The Retinal Implant Project

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Retinal Implant Research Group

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Introduction to the Retinal Implant Project

The Retinal Implant Project is a joint effort of MIT, the Massachusetts Eye and Ear Infirmary, the VA Boston Healthcare System, and the NanoScale Science & Technology Facility at Cornell University to develop a retinal prosthesis to restore some vision to the blind. Diseases targeted include retinitis pigmentosa and age-related macular degeneration, both of which cause loss of the photoreceptors (rods and cones) of the outer retina, but spare the inner retinal ganglion nerve cells which form the optic nerve. As presently envisioned, a patient would wear a camera mounted on a pair of glasses, which transmits image data to an implant attached to the eye. The implant will electrically stimulate the appropriate ganglion cells via an array of microelectrodes. The concept is broadly analogous to a cochlear implant, but for vision rather than hearing.

For many years our group acted as a small research center for the interesting problems facing retinal prostheses. But in December 2002, we changed our direction, expanded our group, and decided to develop our own prototype for chronic implantation. This is a substantial effort, involving fabrication of flexible substrates and electrode arrays, circuit design, chip design and microfabrication, biocompatible and hermetic coatings, development of surgical procedures, and vendor development of RF coils and assembly processes. Our web site gives more information about the project and team: www.BostonRetinalImplant.org.

Development of a Wireless Retinal Implant for Chronic Human Implantation

Sponsors
NIH contract 2-R01-EY016674-04A1
VA Center for Innovative Visual Rehabilitation
MOSIS provides IC fabrication at no cost

Project Staff
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Generation 1 Device

The first implant was developed in 2007-2008 and is shown in Figure 1. In March of 2008, we implanted it in a Yucatan minipig and demonstrated that it was functional following the surgery. In May of 2008, we successfully repeated this surgery twice more. An *ab externo* surgical technique was used in which the secondary coil was sutured temporarily onto the superior sclera while a 7 mm long, 1.5 mm wide, 15 μm thick polyimide array was inserted into the subretinal space. At the completion of the surgery, the whole implant was covered by the conjunctiva. No complications were observed during the surgeries, although some extrusion of the implant through the conjunctiva

was later observed. We then operated the device wirelessly and captured stimulation artifact waveforms via a contact lens electrode placed on the eye of the animal, demonstrating the operation of the device. We completed our first generation *in vivo* experiments in 2009. We were pleasantly surprised by the long life of the implant while submerged in the fluids of the eye, since there is no hermetic case. The longest implantation experiment lasted 10 months. Figure 2 shows the results of conventional histology and immunohistochemistry following explantation of the device. The retina looks quite normal.

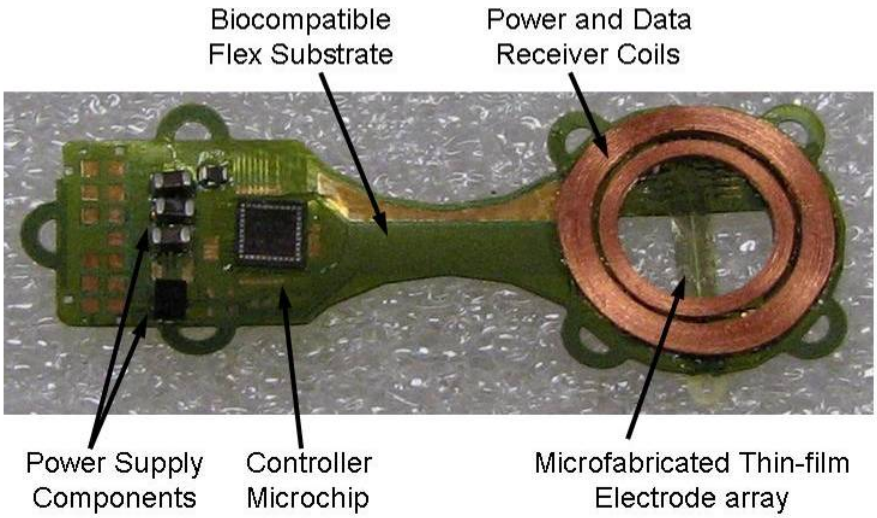

Figure 1. Detailed mockup of the first-generation implant. All parts are mounted on a 25-um thick flexible substrate, which has conducting wires embedded within. The thin neck is placed beneath the superior rectus muscle during implantation. The implant is sutured to the sclera through the seven semicircular tie points shown.

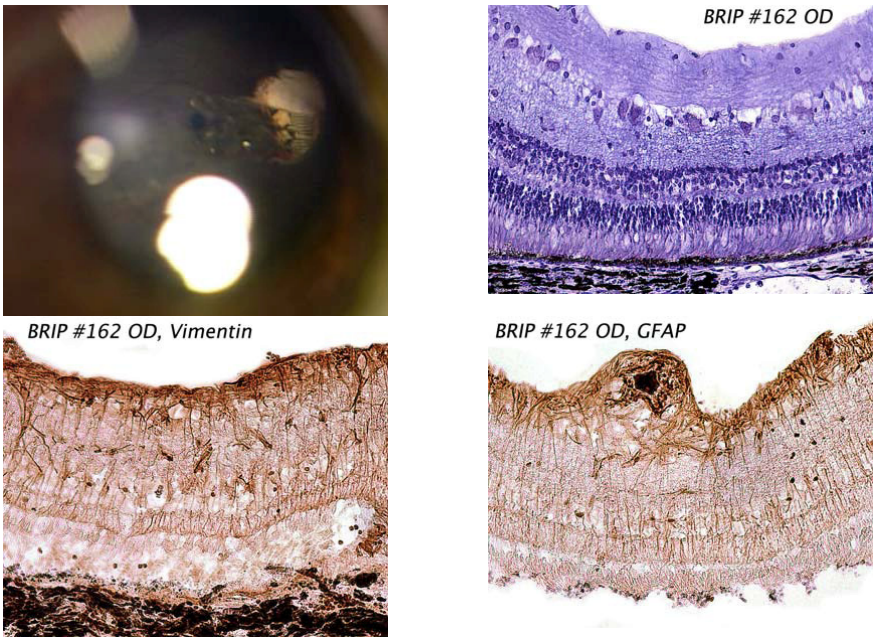

Figure 2: Retinal sections following our first long-term implantation of the Generation 1 implant in Yucatan minipig.

Top Left: Fundus photograph showing the array inserted in the subretinal space.
Top Right: Standard histology.
Bottom Left: Immunohistochemistry slice stained with anti-Vimentin.
Bottom Right: Immunohistochemistry slice stained with anti-GFAP.

Development of the Second Generation Device

The first generation device is not suitable for human implantation for a number of reasons: (i) the chip is not hermetically encapsulated, (ii) there is no reverse telemetry path to monitor chip behavior and electrode impedance, (iii) the signal transmission is not robust enough for chronic human trials, and (iv) the number of electrodes is too small. These problems have been addressed in a sequence of intermediate devices, denoted in chronological sequence as Generations 1.5, 1.6 and 1.9, which lay the groundwork for the chronically implantable human implant, the Generation 2.0 device, which we expect to complete by the end of 2011.

Generation 1.5 Device

This version uses the same chip as the Generation 1.0 retinal prosthesis, a 25,000 transistor stimulator chip designed by Luke Theogarajan in 2005 and modified by Shawn Kelly in 2007. The chips were fabricated at no expense to the project thanks to the generosity of MOSIS. They produce variable current pulse durations, amplitudes, inter-pulse intervals and selections of the set of electrodes to be stimulated. These first versions of the chip worked well enough to be used in prototypes and in early animal experiments.

Figure 3 shows the Generation 1.5 prosthesis. Power and data are transferred wirelessly to the implant via RF fields from a primary transmitter coils mounted in a pair of glasses. The secondary receiver coils are sutured around the cornea. As with the first generation design, this approach avoids a cable connection between the eye and external hardware. The electrode array is placed in the subretinal space beneath the retina.

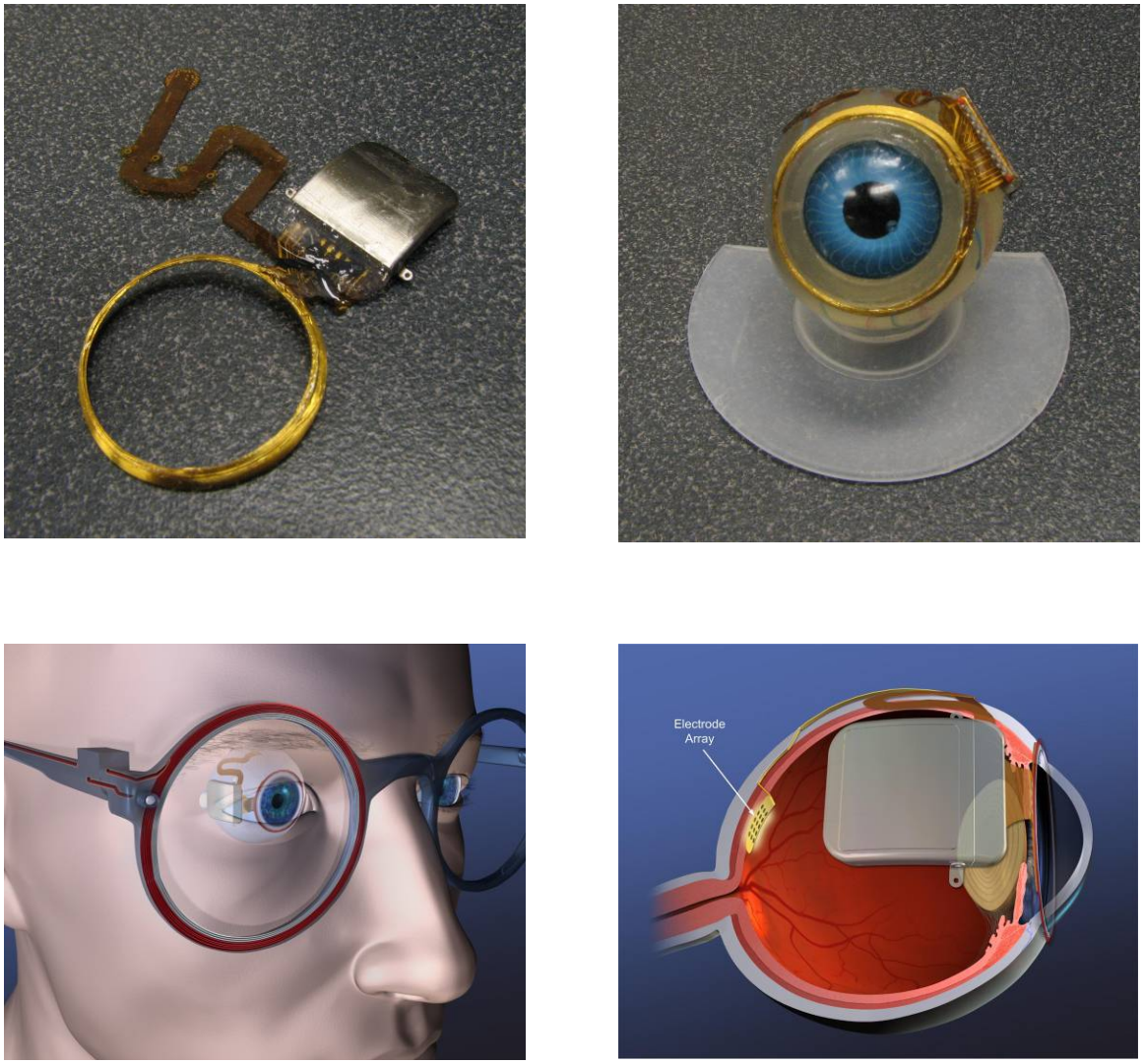

Figure 3. **Top:** Generation 1.5 implant. All electronic parts are hermetically sealed in a titanium case with 19 feedthrough pins connected to an external flex circuit. The power and data coils are sutured to the eye around the iris (under the conjunctiva). **Bottom Left:** Artist's conception of the implant system. The image obtained by an external camera is translated into an electromagnetic signal transmitted wirelessly from the external primary data coil mounted on a pair of glasses to the implanted secondary data coil attached to the outside wall (sclera) of the eye surrounding the iris. Power is transmitted similarly. Most of the volume of the implant lies outside the eye, with only the electrode array penetrating the sclera. **Bottom Right:** The electrode array is placed beneath the retina through a scleral flap in the sterile region of the eye behind the conjunctiva.

To combat problems arising from the lack of a hermetic package for the Generation 1.0 implant, we developed the state-of-the-art hermetic micro-package shown above. Another important change from the first generation device was changing the placement of the secondary coil to be just beyond the circumference of the cornea. This change provides substantially more robust RF communication. The diameter of the coil that can be used in this location is much larger than that of the coil that was compatible with placement on the side of the eye (18 vs. 12 mm). Since received RF power increases as the cube of the diameter of the secondary coil, the anterior position for the secondary coil markedly increases the robustness of wireless communication.

In August of 2008, we implanted an active Generation 1.5 device in a Yucatan minipig and demonstrated that it was functional following the surgery. In April of 2009, we repeated this surgery with a second device. An *ab externo* surgical technique was used in which the secondary coil was

sutured around the cornea onto the anterior sclera while the electrode array was threaded under the superior rectus and inserted into the subretinal space. At the completion of the surgery, the whole implant was covered by the conjunctiva. No complications were observed during the surgeries, and following each surgery we demonstrated the correct operation of the device by placing a contact lens electrode on the surface of the cornea and measuring stimulus artifacts generated by the device upon command from the external controller. Unfortunately both surgeries with the Generation 1.5 device resulted in exposure problems of the device: within the first few weeks following the surgery, the conjunctiva either failed to heal, or eroded away where it was sutured over the device. Consequently, most of our subsequent surgical effort focused on modifying the design and refining our implantation techniques. We made the coil flatter and we moved the incision in the conjunctiva to a more posterior location. To test these changes, we performed three surgeries of mockup (i.e. inactive) devices and found little to no complications or device exposure following the surgery. See Figure 4.

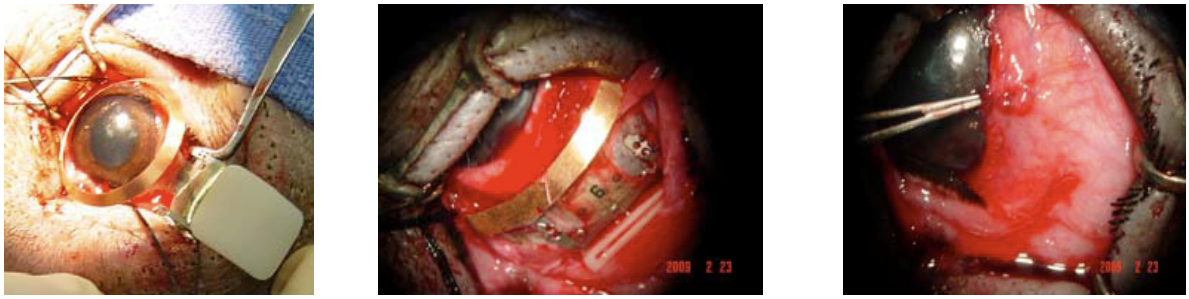

Figure 4: Photos taken during a mockup surgery showing the placement of the device on the eye, the placement prior to closing the conjunctiva, and the results at the end of the surgery.

Generation 1.6 Implant

This past year we have completed and implanted a Generation 1.6 device, a hermetic 16-channel retinal prosthesis with a new chip that includes reverse telemetry and electrode waveform monitoring. This newer chip design, developed by Phil Troyk of the Illinois Institute of Technology and Sigenics, Inc., features a more robust communication link (using FSK instead of ASK) with 16 stimulation channels, each capable of delivering biphasic current pulses of up to 381 μA. It also has a reverse telemetry pathway and records stimulus waveforms to be wirelessly transmitted back to the external controller. It does not, however, provide the safety features and other capabilities required for human trials. This Generation 1.6 implant uses the same hermetic 19-pin feedthrough case as the Generation 1.5 implant, and we have created a new internal circuit board for the new chip.

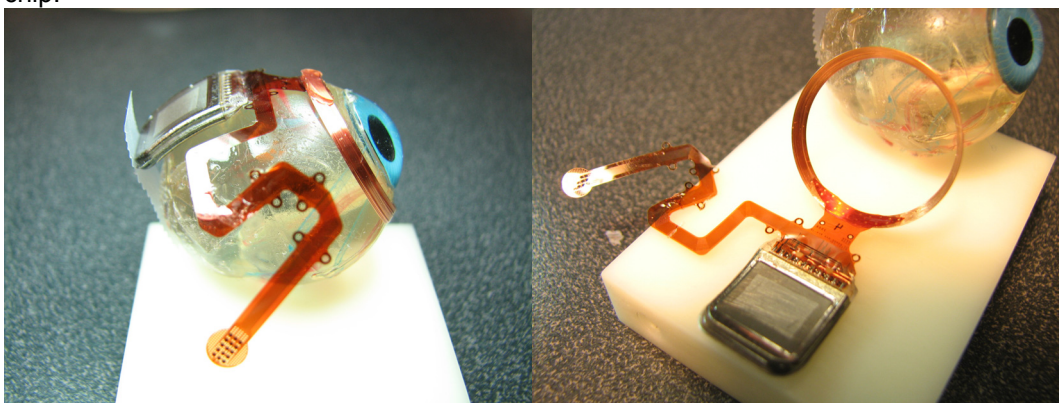

Figure 5: Two views of the Generation 1.6 implant, with a plastic mock eyeball sized to correspond to the Yucatan mini-pig eye.

The photographs below show examples of the test setup used to validate the Gen 1.6 device and to evaluate its performance *in vitro.*

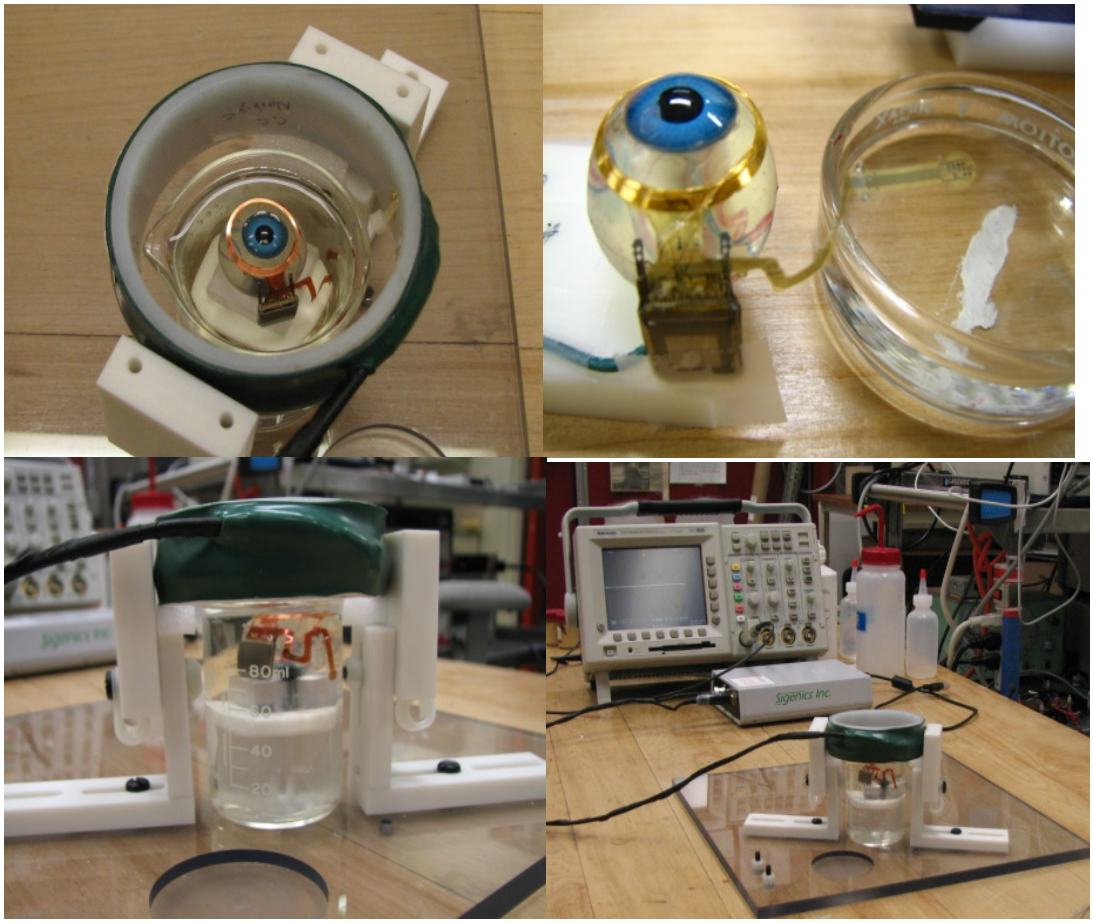

Figure 6: Test setup for the Generation 1.6 device, prior to implantation.

Surgical Trials

This past year we performed five surgical trials. In three, we implanted non-functional mockup devices for the purpose of evaluating the mechanical design of the device, our surgical technique, and the tools we developed to implant the device. In the remaining two trials we implanted active Generation 1.6-based devices. We tested the first device, implanted on 12/14/09, for 6 weeks, after which it stopped functioning, for reasons unknown. We implanted the second device on 4/5/2010 and tested it for 13 weeks prior to euthanizing the animal.

In summary, we have developed a method of implantation that does not damage the delicate conjunctiva. Furthermore, the implants are not damaged by the implantation or the saline environment, and they continue to deliver stimulus currents and transmit waveforms

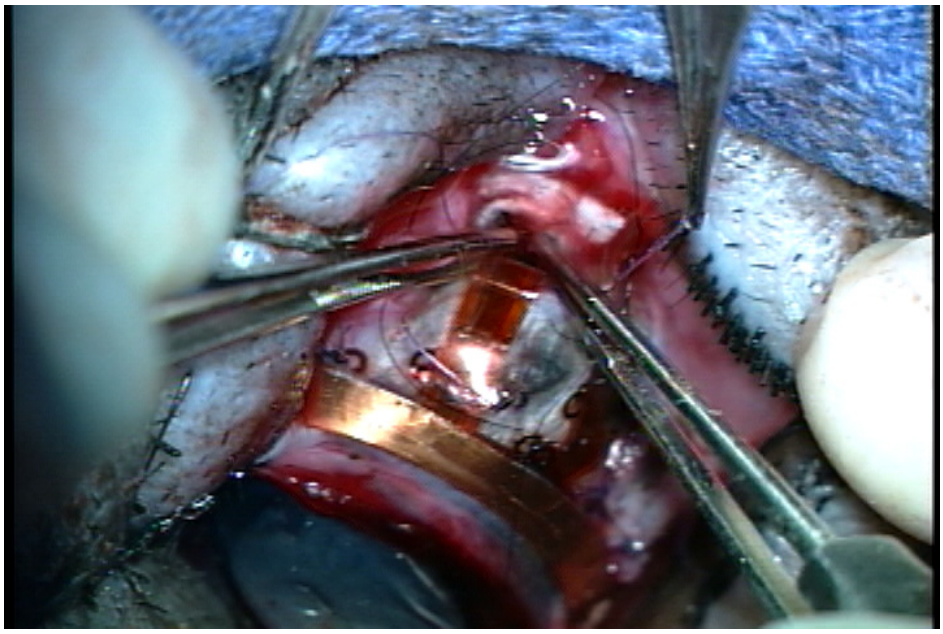

Figure 7: View of implantation surgery on 4/5/2010.

Figure 8 below gives one example of the data we collected from the implanted devices.

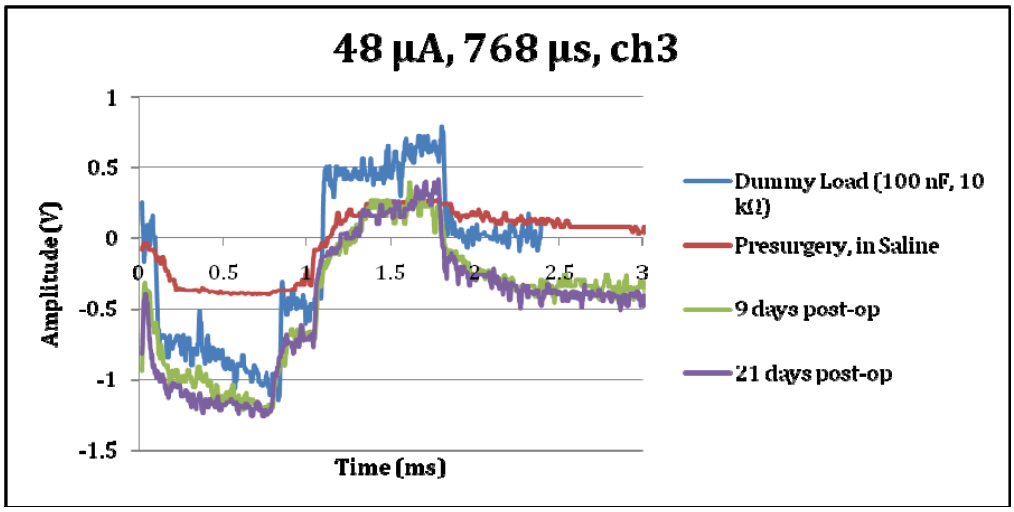

Figure 8: Voltage waveforms recorded by reverse telemetry from Gen. 1.6 device, both before and after implantation.

Progress Toward Generation 1.9

The next version of the implant, Generation 1.9, will use the same chip as the Generation 1.6 device (designed by Phil Troyk and Signetics), but in a hermetic package that permits at least 200 feedthroughs. It should be complete by Spring 2011. This state-of-the-art packaging will have the highest number of hermetic signal feedthroughs of any chronically implantable neurostimulator made to date. Samples were fabricated using a co-fired ceramic process by our key vendors, the Advanced Materials Engineering Research Institute (AMERI at Florida International University) and Hermetric, Inc., in collaboration with our MIT engineers. In fabricating the Generation 1.9 implant, these devices will be tested and implanted in Yucatan mini-pig animal models by Dr. Joseph Rizzo at the Massachusetts Eye and Ear Infirmary. In the photos below, the assembly process for the HD prosthesis packages is outlined step by step, and implantation of an inactive, 'mock' prosthesis in a pig is shown. Custom surgical insertion tools were also developed by our team for this purpose.

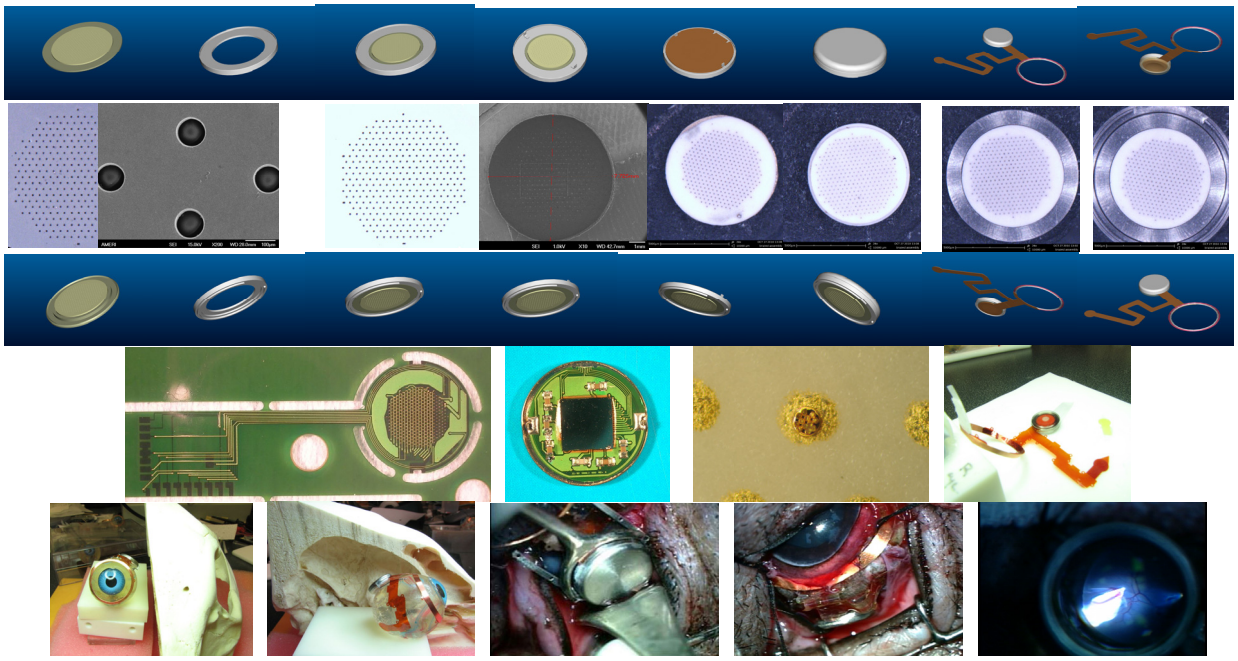

Figure 9. ***Top three rows:*** 3-D drawings showing the assembly steps for the prototype high-density retinal prosthesis. The views from the top of the implant are shown on the top-most row, and the corresponding views as seen from the bottom are in the third row. The progression of assembly is shown from left to right. A co-fired ceramic feedthrough disc is first brazed to a titanium ferrule, then ground tabs are added and the internal circuitry (including the ASIC) is attached. The lid is then sealed and the external components (electrode array and coil) are added, and the interconnections are finally protected by a silicone-filled header. Fabrication of the 200^{+}-channel cofired ceramic feedthrough is shown in between the 3D CAD images. A 'green' or un-fired ceramic tape is punched to create 100 micron diameter holes. These are then filled with Pt-based ink and fired (center photos). The edges of the disc are then prepared for brazing with gold into the case bottom (at right). ***Fourth row:*** The internal flexible circuit has the ASIC added by flip-chip bonding, and an electrode array is bonded to the exterior surface of the feedthroughs; shown is a gold-bumped co-fired ceramic disk with a button-like electroplated contact pad from an electrode array bonded to it. The electrode array has been pulled off in this photo, leaving the contact pad behind; this indicates that the bond strength is greater than that holding the contact pad into the electrode array itself. At right, a complete high-density retinal implant assembly is shown. ***Bottom row*****:** A mock prosthesis is shown on a model right eye of a Yucatan minipig. The orientation of the prototype's components can be seen. At right, surgical implantation of this device in a pig using a custom surgical tool (center); the coil surrounding the cornea and the sealed package can be clearly observed. ***Bottom right:*** Fundus photo after insertion of the electrode array from this device into the sub-retinal space.

Several accomplishments underlie the assembly of the Generation 1.9 implant:

- 3D design of the high density prosthesis package;
- Development of new co-fired ceramic punching and via-filling technology to achieve unprecedented levels of input or output (I/O) density in chronically implantable devices;
- Integration of ceramic feedthroughs with HD iridium oxide stimulating electrode arrays; and
- Adaptation of the existing 16-channel Boston Retinal Implant stimulator chip to the high density prosthesis package.

Progress in device development toward demonstration of a 16-channel device in a high density 200+ channel package has been dramatic. Innovative ceramic fabrication technology, made possible in part by a VA Merit Review grant to my Engineering Manager, Dr. Doug Shire, was developed. This 'co-fired' signal feedthrough and new hermetic titanium case has made possible the construction of an upgraded retinal prosthesis. Additionally, microfabrication technology and manufacturing processes for creating high density iridium oxide electrode arrays to mate with these packages was developed by team members working at the Cornell Nanofabrication Facility in collaboration with the RLE-based staff.

Next Step

This Generation 1.9 implant should be complete and working by the summer of 2011. At that point we will have completed the design and fabrication of a 200+ channel implant chip with all the safety features required by the FDA. The design of that chip is headed by Dr. William Ellersick, and the specifications are given below.

Technical Specifications:
Power: 6.78 MHz telemetry
~30 mW transmitted
Primary coil: 7 μH
Secondary coil: 4.4 μH
Data: 565 Kbps inbound, 47 Kbps outbound
FSK/LSK Telemetry
Current: 0 – 126 μA in 1 μA steps
Pulse width: 17.7 – 4500 μs

The integration of that chip with the hermetic package for the Generation 1.9 device will yield the Generation 2.0 implant, the most sophisticated electronic implantable prosthetic ever developed.

Publications

Journal Articles

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Talks and Posters Presented

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