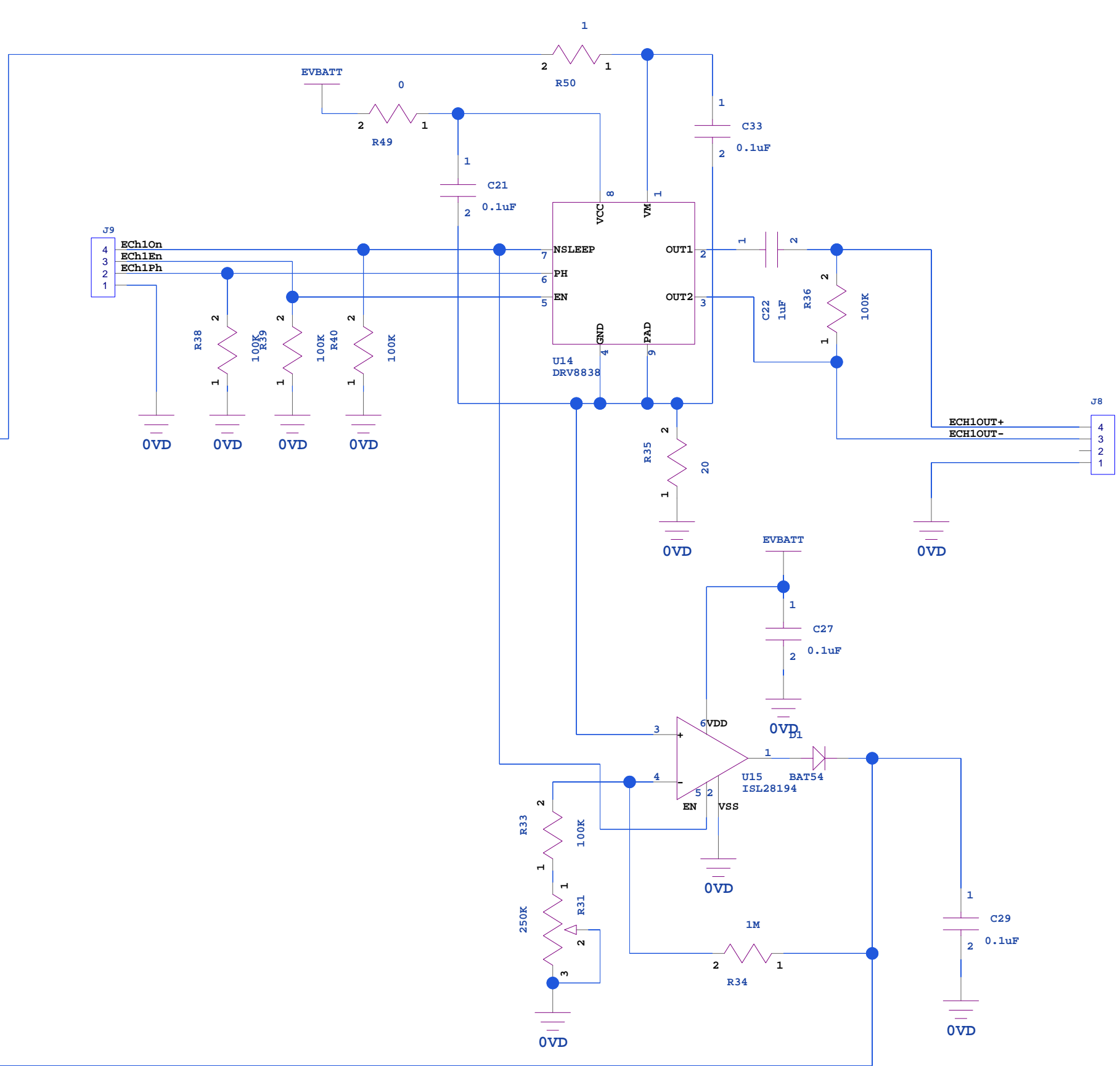
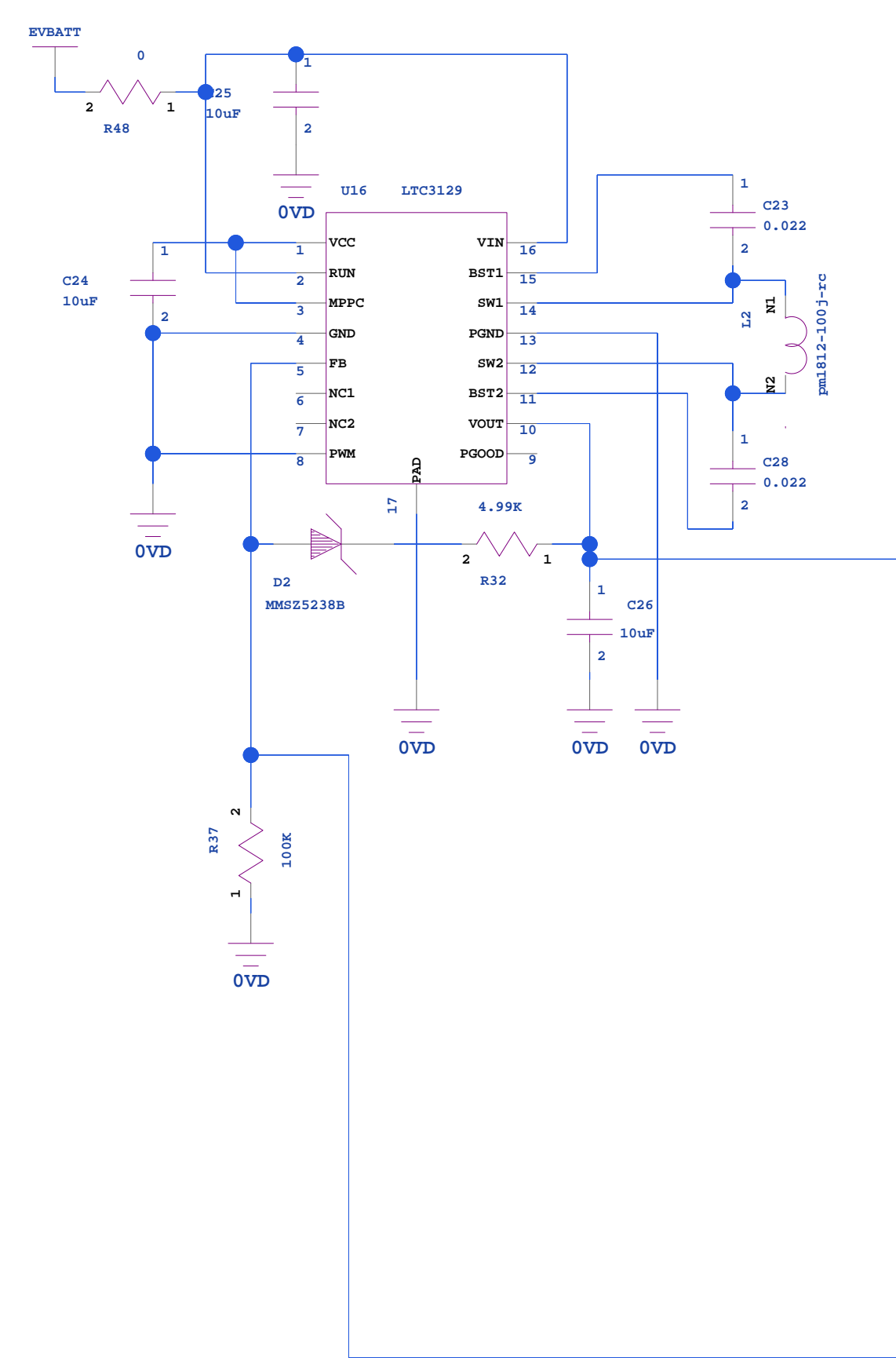
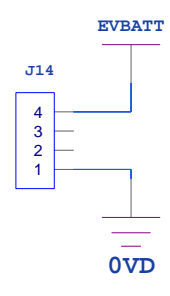
and normal parasympathetic pelvic nerve conduction restrict P-Stim's use to spinal cord injury patients with lesions between T7 and L5. Transverse myelitis is a rare disease contributing few patients to the total population for which P-Stim therapy may be appropriate. Using data from the National Spinal Cord Injury Statistical Center and peer-reviewed publications, the estimated annual incidence of patients meeting all necessary requirements for treatment with the P-Stim device is approximately 2,000 thus supporting the request for Humanitarian Use Designation (HUD).

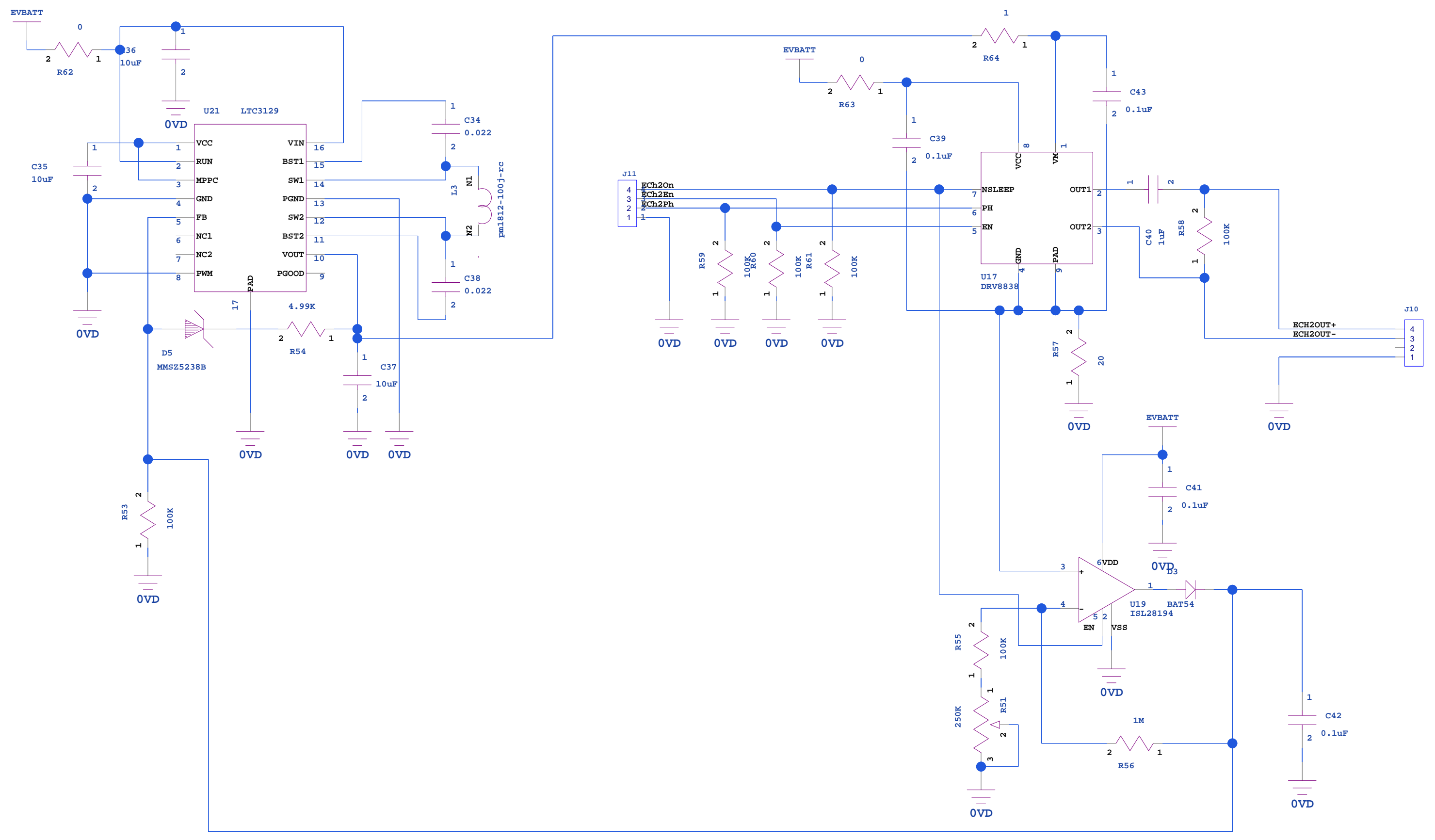
## **7.0 BIBLIOGRAPHY**

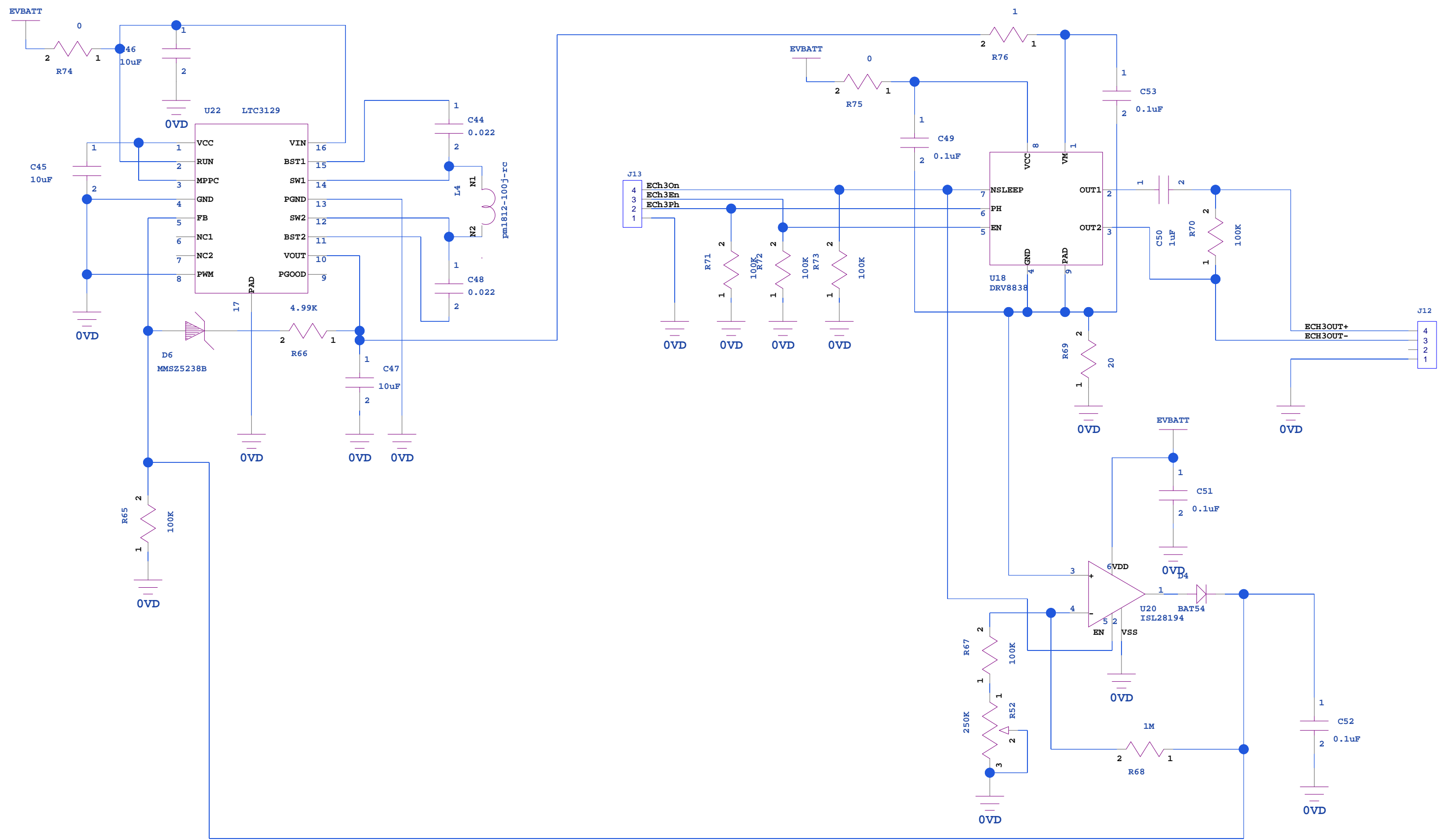


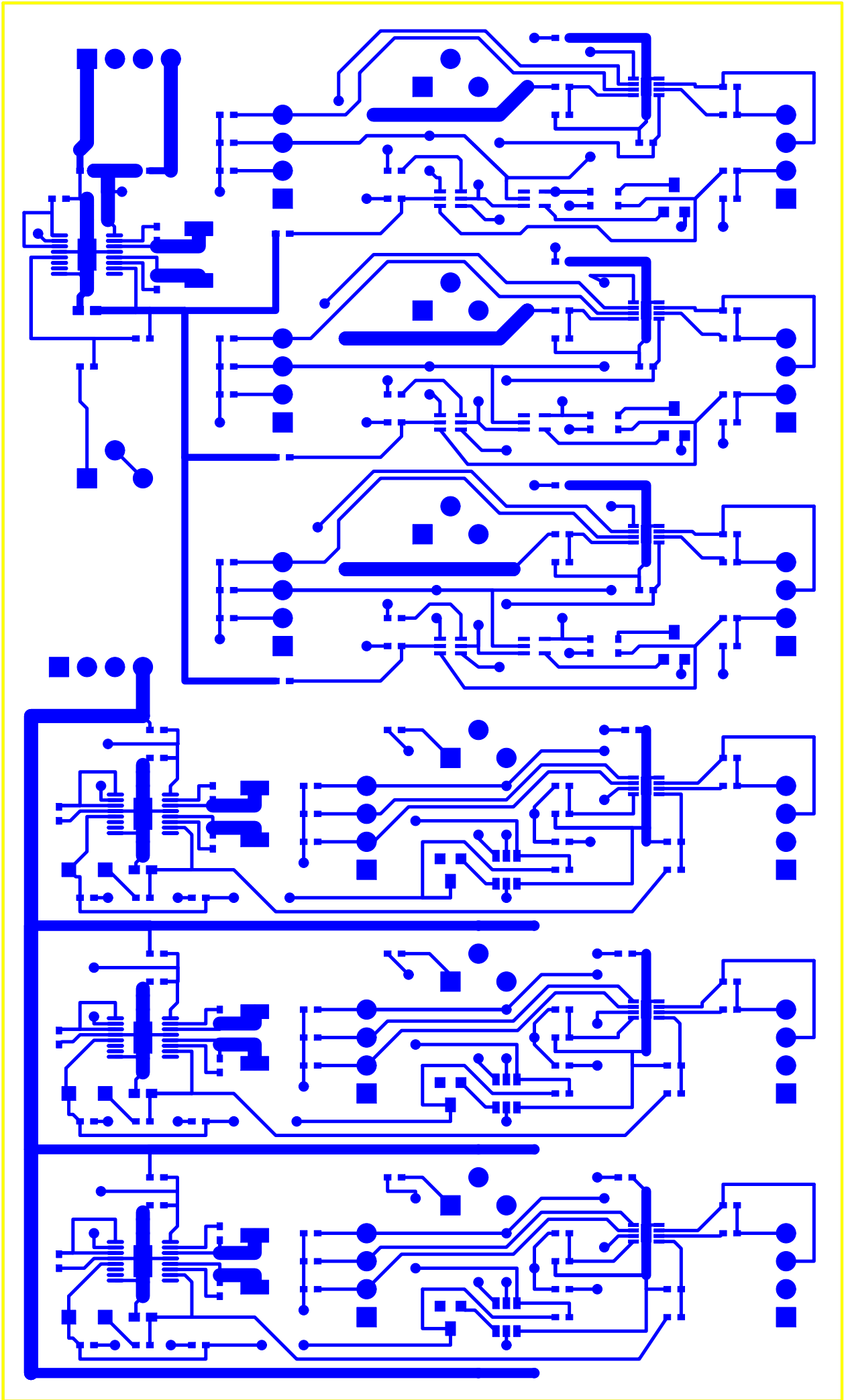
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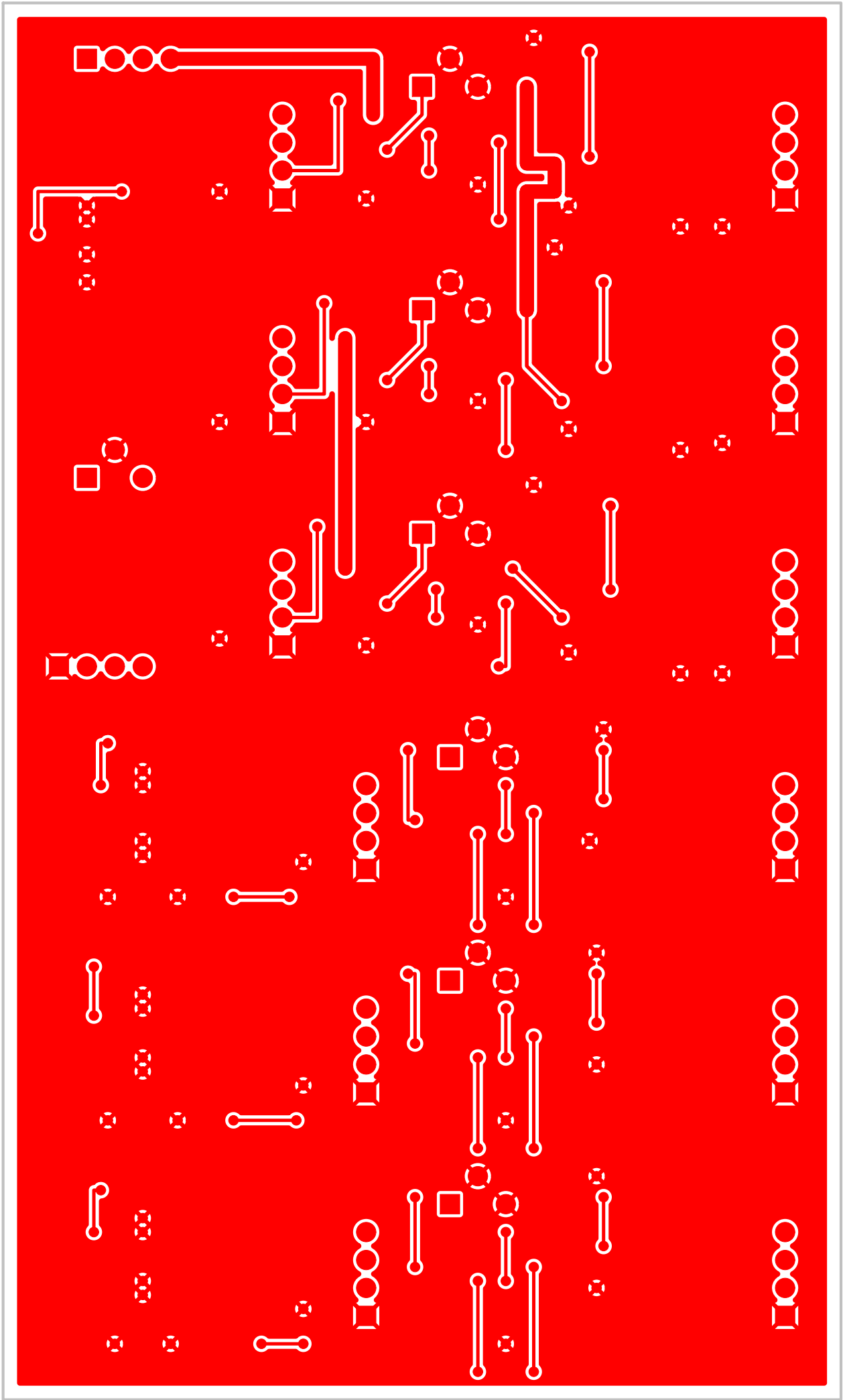


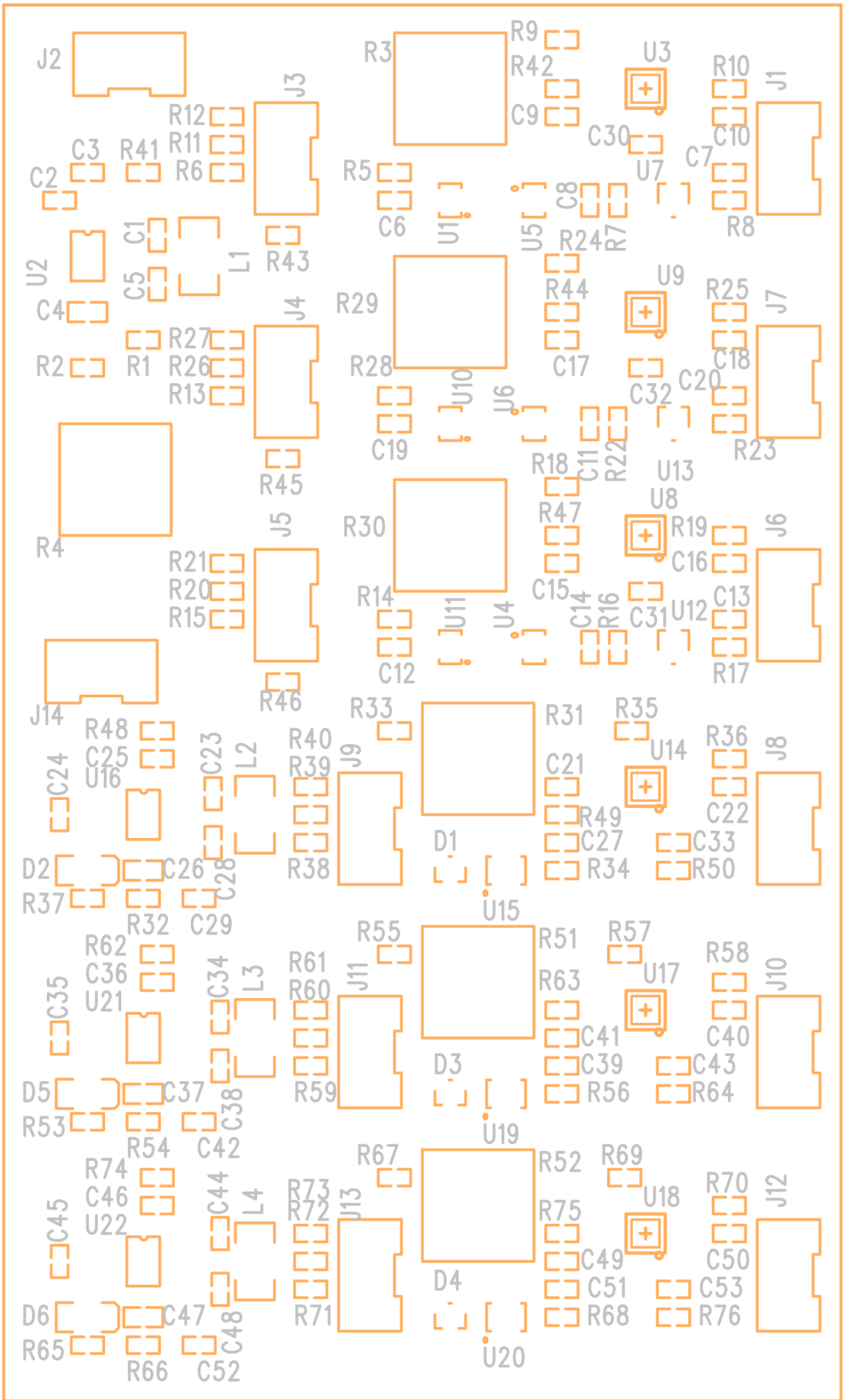


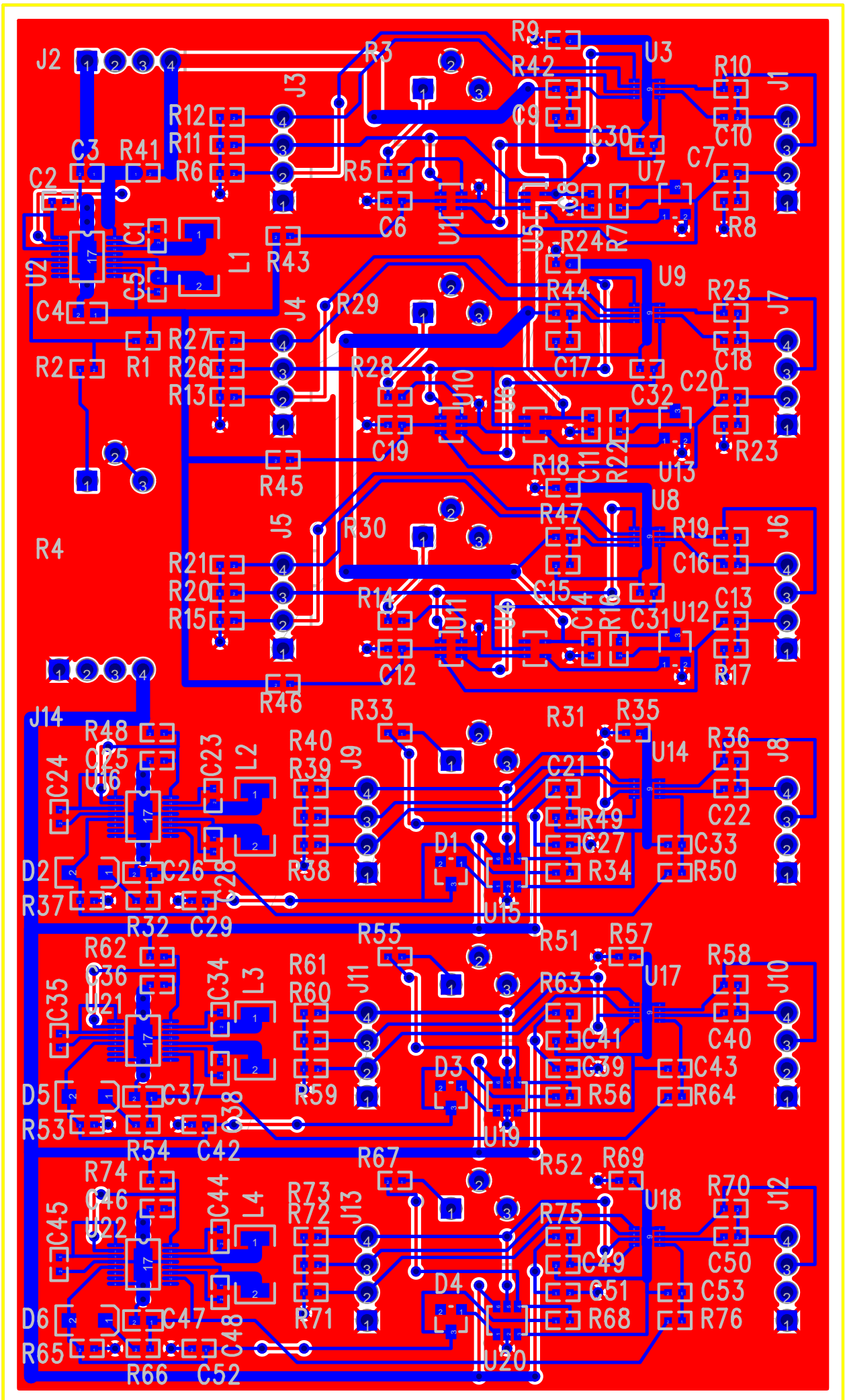












# Development of an Implantable Pudendal Nerve Stimulator to Restore Bladder Function in Human after SCI

JW14007 / W81XWH-15-C-0066



PI: Changfeng Tai

Org: University of Pittsburgh

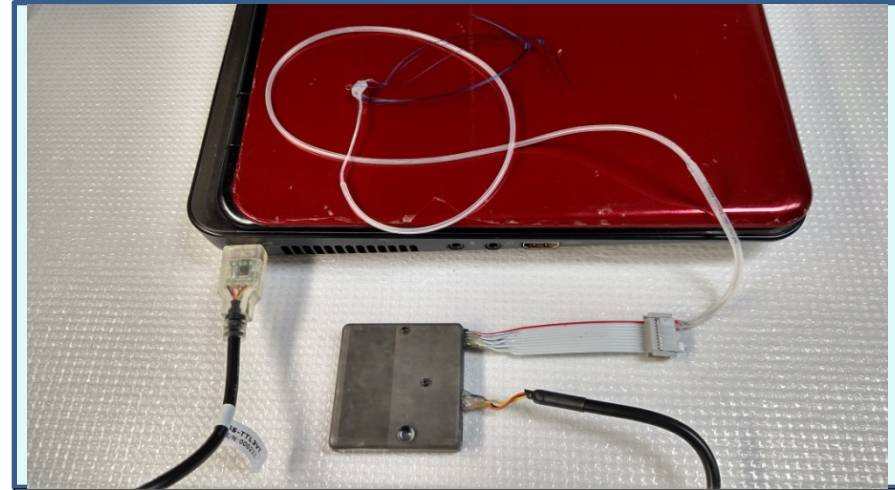
Award Amount: \$10,384,505.00

## Study/Product Aims

- Task 1. Design and develop an implantable pudendal nerve stimulation system for FDA IDE approval
- Task 2. Test the safety and efficacy of the implantable stimulator in chronic SCI cats

## Approach

The long-term goal of our project is to develop a novel neuroprosthetic device to restore the functions of the urinary bladder for SCI people without further damaging the nervous system. Based on our previous studies, we propose in this project to use pudendal nerve stimulation and blockade to restore both continence and micturition after SCI. Our strategy does not require sacral posterior root rhizotomy, preserves the spinal reflex functions of the bowel and sexual organs, and more importantly provides the opportunity for SCI people to benefit from any advance in neural regeneration and repair techniques in the future.



Accomplishment: We have developed a small prototype stimulator and cuff electrodes and tested its functionality in anesthetized animals. We will further develop this implantable stimulator for FDA IDE approval for human use.

## Timeline and Cost

Activities	CY	16	17	18	19
Task 1		█	████████████████████		
Task 2			█	████████████████████	
<b>Estimated Budget (\$K)</b>		<b>\$2,077</b>	<b>\$2,582</b>	<b>\$3,673</b>	<b>\$2,052</b>

## Goals/Milestones

**CY16 Goal** – System demonstration

- Manufacture first stimulator for animal studies

**CY17 Goals** – System validation

- Test the stimulator in normal animal for functionality

**CY18 Goal** – Production readiness

- Test the stimulator in normal and SCI animals

**CY19 Goal** – FDA IDE approval

- Test the stimulator for FDA IDE approval

## Comments/Challenges/Issues/Concerns

- No timeline change.
- Spending is delayed due to the delay of signing subcontract.

## Budget Expenditure to Date

Projected Expenditure: \$2,077K

Actual Expenditure: \$2,077K