**Problem Statement.** The purpose of this proposal is to develop advanced hermetic packaging techniques for the next generation of neural stimulators, with particular focus on our Center’s visual prosthesis. It is generally recognized that restoration of useful vision to blind patients will require prostheses with large numbers of small-area stimulation sites that are close to the target neural tissue [Palanker et al. 2004, 2005]. The technology for designing high density integrated circuits for neuromodulation devices is well established, and existing stimulation and recording circuits may readily be expanded to accommodate larger numbers of input and output (I/O) channels. The next generations of neural prosthetics, however, must feature closed-loop control of implant functioning and/or large numbers (up to hundreds) of monitoring and stimulation sites. These devices will be enabled by two key packaging technologies for the sensitive electronics within. First, scalable hermetic micropackages must be developed to contain the required stimulation and recording circuitry and associated wireless power supply components, preventing ingress of body fluids for periods as long as the patient’s remaining lifetime. Additionally, encapsulation techniques must be developed for flexible electrode array components and their signal feedthroughs to and from the micro-packaged circuits. We propose to develop high-density cofired ceramic feedthrough structures that will form the basis for advanced micropackages having up to 500 or more I/Os within a ~7 mm diameter disk. (This is the largest planar feature that can be incorporated into a package that roughly conforms to the human eye.) Meanwhile, our team will continue our ongoing investigation of inorganic encapsulating films for improving the biostability of flexible, microfabricated iridium oxide electrode arrays containing up to hundreds of stimulation or recording sites. We will then integrate existing wirelessly driven neurostimulator circuits developed by our team into these micropackages, and attach our high-density electrode arrays to create active neural prostheses for accelerated *in vitro* testing and *in vivo* evaluation in Yucatan mini-pig models. In Figure 1, the Aims of this grant (which incorporate the above objectives) are shown in 3D solid model drawings that outline how the engineering developments we propose herein build upon one another to form complete next-generation neural prostheses.

![Figure 1](image-url)

**Hypothesis.** Our hypothesis is that high density cofired ceramic feedthroughs, when brazed to miniature hermetic titanium capsules and coupled with highly biostable silicon carbide-encapsulated flexible microelectrode arrays, will enable the construction of new neuromodulation devices having up to 500 or more inputs or outputs. Such a development would increase by up to an order of magnitude or more the number of channels for simultaneous, closed-loop operation of neural prosthetics that are available to the rehabilitation R&D community. This advance will be enabled by the successful completion of the following Specific Aims of this proposal:
Specific Aim 1: High Density Hermetic Packaging and Assembly of Neural Prostheses.
We propose to develop high temperature cofired ceramic (HTCC) feedthrough assemblies having 200 or more inputs or outputs that are scalable to 500+ channels without a fundamental change in technology. We will design and procure miniature titanium capsules to mate with these assemblies, and develop brazing methods to hermetically join these enclosures together with the feedthrough modules. This Aim may be further broken down as follows:

A. 3-D Design of scalable 200+-channel cofired ceramic and titanium capsule components
B. Optimization of existing punching and drilling methods for forming via holes in green 96% alumina HTCC tape, and mixtures and filling methods to form hermetic metal-ceramic seals after co-firing; and, procurement and leak testing of miniature hermetic capsules and brazing of HTCC feedthrough assemblies to titanium ferrules.
C. Development of gang welding and/or soldering processes for making connections between HTCC feedthrough/ferrule assemblies and internal/external flexible circuitry/electrode arrays.

Specific Aim 2: Highly Biostable Encapsulating Films for Flexible, Microfabricated Iridium Oxide Electrode Arrays
We propose to optimize our current flexible circuit/microelectrode array fabrication process for creating devices that mount outside the hermetic package envelope of Aim 1. To meet FDA requirements for visual prosthetics, these arrays must have a demonstrated lifetime for at least ten years in bodily fluids. Silicon carbide (SiC) barrier layers have been demonstrated in preliminary experiments to solve this encapsulation problem for as many as four layers of metallization. This Aim may be further broken down in the following manner:

A. Optimization of microfabrication processes that are compatible with SiC materials to create new generations of highly biostable, multi-layered sub-retinal iridium oxide microelectrode arrays.
B. Development of appropriate modifications to our current flex circuit fabrication methods and metallization schemes to accommodate the gang welding or bonding processes of Aim 1C.
C. In-vitro environmental and biostability testing of these arrays under accelerated saline soak testing conditions with and without continuous, bi-phasic current pulsing.

Specific Aim 3: In-vivo Biocompatibility Evaluation of Complete Neuroprostheses
We propose to construct and implant our high density, next-generation neuroprostheses in Yucatan mini-pig animal models at the CIVR under the supervision of our Center director, Joseph Rizzo, MD. This Aim may be broken down as follows:

A. Assembly of complete, hermetically sealed visual prosthesis assemblies based upon the technologies developed in Aims 1 and 2.
B. Perform chronic implantation survival surgeries, followed by periods of up to six months of periodic evaluation of animal ocular health, including fundoscopic and ERG evaluations. Based upon these results, necessary modifications to the form and/or materials of construction of our neuroprostheses design will be incorporated in subsequent design iterations.

Current Status. Retinal prostheses aim to electrically stimulate remaining viable nerve cells in the inner retina. It has been established that these cells are present in sufficient numbers to provide functional perception to patients after the loss of their central vision [Marc et al. 2003,7; Margalit et al. 2002]. The feasibility of generating visual perception by electrical stimulation of the retina has been demonstrated in patient volunteers at the CIVR and elsewhere. However, object recognition remains elusive, at least in part due to the limited number and large size of
the electrode sites and the acute nature of the studies [see e.g. Weiland et al. 1999; Rizzo et al. 2003a,b; Zrenner 2007; Hornig et al. 2007; and de Balthasar et al. 2008]. Cochlear prostheses, which also stimulate at the level of a degenerated sensory organ, require as few as eight electrodes for clinical efficacy [Clark 1996]. Retinal prostheses, however, will require many hundreds of electrodes to provide useful visual perception [Cha et al. 1992a,b,c; Hayes et al. 2003; Palanker et al. 2004]. It is generally recognized that the restoration of useful visual function will require prostheses with large numbers of stimulation sites, each having much smaller single-electrode areas than those used in present studies. Thompson et al. [2003] have estimated the number of electrodes required to achieve various levels of visual functioning using simulations of prosthetic vision in human subjects with normal vision. They estimate a minimum requirement of 60 electrodes for spot reading or object recognition, and a requirement of 1,000 electrodes to achieve acuity of 20/200 (appropriate for macular degeneration patients.) Based on geometric considerations alone, Palanker et al. [2005] has also estimated that a pixel size of 2500 µm² (and density of 400/mm²) and a neuron-electrode distance of 20 µm will be required to achieve this same 20/200 acuity.

Given these data from our group and others, some key points related to further development of retinal prostheses and the structure of their stimulating electrodes become clear. These are that:

- Truly useful vision restoration, particularly for the cohort of age-related macular degeneration patients (whose condition is most prevalent among blind veterans), will require hundreds of unique stimulating electrode sites in a visual neuroprosthesis; and
- Smaller stimulating electrodes and spacing will be required in micro-fabricated electrode arrays that interface with neural tissue, and these arrays (as well as the device packaging) must have a projected lifetime comparable to the remaining lifetime of the patient, or, at a minimum, the >10 year survivability recommended by the FDA.
- Our Specific Aims are directed precisely at these concerns.

Implementation of ultra high density hermetic packaging for advanced neuroprostheses (and visual prosthetics in particular) has received the attention of a small body of research; the largest number of outputs in any truly chronically implantable device reported to date are in the 60-channel ‘Argus II’ epi-retinal prosthesis manufactured by Second Sight Medical Products of Sylmar, CA. Few technical details are known about this implant, however, which was developed by a privately held company and is currently reported to be in pilot clinical trials. As has been pointed out, though, even a 60-channel unit does not begin to come close to the channel counts that will be required to generate useful and meaningful artificial vision. Some groups have focused on polymer encapsulated neural stimulators; for example, Meyer et al. [2001] developed a ‘micro-flex’ interconnection technology in which flexible polyimide structures are fabricated as carriers, and individual devices are mounted on the polymer substrates using a bump-bonding technique. Accelerated saline soaking and biocompatibility tests performed by our group on similarly built structures have indicated that the required lifetime of >10 years will not be achieved using polyimide as a primary barrier material; these results will be summarized briefly below. Additionally, the assembly process for bumped interconnects can be quite painstaking and costly when used to integrate high-density devices.

Li et al. [2008] have developed a further improvement to polymer-encapsulated high-density packaging, building on earlier work by Rodger et al. [2005, 2006a,b] on a ‘chip-level integrated interconnect’ retinal implant packaging technology that was based upon Parylene-C encapsulation. This technique for integrating CMOS ICs with prosthetic electrodes has a number of obvious advantages, including the use of standard microfabrication techniques such as photolithography, etching, and physical vapor
deposition to make the required interconnections. Since the density of interconnects thus formed is limited only by the resolution of the lithography tools, such a packaging method would clearly be scalable to hundreds or even thousands of input or output channels. Although Li et al. [2006] and Wolgemuth [2000] claim in un-powered saline soaking experiments that parylene-encapsulated implantable devices can have extrapolated lifetimes from accelerated saline soaking tests of >20 years, experiments by our own group with similarly constructed retinal prosthesis assemblies showed evidence of delamination after several months at 37 °C, and complete breakdown after the equivalent of between 2 and 10 years of soaking in accelerated tests at 87 °C. It is indeed challenging to believe that polymer-encapsulated electronics of any kind will be able to achieve the >10 year benchmark lifetime set forth by the FDA without inorganic and/or metallic barrier(s) that form a gas-tight seal.

Our belief is that a more conservative materials approach to retinal prosthesis packaging, using extensions of materials and methods that are well proven in the implantable device industry in lower channel-count devices, will ultimately prove to be the most successful approach. In particular, hermetically sealed titanium enclosures fused to alumina or other high-fired ceramics and platinum-based feedthroughs can be used to construct the high-density packaging we seek. The biocompatibility and biostability of these materials has been proven through many years of successful implementation in the medical device industry. What is needed at this time, however, are methods to microfabricate these materials to form Pt micro-vias in ‘green’ ceramic tapes, and fuse these assemblies to miniature Ti packages that can be hermetically sealed. This development is the primary goal of Specific Aim 1 of this proposal.

Still other groups have proposed intriguing, high-density packaging approaches which could conceivably be applied to retinal prosthesis applications. Ziaie and coworkers [1996] at the University of Michigan proposed a glass capsule packaging scheme with planar polysilicon-based interconnects/feedthroughs that appeared promising, but the long-term biostability and biocompatibility of such silicon-based packages is not clear, and the concept has not received significant commercial development. An innovative approach to implantable cortical stimulator packaging based upon flip-chip assembly and the use of either silicon or low temperature cofired ceramic package lids (affixed using Au-based solder) and overcoated with a-SiC:H and/or Parylene has been developed by Solzbacher et al. [2007] at the University of Utah [see also, Hsu et al. 2007a,b and Kim et al. 2007,8] While their initial results are promising, our chosen packaging approach using miniature titanium capsules, alumina ceramic feedthroughs and platinum conductors, which we outline below, was deemed a more rapid path to approval of FDA Investigational Device Exemption applications for devices based on these technologies. By utilizing proven brazing methods and materials of construction in the implantable medical device industry, albeit in new ways, we hope to speed the transition of our high-density neuroprostheses from bench to bedside. It is clear, too, that the Utah approach could only be adapted to packaging the internal components of the CIVR retinal prostheses after a major microfabrication research effort (and an accompanying extended development time-line), compared with the optimization of established fabrication approaches that we propose here. A variant of their silicon carbide/polymer encapsulation technique, however, has proven in our tests to appear quite promising for long-term protection of the external electrode array/flex circuit components of our prosthesis, and indeed, optimization of this process is a primary goal of Specific Aim 2.

**Significance of Research.** The primary mission of our Center is the development of retinal prostheses for patients with vision loss due to degenerative retinal diseases such as age-
related macular degeneration (AMD) or retinitis pigmentosa (RP). AMD is the leading cause of blindness in the United States (and elsewhere in the developed world) for people older than 50 years; an inclusive definition of AMD that includes all patients with significant drusen in the posterior pole, with or without vision loss, estimates the prevalence at greater than 20% of the population over 60 [Bird et al. 1995, Hawkins et al. 1999]. What is more, one in three Americans will be over this age by the year 2030. In RP, there is an early loss of night and peripheral vision, with retention of central vision until the latest stages of the disease. In contrast, in AMD there is a loss of central vision (either suddenly in exudative AMD or slowly in non-exudative AMD), with retention of both peripheral vision and night vision. Both diseases result in degeneration of retinal photoreceptors, but a significant number of inner retinal neurons, including both bipolar and retinal ganglion cells, are retained [see e.g. Stone et al. 1992; Santos et al. 1997; Humayun et al. 1999; Kim et al. 2002; Jones et al. 2005; and Marc et al. 2007]. RP is the leading cause of inherited blindness, occurring in approximately 1 in 4000 births. Many different genetic mutations for RP have been described including those involving the protein rhodopsin, the RDS/peripherin gene, and the enzyme β-phosphodiesterase [van Soest et al. 1999]. There exists no treatment for either disease that effectively restores lost vision in the majority of patients, and particularly in those patients with advanced disease. Current clinical treatments only serve to slow their course, and persistent vision restoration e.g. by drug therapy has not been demonstrated. Recently, some success has been reported using a gene therapy approach for the RP-like condition, Leber's congenital amaurosis [Maguire et al. 2008]. While intriguing, this field is still in its early stages.

The primary mission of the CIVR, which is the creation of a retinal neurostimulator system capable of restoring useful vision, has been a key priority for VA RR&D since the Center’s inception in 2001. It could reasonably be argued, however, that the crude form vision which our team and others have been able to restore to blind patient volunteers to date would be of only marginal utility (but significant emotional value) to patients currently with little or no sight. A significant fraction of the candidate patient population has a degree of extant (but low) vision, though, and these patients must be offered the potential for much higher quality vision to shift the risk/reward balance in favor of implantation. Successful completion of the Aims of this proposal will make implementation of such a device possible, and, in turn, the fulfillment of the vision behind the Center’s creation.

In the broadest perspective, blindness is one of the most common forms of disability. The effect of blindness permeates one’s life, in that blind patients usually lose their independence, develop financial dependency, experience less fulfilling social interactions, and have higher rates of depression. The cost to the government to provide support services for the blind is quite large, reaching $4 billion annually [Prevent Blindness America 2002].

**Relevance of Proposed Work to the VA Patient Care Mission.** As the veteran population and the US citizenry as a whole age in the years to come, the loss of the ability to perform the activities of daily living and subsequent independence resulting from vision loss due to AMD and RP will occur with great social costs unless action is taken soon to develop a viable visual prosthesis. It is this larger goal toward which the current effort is aimed. According to the VA's own estimates, the number of veterans with significant visual impairment will reach 430,000 by the year 2011 [Williams, 2005]. The CIVR is one of a small number of multidisciplinary bioengineering-based implantable device research teams within the VA system, and the development of the VA’s human resources in this field is key to future RR&D contributions to the well being of our veteran community, as well.
Background and Work Accomplished. There is a broad effort underway to develop retinal prostheses that will function by electrically stimulating remaining viable cells in diseased retinae, both at the CIVR/Boston VAMC and at other sites internationally [see e.g. Rizzo et al. 2003 a,b; Winter et al. 2007; Zrenner 2007; Hornig et al. 2007; and de Balthasar et al. 2008]. To date, our group has developed a minimally invasive, wirelessly-driven, sub-retinal 15-channel neurostimulator for chronic implantation in mini-pig animal models [see Shire et al. 2008a,b; the manuscript of the latter paper, which has been accepted for publication in the IEEE Transactions on Biomedical Engineering, is appended to this proposal as Appendix 2]. The primary goal of this development effort was to demonstrate the feasibility of our team’s ab externo, sub-retinal surgical approach by using conventional surface-mount electronic assembly techniques to create and implant a wirelessly-driven microstimulator device (see Figure 2).

Figure 2. a) Engineering design of the sub-retinal microstimulator system. Implanted components are built on a flexible, polyimide substrate. After assembly, the entire unit was coated in poly(dimethylsiloxane) except for the stimulating array and the current return electrode. The overall dimensions of the device are 12 x 31 mm.

b) Schematic diagram showing wireless operation of the visual prosthesis system. A camera (or external computer) generates an image and this signal is then broadcast to the implanted stimulator chip by commanding it to re-transmit biphasic current pulses, in patterns corresponding to the target image, to the stimulating electrode array that is located in the patient's sub-retinal space.
In accelerated life tests, our team determined that parylene-C encapsulated implants could be exposed to saline environments for several months, until evidence of fluid leakage became apparent. Based on these tests, poly(dimethylsiloxane)-insulated devices were adopted for perfecting surgical techniques during animal surgical trials anticipated of limited duration, since this material outperformed thin parylene-C coatings in our tests. The overall system design, outlined in Figure 2(b), incorporates an external video capture unit (or computer) and a transmitter that sends the image data wirelessly to the implanted portion of the device. There, a custom, application-specific stimulator IC (ASIC) translates the image information into biphasic current pulses of programmable strength, duration, and frequency that are delivered to the electrode array. Since the optimal current levels and stimulation protocols for providing restoration of usable visual percepts are not known, our design concept was to keep the ‘smart’ image processing hardware and/or firmware in the external control unit, and for the implanted system to be as flexible and simple as possible. The implanted ASIC received data and power by inductive coupling on independent channels, and the data included configuration values and stimulus current values; real-time commands were sent to start and stop each stimulus pulse.

The sub-retinal electrode arrays were fabricated with materials that have previously been well-tolerated during chronic implantations in Yucatan mini-pig models. The ASICs were mounted by stud bumping with 75 μm-high Au bumps, followed by flip-chip die attachment to the host substrates. Stud bumping was also used for the flex-to-flex connections between the flex circuits and the electrode arrays. Once the electrode array was attached and the stud bump connections were encapsulated in non-conductive epoxy, the power and data coils were added. The resulting assemblies were then coated with the exception of the active electrode array and the return/reference electrode on the host flex circuit.

Figure 3. a) Schematic cross section diagram showing the electrode array fabrication process. b,e) Light micrograph of an IrOx stimulating site immediately post-fabrication, and at right, an SEM photo of an identical 400 μm-diameter site after 1 year of continuous, biphasic current pulsing (0.76 mC/cm², 0.95 μC/phase). c) A 100 mm diameter Si host wafer with IrOx electrode arrays for both acute and chronic stimulation studies. d) Close-up micrograph showing numerous arrays, each having 15 IrOx electrode sites (small dark circles).
The arrays, shown in Figure 3, were fabricated by first spin-coating and curing a 12 µm thick base coating onto a 100 mm-diameter silicon wafer using HD Microsystems PI-2611 polyimide. A 3-layer metallization, comprised of two titanium adhesion layers and a gold conductor layer (Ti/Au/Ti), was deposited on the polyimide by physical vapor deposition and patterned using a lift-off resist process. (The Ti and Au films were 50 nm and 1.5 µm thick, respectively.) A 3 µm-thick polyimide overlayer was spun over the metallized polyimide and cured at 350°C. Electrode sites and contact pads were formed by patterning the wafer with photoresist and exposing the underlying metallization by O₂ reactive ion etching (RIE). The wafer was then re-patterned to expose only the electrode sites, which were then coated with 300 nm of a reactive DC-sputtered iridium oxide film (SIROF) from an iridium metal target [Cogan et al. 2008, Mokwa et al. 2008]. A reactive gas mixture of Ar, O₂ and H₂ was employed to produce SIROF with a mixed Ir³⁺/Ir⁴⁺ reduction-oxidation state. The wafers were patterned a final time, and O₂ RIE was used to define the perimeter of each individual array by etching through the combined 15 µm thickness of the polyimide layers. After soaking in water, the individual arrays were then readily removed from the silicon wafers for testing; typical yields of perfectly functional devices depended on array size, but exceeded 80%.

Long-term pulsing studies were performed on 400 µm-diameter electrodes at a charge-injection density of 0.76 mC/cm² for 16 pulses/s while the inter-pulse potential floated freely (no applied potential bias). A representative comparison of the cyclic voltammogram (CV) of a site on one array is shown in Figure 4 at the initiation and at the 228-day time point of the pulsing study. The observed increase in charge storage capacity (determined from the time-integral of the cathodal current in one CV cycle) occurred early in the experiment, and is related to rehydration and possibly some structural modification of the SIROF during pulsing. In this experiment, the metallization of ten electrodes became discontinuous due to gold dissolution at sites where the polyimide did not completely cover the metal traces, and 15 sites were judged to have failed because of separation of the gold metallization from the underlying polyimide at the charge-injection site. In only one electrode was there evidence of SIROF delamination from the underlying gold due to pulsing, and this was limited to a small area along the perimeter of the electrode adjacent to the polyimide. In general, those sites exhibiting partial or full gold delamination from the polyimide exhibited normal driving voltage and CV responses until the charge-injection coating (Au and SIROF) separated from the array. Our team judged from these data that electrode arrays constructed in the manner described above would be quite adequate for months-long animal implantation trials, but that further work was necessary to improve the long-term integrity of these flexible, polyimide-based structures to create clinically appropriate devices. We now have encouraging preliminary results indicating that the lifetime of arrays made with an improved process based on amorphous silicon carbide (a-SiC:H) encapsulating coatings can be extended to >10 years, using accelerated tests performed at 87 °C.

![Graph of cyclic voltammograms](image)

*Figure 4. Comparison of the cyclic voltammograms of a representative SIROF stimulating electrode, initially and after 228 days pulsing (0.76 mC/cm², 0.95 µC/phase) at 16 pulses/s. The increase in charge storage capacity is attributed to rehydration and possibly structural modification of the SIROF during pulsing.*

*In vitro* evaluation of our devices consisted of dry and “wet” testing in saline baths. In both cases, the prosthesis was placed in close proximity to a primary coil assembly while data...
waveforms to drive the device were generated by a portable PXI computer system that allowed selection of current levels, pulse timing, bias values, data carrier frequency, and data rate. Prior to encapsulating the completed implants for surgery, a ‘test tail’ extension to the electrode array was used to measure output waveforms at the electrodes while the device was wirelessly driven. Figure 5 shows a typical electrode waveform measured in this manner; a dummy load configured as an equivalent circuit model of the in vivo site impedance was connected for this purpose.

Figure 6 shows the test setup and a sample waveform measured using a reference electrode and two needle electrodes in the saline bath; note the difference between this signal (which is proportional to current) and the electrode voltage waveform of Figure 5 (which reflected the effects of the access resistance and of the electrode-tissue impedance.)

Figure 5. A typical electrode voltage waveform. The top trace shows the binary bit-stream used to command the device. The bottom trace shows the voltage waveform at the output while it drove a dummy load representing an equivalent circuit model of the electrode-tissue interface, consisting of a resistor in series with a parallel RC circuit.

![Figure 5](image)

Figure 6. a) Testing the wireless microstimulator in a saline bath. b) In vitro test setup. c) Measured potential difference (in mV) between two needle electrodes placed in close proximity to the prosthesis in a saline bath. Time scale: 1 msec/division.

Representative waveforms recorded in vivo in the mini-pig eye are shown in Figure 7. The ‘control’ signal was collected by reducing the transmitted power to the implant sufficiently to prevent the stimulator from starting operation; clearly, there was no stimulus artifact in this case. The magnitude of the artifacts measured was strongly affected by the position of the contact lens electrode used to sense them; thus, Figure 7 should be interpreted primarily as an indication of ongoing microstimulator functioning, rather than any physiological phenomenon.

We have also packaged these prototype retinal implants in custom fabricated ultraminiature hermetic titanium packages with 19 PtIr feedthrough pins brazed with gold into a drilled ceramic pre-form [Shire et al. 2003]. The pin spacing was 475 microns, and the entire case is less than 11x11x2 mm in size (comparable to a dime – see Figure 8.) The case was shaped to conform to the eye orbit, and active devices based on this packaging technology have also been implanted in mini-pig animal models for periods of 5 months and longer [Shire et al. 2008a,b].
These devices, which are among the smallest chronically implantable neurostimulators ever made, offer a range of applications in that can be implemented by attaching a clinically appropriate microelectrode array for the desired rehabilitation objective. These include, for example, deep brain stimulation units to aid in recovery from severe TBI.

Figure 7. Representative waveforms of stimulus artifacts from wirelessly driven retinal microstimulators in Yucatan mini-pigs at 0, 2, 6, and 12 weeks post-operation. The ‘control’ waveform was collected when transmitted power to the implant was reduced below the threshold which was required for stimulation to begin. The potential scale (in mV) is only relative, as the readings were highly sensitive to changes in the position of the contact lens electrode. Time scale: 1 msec/division.

Figure 8. 15-channel retinal neurostimulators in hermetically sealed Ti cases with 19 PtIr feedthrough pins, each spaced 475 microns apart. Note the laser welded lid which was sealed after mounting the internal flex circuit (upper right.) The external flex circuit is attached to the feedthrough pins using gold-based solder. Middle right: photo taken during in vivo implantation of the device, with the anterior coil surrounding the Yucatan mini-pig cornea.
In order to enable the next generation of neuromodulation devices, our signal feedthrough fabrication technology must be completely revamped from the conventional approach taken in Figure 8 to incorporate cofired ceramic assembly using custom-developed brazing techniques and heat treatment cycles. This forms a major component of Aim 1 of our proposed effort.

We have also developed advanced multielectrode arrays for current and future neural prostheses [Cogan 2008; Cogan et al. 2008]. Our focus was and is on achieving long-term stability with high charge-capacity electrodes. This work led to the development of single- and multi-layered polyimide arrays employing amorphous SiC (a-SiC:H) to encapsulate the embedded metal traces. Multielectrode arrays with a-SiC:H readily tolerate accelerated soak testing at 87°C in physiological saline. After 20 weeks at 87°C (equivalent to ~10 years at 37°C), the arrays are undamaged, showing no evidence of physical or electrical degradation (see Figure 13). By contrast, identical arrays without a-SiC:H degrade by interlayer delamination after only 4 weeks (equivalent to about two years at 37 ºC). Our multielectrode arrays employ sputtered iridium oxide (SIROF) as a low impedance coating that is intended for either recording or stimulation. SIROF is superior in charge capacity to platinum and porous titanium nitride, and provides reversible charge-injection at levels well-above functional thresholds for cortical, deep brain, spinal, and retinal stimulation. SIROF electrodes on our polyimide arrays have undergone 894 days of continuous current pulsing (1 mC/cm² charge) in physiological saline at 37°C with complete preservation of electrical properties. The second major Aim of the proposed work will also comprise continued development of these high- density single- and multi-layer electrode arrays, and extension of these processes to accommodate the creation of robust electrical connections to cofired ceramic feedthroughs (e.g., using welding, soldering, or bumping techniques.) We will also protect the resulting joints with molded ‘headers’ to prevent infiltration of biological fluids. Examples of such headers formed from EpoTek 301 biocompatible epoxy on our existing, hermetically sealed 15-channel neurostimulator using molding techniques standard to the implantable medical device industry are shown in Figure 8 (top, left).

A main objective of Aim 2 is development of multi-layered flexible circuitry for the internal and external components of future neural prostheses. We have very encouraging preliminary results on extending our flexible, polyimide-based IrOx electrode arrays with single- level metallization (with and without a-SiC:H encapsulation) to as many as four independent layers (see Figures 9 and 10). Such multi-layered designs will be essential as we transition to many hundreds of stimulating and/or recording electrodes, since a) the width of the surgical incision which can be made in the sclera must be minimized to reduce surgical risk and b) clearly, with potentially as little as 100 µm between adjacent electrode sites or individual feedthrough vias in our proposed designs, there will not be sufficient room to route all of the required signal traces in a single metal layer, or even two.

In Figure 10, we show a comprehensive set of test structures designed to test conductor sheet resistance, inter-conductor contact resistance, continuity over topographical steps, inter- and intra-conductor capacitance, and physical flexibility of multi-layered electrode arrays of varying design and thickness. Conductor width, contact size, and overlap between conductors on adjacent layers were varied from 3-25µm. The wafers were fabricated by adapting our standard polyimide fabrication process to repetitively stack and interconnect successive layers of lithographically patterned gold conductor metallizations, each of which was separated by a ~1.5µm-thick layer of polyimide. Electrical testing was performed after each metal layer deposition and patterning step, and again after via holes were cut through the overlying polyimide layer. The resistance of the 3µm contacts through vias was 0.05-0.17Ω, and larger contact sizes had even lower resistance. The metal sheet resistance was <0.07Ω/sq. for a single 0.75µm thick Au metallization.
These four-layered parts, below, had good inter-layer isolation and step coverage; the total thickness of our 4-layer structures was ~12µm, and their mechanical stiffness was comparable to that of the thicker single-layer arrays that we fabricated previously.

Figure 10. Demonstration of a four-layered, 64-conductor test electrode array with connection pads and test electrodes shown in the middle figures. This array had the same footprint and overall thickness as the single-level electrode array of Figure 5, but electrodes were randomly distributed among the four available metal layers. The vertical lines through the electrode sites are actually areas where traces on layers below the electrode run underneath. At bottom, a photo of a 4 inch Si wafer with multi-level arrays is shown, together with a close-up of a ‘railroad track’ test pattern.

Our four-layer array results demonstrate that if micro-patterned metal traces of ~4µm in width are used, ~1000 conductors could be incorporated into a 2mm-wide electrode array/flex circuit structure with only a 2.5X increase lead resistance over present values. For neurostimulation, the impedance of the electrode-tissue interface dominates, and series resistance in our leads is not significant. The resolution required to print these traces is easily achieved using the optical lithography tools of the Cornell NanoScale Science and Technology
Facility, where the PI is stationed. In another important preliminary result, the single-layer a-SiC:H-encapsulated electrode arrays of Figure 9 have also been extended to four metal layers, as can be seen in Figure 11. These structures are currently being tested in our laboratory in long-term accelerated saline soaking experiments, and optimization of these multi-layered, silicon carbide-encapsulated structures is a key goal of Aim 2 below.

In sum, the PI has over 22 years of prior microfabrication experience, including 8 years of fabrication effort developing electrode array structures for retinal stimulation and recording [see e.g., Shire et al. 2004, 2005, and 2006]. The PI and his colleagues have developed a robust process for manufacturing single- and multi-layered iridium oxide stimulating electrode arrays and flex circuits using the exceptional fabrication capabilities of NSF-sponsored national nanofabrication user facilities. The IrOx electrode arrays cited above have been extensively tested in vitro by pulsing the electrodes continuously at moderate to high charge injection levels in saline solution at 37 C for >1 year. The performance of these arrays has been shown to be stable in this time frame [Cogan et al. 2004, 2007]. In addition to this electrode array technology, the PI has also patented a process for microfabricating flexible inflatable arrays that can be folded to fit through a narrow incision, then unfurled once inside the eye [Shire et al. 2005]. These structures allow a useful area of retina to be stimulated (avoiding ‘tunnel vision’ for the patient) while retaining the safety of a small entry point. We have also recently developed flexible, transparent recording electrode arrays for the retina; these arrays would not significantly interfere with the transmission of light to an ambulatory animal's retina from its environment when the array is mounted with a tack on the epiretinal surface [Shire et al. 2006]. These polyimide–based arrays have ion-milled indium tin oxide (ITO) electrodes in the transparent region, and gold conductors elsewhere. The PI also has extensive experience with photodefined, biocompatible epoxy compounds. Structures such as custom SU-8 retinal tacks [Shire et al. 2000], electroplating molds, and fluidic channels are readily formed in these materials by photolithography and etching. Additionally, Dr. Shire has been the Engineering Manager of the CIVR for the last two years, managing a complex, interdependent research program across multiple work sites and involving coordination of the efforts of numerous external vendors.
Work Proposed:
Aim 1- High Density Hermetic Packaging and Assembly of Neural Prosthesis

1A. 3-D Design of scalable 200*-channel cofired ceramic and titanium capsule components

Methods. The designs will be iteratively developed with our vendors and implemented as 3-D ProEngineer files by long-time CIVR vendor Sonny Behan Consulting, Inc., Duluth, GA. Mr. Behan has over 30 years of experience as a mechanical designer in the medical device field, and he created the preliminary solid model drawings of Figures 1 and 16 for this proposal at the PI's request. We will work with Mr. Behan to specify the fit, finish, and materials of construction of the hermetic package and feedthrough assemblies, and he is familiar with quality management and documentation processes used in the implantable medical device industry. This will help to ensure that all resulting designs and engineering change notices are incorporated into the Web-based CIVR document management system, so that the latest documents are made available to our vendors and engineers at the VA and elsewhere. Ongoing interaction will be required with Mr. Behan as updates are made to our designs based on the findings of sub-Aims 1B and 1C below; his substantial experience in mechanical assembly of implantable neuroprosthetics and industry contacts are also expected to be invaluable. His services are paid for through a retainer subcontract maintained by the Center for Innovative Visual Rehabilitation, and thus will incur no cost to the proposed program.

In Figure 12, draft 3-D drawings of a 750-channel high-density neuroprosthesis package measuring 11 x 11 x 2 mm are shown; see also Figure 1. The feedthrough vias are .004" in diameter (in the ‘green-fired’ ceramic state), and the pitch is .008". The array measures 25 rows by 30 columns, and the entire feedthrough ceramic disk is just over 7mm in diameter in this design; it also represents our fabrication goals for Year 2 of this effort. The order of assembly is proposed as follows. The cofired ceramic feedthrough disk (developed under Aim 1B) will be fired together with its Pt-filled vias in tape form and then machined to size. This will then be brazed with Au to a titanium ferrule (see Fig. 12a,b). Bumps will be screened or otherwise applied to both surfaces of the ceramic disk (see Fig. 12c) that are comprised of materials that are compatible with the welding / bonding process (of Aim 1C), so that the disk can be mated with the internal or external flexible circuitry (see Fig. 12d,e). Note that the outer rim of the titanium ferrule has a machined ridge that will be used in a subsequent projection or laser-welding step (see Aim 1C) to hermetically seal the ferrule to the titanium case body (e.g., that in Figure 1c above and in Figure 12h). After the case body (that is not shown in Fig. 12f,g for clarity) is joined to the ferrule, the internal and external flexible circuits/electrode arrays will next be attached. Note, the internal flex circuit of Fig. 12e will first have had an application-specific neurostimulator chip attached by flip-chip stud bump bonding, in addition to discrete power supply components, prior to final assembly. Last, after completion of electrical tests, the bottom lid of the hermetic case will be sealed by laser welding, and a molded ‘header’ of biocompatible epoxy (e.g., EpoTek 301 or a Tecothane cap that is back-filled with medical-grade silicone) will be applied to keep biological fluids away from the electrode array–feedthrough via connections. Below, we provide proposed primary and alternate fabrication methods for the key elements of this assembly process.

Alternate Methods. In the event that Mr. Behan’s design services become unavailable to the PI, we will develop 3D computer models for our proposed neuroprostheses using the CAD workstations available at the Cornell NanoScale Science and Technology Facility in Ithaca, NY where the PI is stationed.
1B.1 Optimization of existing punching methods for via holes in green 96% alumina HTCC tape, and mixtures and filling methods to form hermetic metal-ceramic seals after cofiring.

Methods. The current hermetically sealed neuroprosthesis used by the PI’s group at the VA CIVR consists of a 15-channel stimulator that has Pt feedthrough pins brazed with gold into a pre-drilled, machined alumina block in a titanium micro-package (see Figure 8). This well-known, biocompatible structure has a proven track record of reliability in the implantable medical device industry. We propose to replace this feedthrough assembly with a high-temperature cofired ceramic (HTCC) feedthrough structure having Pt-filled vias. Our reasoning for doing so is in part due to the widespread acceptance of these materials and methods of hermetic package construction by neuroprosthesis manufacturers and the FDA. We thus aim to reduce the burden of proof of biocompatibility that will be required by the FDA for Investigational Device Exemption applications for devices based up on this technology.

As a demonstration of the capabilities of the Advanced Materials Engineering Research Institute (AMERI) of Miami, FL, who is the proposed vendor to the PI’s program for this aspect of the effort, preliminary data has been generated on a cofired ceramic feedthrough structure having 197 channels (see Figure 13.) From prior work in high-density vertical channels in cofired ceramics, this prototype was developed using laser processing to create holes in standard LTCC green-fired tape materials (Dupont 951/Ag metallization) as a proof of concept.
Since AMERI also has complete tape casting and ink manufacturing capabilities, preliminary HTCC cofired Pt feedthrough was developed using a 96% alumina substrate; this is the proposed materials system for the implantable devices of this program. Figure 14 is a fracture microphotograph of a 250 µm (10 mil)-diameter Pt via structure showing excellent densification and adhesion to the cofired alumina substrate. A 61 I/O test structure was fabricated in this alumina-based materials system with .010" diameter Pt vias. This structure was tested for hermeticity using an O-ring to connect the structure to the leak detector, and its leak rate (below 2 x10⁻⁸ std cc He/sec) provided an indication that a successful hermetic feedthrough structure could indeed be built by this method. Naturally, leak rates below 10⁻⁹ cc-He/sec will be necessary in our finished packages, especially given the ~nanoliter-size included volumes within. Brazing of these assemblies into machined packages (the objective of Aim 1B.2) will be necessary before more conventional helium 'bomb' testing methods can be used.

In our proposed work, we will first employ commercially available cofire-able Pt-based inks from ElectroScience Laboratories of King of Prussia, PA. This formulation of the platinum ink will then be optimized for fired density, conductivity, and adhesion and will be applied using a high-viscosity bladder filler at AMERI. The ink in the preliminary HTCC prototype of Figure 14 used a mixture of nano-sized Pt black with a micron-size Pt and alumina powder to control the thermal expansion of the resulting paste. The nanoscale Pt melted below 1550°C (which is the firing point for the 96% alumina). This temperature was greater than 200°C below the nominal melting point of Pt (at 1772 °C). In this way, we were able to provide liquid phase sintering of the micron-size Pt particles in the mixture. Since Pt does not form thermodynamically stable oxides, solid solution additives (e.g., Ru, Rh, or Ir) that will form stable oxides and react to the alumina will be evaluated to enhance adhesion. Three-point bend tests (per ASTM standards for testing ceramics) will be performed on samples with rows of feedthroughs in the alumina to evaluate the adhesion of the via materials. AMERI is currently working with Heraeus, Inc. of Conshohocken, PA, one of the leading suppliers of Pt powders and thick film inks in the world, to optimize its ink performance. It should be noted that previously, AMERI partnered with Heraeus to develop cofire-able solid Ag pastes (up to 0.5 mm thick) that are compatible with various commercial LTCC tapes [Wang et al. 2001].

Typically, when punching green ceramic tape to prepare an assembly to co-fire, the tape thickness should be no greater than the diameter of the micro-punch. In the proposed work, green tape thicknesses of 100 and 50 µm (4 and 2 mils) will be developed using two tape casting formulations, one based on an acrylic binder, and the other on polyvinyl butyral (PVB).
The PVB tape has a higher glass transition temperature and exhibits higher mechanical strength properties that might have advantages in thinner tapes, while the acrylic system will provide better lamination performance at lower pressure (an advantage for the Keko optical stacker/tacker system that AMERI uses). Both tapes will be cast and evaluated for optimal processing conditions based on the size and pitch of the particular via structures chosen.

We propose to develop an initial feedthrough assembly that has 100 \( \mu \text{m} \) (or .004") diameter vias in the green tape, and a 0.38mm (or .015") pitch in a disc that is 7.32 mm (or .288") in diameter. This will yield a 200+ I/O feedthrough assembly in Year 1. This initial design will then be scaled to smaller via pitches in Years 2 and 3 of the proposed program, with a Year 2 target of \(~85 \mu \text{m}\) diameter fired vias on a .008" pitch, in a close-packed arrangement. This feedthrough design will yield 750 I/O in the same 7.32 mm diameter disc; this is the structure drawn schematically in Figure 12. By using 50 \( \mu \text{m} \)-thick green tape, via diameters could ultimately be down-sized to 50 \( \mu \text{m} \) with a pitch of 150 \( \mu \text{m} \), resulting in an improvement of the I/O count to over 1000 in Year 3 without any fundamental changes to the process technology. There should also be minimal changes to the platinum ink formulation during this scaling process, as the reduced dimensions will only assist in reducing any effects of the thermal expansion mismatch between the platinum and alumina-based materials involved.

The PI’s role in this effort will be to oversee the fabrication of the HTCC structures at AMERI and ensure that all process details are recorded and transferable to volume manufacturing. Additionally, the PI (and AMERI) will make use of the Motorola Nanofabrication Facility (MNF) at Florida International University, Miami, FL to deposit precious metal coatings in post-processing operations on the as-formed vias to make them compatible with welding or joining processes for attaching flexible circuitry to the ceramic surfaces (see Aim 2). These steps will include, for example, post-firing of patterned PtPdAu thick-film solderable paste over the via sites, or electroplating of the Pt via surfaces with gold.

**Alternate Methods in Case of Fabrication Issues.** We have proposed two green HTCC tape formulations, two tape thicknesses, and three possible additives to commercial Pt inks (Ru, Rh, Ir) which together will permit considerable process latitude for creating truly hermetic feedthrough structures. In the event that mechanical punch processing proves challenging, AMERI also has laser processing capabilities for creating via holes in ceramic materials. The MNF also offers a range of sputtering capabilities for Au, Pd, Pt and other metals for creating customized thin-film metallizations on the via or ceramic surfaces.

**1B.2 Procurement and leak testing of miniature hermetic capsules and brazing of HTCC feedthrough assemblies to titanium ferrules.**

**Methods.** The HTCC ceramic feedthrough assemblies of Aim 1B.1 will be brazed into titanium ferrules, which in turn will be welded to a titanium capsules (see e.g. Figure 12 and Aim 1C). Gold brazing processes will be evaluated and optimized by the team at AMERI with the PI’s input to insure that hermetic feedthrough assemblies are provided. Our preferred method will employ industry-standard materials and processes for biocompatible assembly of alumina-based feedthrough assemblies into titanium housings. For example, Morgan Advanced Ceramics, Inc., New Bedford, MA used a 99.99% Au braze pre-form for fabricating the 19-pin feedthrough assembly currently used by the CIVR (and that is pictured in Figure 8). The surfaces of the ceramic were prepared for brazing in that case by application of thin films of biocompatible metals (e.g., platinum, niobium or titanium) using PVD deposition methods. This same process will be used by the PI and AMERI to coat the edges of our HTCC feedthrough assemblies, and thin-film coatings of biocompatible metals will also be evaluated as adhesion layers that are compatible with Au brazing methods, and that minimize any adverse reactions
between the Au and the Ti. AMERI has a 2400 °C vacuum furnace (capable of 1 X 10⁻⁶ torr) which will used to develop these gold braze processing methods to hermetically attach our feedthrough discs to machined titanium ferrules; the PI also has access to equivalent facilities at Cornell University. The ferrules will be procured from third-party vendors, as will the Ti capsule blanks.

In parallel with the more conventional brazing methods above, in Years 2 and 3 we further propose to investigate new nanoparticle-based gold brazing schemes that will afford a significant reduction in the melting point of the Au to substantially lower temperatures than that of standard gold brazing methods, possibly by hundreds of °C [Lee et al. 2007]. As was demonstrated in the preliminary Pt feedthrough development effort described above, nano-sized Pt particles have already been employed to lower melting points by over two hundred degrees below the nominal value for Pt. Brazing alloys, including biocompatible gold alloys such as AuSn, will be developed using nanoparticle-Au to reduce their melting points below the α to β phase transition of CP titanium (at 883 °C). Melting will be evaluated at AMERI using differential scanning calorimetry, optical dilatometry, and in-furnace optical imaging. Lower-temperature processing will minimize grain growth in the titanium during firing, a problem that can lead to metal deformation and softer titanium upon completion of processing of hermetically sealed structures.

Since the use of AMERI as a vendor to our research program is so key to our success, additional background on their equipment and prior experience has been appended to this proposal as part of the Facilities description.

Alternate Methods in Case of Fabrication Issues. We have proposed primary (Au-based) and alternate (nano-gold/AuSn) brazing processes for sealing the HTCC feedthroughs to Ti rings. The AuSn brazing process has been successfully used by MicroChips, Inc. in development of a 108-channel drug delivery device. In the event that He leak testing methods prove too insensitive (because the case volume is so small that a leak rate at the noise floor of the system would still prove problematic over years of exposure to body fluids), we will investigate Kr leak testing as an alternative.

1C. Development of gang welding and/or soldering processes for making connections between HTCC feedthrough/ferrule assemblies and internal/external flexible circuitry / electrode arrays.

Methods. The Pt feedthrough metallization that fills our vias must be made compatible with the first-level microelectronic assembly process for attaching the hermetic HTCC-Ti ferrule assembly to the internal and external flexible circuitry. For the interior surface, we propose that our HTCC/Pt feedthrough disk can be post-fired with solder-able Pt/Pd/Au thick film ink prior to the brazing step above. This thick-film ink, which has a proven history of minimizing solder leaching and inter-metallic formation, allows ready solderability with standard commercial solders for attaching the internal flexible circuitry to the interior surface of the neurostimulator body (see Figure 12.) Other surface processing methods, including electroplating and thin film deposition, will be evaluated by the PI at the CNF and/or MNF to optimize the interconnections to the electrode arrays on the surfaces of the vias. Such post-processing would, for example, enable the use of thermo-compression joining of gold mating surfaces using a gang processing thermode to make these external connections, in a similar manner to gang-bonding methods for tape automated bonding (TAB) structures in common use in the electronics industry. The connection technology to be used for joining the external flexible circuit/electrode array must be one that will not cause degradation or melting of the interior interconnects. Processes that qualify for this task are pulsed laser welding, ultrasonic bonding, thermosonic bonding, parallel gap bonding, and the above mentioned thermo-compression technique. Preliminary work on
attaching external components to the HTCC Pt feedthrough assemblies of Figure 14 has concentrated on micro-resistance welding of Pt and/or PtIr wires to the via surfaces. In the event that resistance welding does not prove feasible, the welding/bonding vendor, Hermetic, Inc. of Bedford, MA, will evaluate the above alternate attachment technologies. The PI’s role will be to work with this vendor to create microfabricated electrode array/flex circuit structures which are compatible with the selected welding process using thin- and/or thick-film processing methods, that will form a robust mechanical as well as electrical joints (see Aim 2). Preliminary bonding development will be performed on HTCC ceramic feedthrough disks without Ti ferrules, and the PI will obtain these from AMERI in the first months of the proposed program (see the project Gantt chart in Figure 16). Hermetic’s welding expert, Mr. Tom Salzer, will utilize the services of third-party welding vendors as necessary to provide the PI with appropriately joined assemblies. Again, since the success of our proposed program depends to a significant degree on the competence of the vendors selected, Hermetic’s capabilities are more fully described in the Facilities appendix to this grant.

Hermetic will also perform sealing of the HTCC – Ti ferrule assemblies to the hermetic titanium case blanks. This will be accomplished by projection welding of the machined ridge on the under-side of the ferrule lip to a shelf machined into the case frame. Projection welding is the preferred method for producing this type of joint because of the high performance / cost ratio of this process. Test ferrule blanks fabricated for projection welding trials need not have the internal hole machined for brazing in the ceramic insert. The lack of a hole will simplify hermeticity testing of the welded joints. Welding electrodes will be designed and fabricated, and weld schedules will be established by the vendor prior to welding actual neuroprosthesis assemblies. These non-recurring engineering costs are built into Hermetic’s quotation, which is included in the Budget Justification of this proposal. Welded samples will be subjected to destructive mechanical testing and microanalysis in order to determine the characteristics of the welded joints. Additional samples will be tested for hermeticity at selected laboratories. The performance goal for this effort is that no leak through the weld joint should be detected when tested with equipment having basic sensitivity of 1x10^{-9} std cc He/sec.

**Alternate Methods in Case of Fabrication Issues.** We have proposed both thick-film (PtPdAu paste) and thin-film (plating/PVD) methods for creating weldable/bondable structures to mate with the HTCC feedthrough discs of Aim 1B. We anticipate that the welding process development will be interdependent with the feedthrough via metallization process, and the PI’s role will be to coordinate activities between the two vendors involved and provide rapid turn-around of alternate metallization schemes for iterative experimentation. Should the projection welding procedure for joining the Ti ferrules to the case blanks prove problematic, we will instead use a flat ferrule lip and join the two Ti parts by laser welding in the same manner as the current CIVR neuroprosthesis lid. That service was procured from Texcel Medical, LLC of East Longmeadow, MA (see Figure 8 for an example.)

**Specific Aim 2: Highly Biostable Encapsulating Films for Flexible, Microfabricated Iridium Oxide Electrode Arrays**

**2A. Optimization of microfabrication processes that are compatible with SiC materials to create new generations of highly biostable sub-retinal iridium oxide microelectrode arrays.**

**Methods.** We propose to optimize our processes for creating single- and multi-layered flexible, polyimide-based electrode arrays in support of our long-term *in vitro* and *in vivo* testing objectives. This process, which was outlined in schematic form in Figure 11, has been developed over the last 10 years by the PI using the facilities of the Cornell NanoScale Science
and Technology Facility (CNF) and the Motorola Nanofabrication Facility at Florida International University. The proposal budget incorporates funding to cover the PI’s user fees at these facilities, which represent considerable cost sharing by other government agencies (NSF in the case of the CNF, and DoD/State of Florida in the case of MNF). Both facilities are made available to outside government users at reduced hourly rates.

The methods we will use to fabricate these a-SiC:H – encapsulated arrays are as follows. The arrays, similar in appearance and design to those shown in Figure 3, will be fabricated by first spin-coating and curing a 10 µm thick base coating onto a 100 mm-diameter silicon wafer using HD Microsystems PI-2611 polyimide. A layer of a-SiC:H will then be deposited by plasma enhanced chemical vapor deposition (PECVD) at 350°C. A 3-layer metallization, comprised of two titanium adhesion layers and a gold conductor layer (Ti/Au/Ti), will then be deposited on the SiC by physical vapor deposition and patterned using a lift-off resist process. (The Ti and Au films will be 50 nm and 750 nm thick, respectively.) The previous two steps will then be repeated for each metallization level until the target number of layers (anticipated to be 4) is reached. Figure 11 (bottom) shows an SEM photo of a cross section of an array that was fabricated in just this manner; the waviness in the SiC layers is attributed to the sectioning process and is not inherent in the film. Next, 3 µm-thick polyimide overlayer will be spun over the metallized SiC layers (which end with an SiC deposition to seal in all of the patterned traces) and cured at 350°C. Electrode sites and contact pads will then be opened by patterning the wafer with photosresist and exposing the underlying metallization(s) by O₂ reactive ion etching (RIE). Next, the wafers will be re-patterned to expose only the electrode sites, and these will be coated with 300 nm of reactive DC-sputtered iridium oxide (SIROF) from an iridium metal target. The wafers will then be patterned a final time, and O₂ RIE will be used to define the perimeter of each individual array by etching through the combined 13 µm thickness of the polyimide layers. After soaking in water, the individual arrays will then readily be removed from the silicon carrier wafers for testing.

The key fabrication issues which we anticipate needing to address in this process optimization effort are step coverage over increasingly tall topography on the wafer surface as successive layers of the flexible circuitry are added, and adhesion and integrity the array materials. During preliminary development work, the PI noted that substantial thinning of the SiC could be observed at step edges as metal layer 4 was added over layer 3, for example. Should this occur in the proposed effort, we will investigate the use of polyimide inter-layers between the SiC/metal/SiC “sandwiches” to reduce step heights due to the self-planarizing nature of the liquid polyimides. Another alternative would be to use only polyimide as the inter-layer dielectric, and use SiC only as a coating above and below the multi-layered structures. With regard to the durability of polyimides as the outermost protective coatings for our arrays, our preliminary data is excellent (see Figure 9). Should this material break down under accelerated testing (in Aim 2C), we will investigate the use of parylene compounds as outer encapsulation materials. Naturally, our process would need to be modified in order to do so, owing to the high deposition temperatures required for high-quality SiC thin film deposition. Our proposed method in this case would be to remove the polyimide/SiC-based devices from their carrier wafers after patterning to mask off the electrodes and contact pads, then etch away the outermost polyimide films, and deposit parylene over all surfaces and selectively lift this off of the electrodes. We will also investigate the use of organosilane adhesion promoters to improve inter-layer adhesion and integrity of the completed devices, particularly if parylenes are used as an outer encapsulant. Other tasks in this effort will be to optimize our current a-SiC:H and metal layer thicknesses to minimize stress in the resulting devices, and continue improvement of existing processes for removing completed arrays from their host silicon wafer after processing.

Alternate Methods in Case of Fabrication Issues. The preliminary data presented above lends confidence to our proposed approach; we have proposed alternate approaches for multi-
layer stack-up configurations to minimize step coverage issues, and adhesion and integrity of the outermost encapsulation materials will be addressed through the use of adhesion promoters and/or substitution of parylene coatings (e.g., parylene-HT from Specialty Coating Systems, Indianapolis, IN).

2B. Development of appropriate modifications to our current flex circuit fabrication methods and metallization schemes to accommodate the gang welding or bonding processes of Aim 1C.

Methods. It is anticipated that the flexible circuits and electrode arrays that are fabricated under this program will need to be modified from the current configuration (shown in Figure 11, top) in which the metal layer(s) are exposed from one side of the array only. By creating structures which allow access to the embedded conductors from both the top and the bottom side, we will enable a bonding or welding tool to approach from the outside of the flexible circuit, opposite the previously-prepared feedthrough via surfaces on the HTCC ceramic disk. This will facilitate the desired thermo-compression or gang interconnection operation by the welding vendor. If the metal membranes thus created are not sufficiently robust to withstand the pressure applied during the joining process, electroplating techniques will be used to increase the metal thickness in these regions to improve their physical robustness. A greatly simplified schematic representation of a four-layer electrode array structure demonstrating the alteration in the fabrication process that will be required is shown below in Figure 15.

We propose to implement this double-sided electrode array structure by locating the required metal membrane close to one surface of the device. In this way, the bottom side of the array metallization may be exposed by free RIE etching of a sacrificial layer on the bottom of the array after it has been removed from the host substrate. A related process for double-sided flexible circuit fabrication has already been developed by the PI’s team at Cornell to create substrates similar to those in Figure 2 onto which flexible, wireless neuroprostheses were built. In the event that the as-fabricated suspended metal membranes are too delicate to survive post-processing and/or bonding, the metallization thickness created by PVD during the initial fabrication steps will be increased to improve robustness.

Figure 15. Simplified schematic representation of a four-layered electrode array structure embedded in a polymeric substrate, which has the contact pads exposed from both sides of the array to create a suspended metal membrane. Such structures may be required to facilitate joining these arrays to specially prepared feedthrough via surfaces in bonding/welding operations.

Alternate Methods in Case of Fabrication Issues. Aside from increasing metal thickness to improve mechanical stability, if experience further difficulty in fabricating the desired freestanding metal membranes we will investigate a variation on the process of Meyer et al. [2001]. This approach used rivet-like interconnections made through metallized holes in flex
circuits. A second alternative will be to employ electroplated ‘beam lead’ – like structures that have protrusions of traces beyond the edges of or holes in the circuits (see e.g. Figure 15, left.)

2C. In-vitro environmental and biostability testing of these arrays under accelerated saline soak testing conditions with and without continuous, bi-phasic current pulsing.

Methods. The PI will work in the laboratory of long-time CIVR collaborator Dr. Stuart Cogan of EIC Laboratories, Inc., Norwood, MA to conduct accelerated testing of the microfabricated electrode arrays and of complete prosthesis assemblies in biological saline at 87 ºC. These tests will be performed on both pulsed and un-powered devices to determine any long-term electrochemical degradation effects. At these temperatures, the equivalent of 10 years’ implantation in the body at 37 ºC occurs in a span of approximately 5 months. Measurements will be performed in specially prepared ovens using nominally sealed glass beakers to contain the saline solutions, to minimize evaporation loss. Additionally, our team will conduct environmental testing of completed neurostimulators, encompassing 85 ºC-85% RH testing, shock, vibration, and thermal cycling experiments, also at the EIC facility.

Alternate Methods in Case of Testing Issues. It is possible that the predicted package lifetime based on these accelerated life tests could be less than the 10 years that has been identified by the FDA as a minimum benchmark for retinal neuroprostheses. In this event, we will investigate the use of a water gettering device that can be incorporated into the package envelope to increase its effective volume if leakage into sealed units appears problematic upon destructive testing and RGA analysis.

Specific Aim 3: In-vivo Biocompatibility Evaluation of Complete Neuroprostheses

3A. Assembly of complete hermetically sealed visual prosthesis assemblies based upon the technologies developed in Aims 1 and 2.

Methods. A quantity of ~150 complete high density neural prosthesis assemblies will be procured and assembled by the PI in each of the three years of the proposed program. The project Gantt chart, shown below in Figure 16, details the process by which this effort will be completed by combined use of vendor and microfabrication user facilities. We propose to perform the development of progressively higher density packages in each year of our program. In Year 1, our target device will have 200+ I/O, in Year 2 we will focus on a 750 I/O device, and in Year 3, prostheses with 1000+ I/O will be built. The progression of process and product development, detailed thoroughly in the chart for Year 1, will be repeated in Years 2 and 3 in an iterative fashion as learning about assembly and fabrication techniques progresses. While the in vivo implantation trials of Aim 3B will only require a handful of completed units per year, significant numbers will be required for destructive testing and subsequent analysis, and to obtain statistical confidence in the lifetime and environmental test results of Aim 2C. The high materials and supplies line item in the proposal budget reflects not only the expenses related to vendor services that have been outlined above, but the precious metals used in the proposed assembly process are quite expensive (e.g., $41/gm for cofire-able Pt ink). Additionally, the proposed vendors for the required prosthesis components project substantial non-recurring engineering expenses.

Alternate Methods in Case of Cost Issues. Should budgetary constraints limit the number of hermetically packaged neurostimulators which can be fabricated in a given year, the target package count will be reduced separately or together with the number of implantation trials.
3B. Perform chronic implantation survival surgeries, followed by periods of up to six months of periodic evaluation of animal ocular health, including fundoscopic and ERG evaluations.

Methods. The PI’s co-investigator, Center director Dr. Joseph F. Rizzo, MD, will oversee the chronic implantation of high density neuroprosthesis packages (both passive and active) in Yucatan mini-pigs at the Boston VAMC according to existing, pre-approved IACUC protocols. Expenses for animal purchase, housing, and surgical/examination supplies are incorporated into the grant budget. The actual surgical implantation experiments will be conducted by CIVR retinal surgeon Dr. Jinghua Chen, MD. Dr. Chen is separately funded through grants to the Massachusetts Eye and Ear Infirmary, and her effort is provided to this program under a cost sharing agreement with the CIVR. Likewise, Dr. Rizzo’s salary is also paid from other VA research support, and funding for his effort under this program is not required.

The purpose of the in vivo survival surgical trials shall be to assess the long-term biocompatibility of the materials of construction of the implants, and to determine whether changes to the overall form factor of the prosthetics would improve these results and reduce discomfort. These changes will be incorporated into our designs in Years 2 and 3. Ultimately, our team will conduct a full battery of biocompatibility tests on our high-density prostheses to ISO standard 10993, in support of Investigational Device Exemption application(s) to the FDA. Such experiments, however, are beyond the scope of this proposal. The primary goal of the five exploratory long-term implantation trials that we propose for each year will be to optimize the package design and maximize biocompatibility in subsequent trials. Funds are included in the budget to cover periodic examinations of the health of the mini-pig eyes over the average 90-day period of implantation, which may include fundoscopic and ERG evaluations and OCT studies.

Alternate Methods in Case of Surgical Complications. Our surgical team is highly trained and experienced in the methods proposed herein. Should previously unobserved biocompatibility issues be noted with the materials of implant construction proposed here, the PI will take immediate corrective action by changing these materials, coating methods, or attempting modified implantation methods such as alternate suturing strategies.

* * * * *

Expected Outcomes

We anticipate successful development of 200, 750, and 1000+ I/O prosthesis packages and successful demonstrations of their biostability and biocompatibility in Years 1, 2, and 3 respectively. Our excellent preliminary results to date lend us confidence in our proposed approach, and we anticipate ready acceptance of medical devices based on our proposed technologies by the FDA in future IDE applications. Entirely new generations of neural prosthetics will also be enabled by these advancements.
Figure 16. Gantt chart detailing the sequencing of development tasks for the proposed neuroprostheses in Year 1; Years 2 and 3 follow a nearly identical path, but at higher densities. The fundamental technologies on which the proposed high-density packages are based are the same in each case. The Year 2 and Year 3 product development steps have been omitted for simplicity.