ABSTRACTS

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I. Scientific Session
Degenerations of the visual systems - from genes to function

01 L Thomas Theelen, N.M. Bax, C.B. Hoyng (Nijmegen/NL)
*Early onset Stargardt disease - a candidate disorder for artificial vision and gene therapy*

**Objective:** Autosomal recessive Stargardt disease (STGD1) clinically embraces a large spectrum of inherited photoreceptor degenerations of the posterior pole. We describe a clinical subtype of STGD1 with exceedingly bad visual prognosis.

**Materials and Methods:** A large database on patients diagnosed with clinically and genetically proven STGD1 was reviewed. Patients with disease onset before the age of 10 years were selected. The clinical course as well as imaging appearance and electrophysiological properties of these patients were analyzed.

**Results:** 46 out of 248 patients in our database had early onset Stargardt disease. Frequently, typical flecks were not seen in the first year but developed later in the due course. Instead, a peculiar intraretinal autofluorescence signal with increased OCT reflectivity were visible on imaging. Eventually, extensive retinal atrophy occurred covering the whole posterior pole occurred in adolescence or early adulthood.

**Discussion:** Early onset STGD1 shows enhanced clinical progression. Due to their young age, these patients may take a large benefit from artificial vision. Due to the rapid progression, gene therapeutic effects may be measured relatively easy.

02 L Carel B. Hoyng, A.I. den Hollander, R.K. Koenekoop (Nijmegen/NL)
*Leber Congenital Amaurosis Studies on phenotype and genotype*

**Objective:** Leber Congenital Amaurosis (LCA) is a heterogenous group of retinal dystrophies defined as congenital or very early onset of rod-cone dystrophy. Nineteen causative genes have been identified for LCA.

**Materials and Methods:** In a large international database, patients diagnosed with LCA were studied with respect to clinical features, including retinal imaging and genetic aspects.

**Results:** An overview will be given on the phenotypes of various genotypes in LCA.

**Discussion:** The best preserved retinas are those of patients with RPE65, LRAT, GUCY2D and CEP290 mutations.

03 L Sonia Biswas, F. Müller (Jülich/D)
*Characterization of the Retinitis Pigmentosa (RP) mouse model, RD-10: A morphological and electrophysical study*

**Objective:** In retinitis pigmentosa (RP) the photoreceptors degenerate over time but the retinal network, in particular the ganglion cells (RGCs) persist, providing a target for electrical stimulation by retinal prostheses. However, changes induced by retinal remodeling might interfere with this therapeutic
approach. We, therefore, investigated changes in the inner retina of a mouse model of RP, the rd10 mouse.

**Methods and Results:** Using immunohistochemistry, we observed that the photoreceptors degenerate over time. Inner retinal cells did not degenerate but we observed both losses of dendrites as well as dendritic sprouting in the horizontal cells and bipolar cells. In electrophysiological recordings using multielectrode arrays (MEA), we observed rhythmic electrical activity. Regular patterns of local field potentials (LFP) occurred with frequencies between 3-5 Hz. Rhythmic bursts in RGC spiking were often observed phase-locked to LFPs. This kind of activity was not observed in wild type retinae. Preliminary pharmacological analysis suggests that both excitatory as well as inhibitory mechanisms are involved in the generation of spontaneous rhythmic activity in rd10 retinae.

**Conclusion:** In rd10 retinae, a pronounced rhythmic electrical activity is observed. It will be important to investigate, whether this activity compromises the efficacy of electrical stimulation by retinal prostheses.

**Acknowledgment:** This work was supported by the DFG grand MU 3036/2-1.

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**Electrophysiological Differences in Retinae of Wild Type and rd10 Mice influence the Electrical Stimulation Efficiency**

**Introduction:** Retinal degenerative diseases, like retinitis pigmentosa (RP), begin with the loss of photoreceptors, followed by a remodeling process of the remaining inner retina. Retinal prostheses, used to restore vision in RP patients, are not adjusted to these changes. We examine whether electrical stimulation patterns of newly developed prostheses need to be adapted to the electrophysiological properties of degenerated retinae.

**Methods:** To investigate the changes in electrophysiological properties of degenerated retinae and their reaction to electrical stimulation in comparison to healthy retinae, we recorded in vitro from whole mount retinae using a microelectrode array (MEA) system. Recordings from retinae of wild type (wt) and retinal degeneration 10 (rd10) mice in different phases of degeneration were carried out. Biphasic current pulses of different amplitudes and durations were applied to one predefined electrode.

**Results:** As described previously, spontaneous activity differed between wt and rd10 retinae. In wt, baseline was stable and spikes appeared in different frequencies in a stochastic manner. In rd10, oscillatory potentials of 3-6 Hz (“slow waves”, SW) were recorded. Occasionally, SW appeared and disappeared over time and a phase-locking behaviour between SW and spiking was observed. Increasing spiking frequencies due to electrical stimulation were recorded both in wt and rd10. However, the evoked responses in rd10 retinae, in which photoreceptors were already degenerated, differed from wt retinae.

**Conclusion:** Our results showed that, regarding stimulation behaviour, there are non-negligible differences between the electrophysiological properties of healthy and degenerated retinae. Therefore, these results confirmed the necessity to account for changes that occur during the remodeling process in the degenerated retina in the design of new retinal prostheses. Stimulation
devices that can adjust the stimulation parameters to the acute electrophysiological status may be favorable for successful retinal stimulation.

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What is the optimal electrical stimulus for most RGCs?

Objective: To determine optimal stimuli for wild type (wt) and rd10 retinas.

Material and Methods: Retinal ganglion cell (RGC) spiking responses were recorded in vitro from patches of wt (C3H & C57BL/6) and degenerated (rd10) retina, using a planar multi-electrode array (MEA, 60 electrodes, 200µm interelectrode distance, 30µm diameter, MCS, GmbH). Epiretinal stimuli were delivered via one of the 60 electrodes while the other electrodes recorded electrically-evoked responses. Stimuli consisted of square-wave, monophasic voltage pulses in incremental blocks (0.1V-2.5V) with randomized pulse durations. Responses were processed & analyzed offline using spike sorting software (Offline Sorter & NeuroExplorer, Plexon Inc, TX) and custom Matlab scripts (The Mathworks, Natick, MA) to generate rastergrams, peri-stimulus time histograms, and response surfaces over the 2D stimulus space.

Results: Electrical responsiveness of RGCs is a nonlinear function of both voltage and duration. By sampling a complete response surface for each RGC, we were able to determine the fraction of the recorded population that would respond to each unique stimulus at a rate both above threshold and below saturation. This allowed us to identify a small number of optimal stimuli that can be used in future studies to activate the majority of RGCs.

Discussion: Our findings present one of the first examinations of electrical stimulation in rd10 retina. Based on these findings, we propose tentative stimulation parameters appropriate for activation of rd10 and wt retina in our continued development of more efficient stimuli for the Tübingen retinal prosthesis.

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The importance to retinal prostheses of functional diversity across the ganglion cell population.

Objective: To examine the diversity of ganglion cell responses to electrical stimulation and the influence this diversity may have on standardized stimuli that are derived from simple population averages.

Materials and Methods: Mouse RGC spike trains were recorded with a multi-electrode array from the isolated retina during epiretinal stimulation with square wave, monophasic pulses of varying voltage and duration.

Results: Only about half of RGCs respond to electrical stimulation. Contrary to common assumptions, many RGCs do not respond to increasing electrical
stimulus with a sigmoidal function. The diversity of response patterns appears to reflect the diversity of network inputs and physiological properties across the RGC population.

**Discussion:** Standardized stimuli currently being used in the field of retinal prostheses should be reevaluated with an awareness of the large range of RGC classes. Future in vitro studies should take care to account for the true diversity of RGC classes rather than assuming that all RGCs are equivalent.

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**Different response patterns evoked via epiretinal stimulation in the royal college of surgeons rat**

**Objective:** Photoreceptor degeneration in neurodegenerative diseases like retinitis pigmentosa leads to blindness. Animal models with a genetically caused retinal degeneration showed that photoreceptor degeneration induces a remodeling process. Little is known about the impact of this process on the electrophysiological connectivity. In this study we investigated the stimulation properties, after photoreceptor degeneration in the retinal dystrophic Royal College of Surgeons (RCS) rat.

**Materials and Methods:** Isolated pieces of retina were placed with their GC layer facing down onto multi electrode arrays. The retina was epiretinal stimulated and perfused with Ames medium or for investigations on the stimulation circuitry, with pharmacological blockers. Data acquisition was performed with the Multi Channel Setup software.

**Results:** Epiretinal stimulation of GC with current pulses evoked different types of response patterns. These patterns could be divided by the response latencies and the number of evoked spikes into bursty and single, delay or no response patterns. Inhibition of the excitatory signal pathways with CNQX and D-AP5 seems to have no impact on the evoked response patterns, whereas the blockage of inhibitory signals leads to a variation.

**Discussion:** Analysis of electrically evoked responses of GC in blind rats showed several response patterns after current stimuli. We assume, that the epiretinal stimulation could introduce, additionally to the direct stimulation of GCs, stimulation cascades within the inner nuclear layer which in turn leads to indirect stimulation of the GC. This finding will be helpful in developing an effective stimulation paradigm for visual prosthesis.

**Acknowledgement:** This work was supported by DFG Grant WA 1472/6-1

**Effects of intravitreal injection of iodoacetic acid and N-methyl-N-nitrosourea on photoreceptor survival in mice**

**Purpose:** To induce unilateral photoreceptor degeneration by intravitreal injections of iodoacetic acid (IAA) and N-methyl-N-nitrosourea (NMU) in comparison to their systemic application and the genetic rd10 mouse model.

**Methods:** C57BL/6J wild type mice were treated with intraperitoneal (MNU), intravenous (IAA), and intravitreal injections (IAA and MNU) at different concentrations. Mice were observed with ERG and OCT in a two week
follow-up and finally analyzed by immunohistochemistry.

**Results:** Systemic injections of both IAA and MNU induced high systemic toxic effects and weight loss, an extinction of the ERG, and a thinning of the retina as observed by OCT and immunohistochemistry. Animals systemically treated with MNU, showed a selective outer retinal degeneration comparable to that observed in rd10 mice as verified by immunohistochemistry. Mice receiving intravitreal injections nearly exhibited no reduction of welfare. After intravitreal injection of IAA, cataractous changes and inflammatory reactions as well as a thinning of the entire retina was observed, mostly prominent in the inner part of the retina. Intravitreal application of MNU displayed photoreceptor degeneration comparable to that found after systemic application or in the rd10 model; immunohistochemistry revealed selective photoreceptor degeneration of variable degree.

**Conclusion:** Intravitreal injection of MNU led to comparable retinal changes as observed after intraperitoneal application or in the genetic rd10 mouse model and is useful to induce photoreceptor degeneration without systemic side effects, while maintaining a healthy intraindividual control eye.

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**II. Scientific Session**

**Technology for stimulation of the visual system – from electrodes to systems**

09  Abdel Moneim Marzouk¹, A. Stanitzki², R. Kokozinski¹ (¹Universität Duisburg-Essen Fachgebiet Elektronische Bauelemente und Schaltungen, Duisburg/D. ²Fraunhofer IMS Duisburg/D)

**High Frequency Pulse-Density Modulated Switched-Capacitor Based Functional Electrical Stimulation of Retinal Bipolar Cells**

**Objective:** To introduce a high frequency electrical stimulation mechanism tailored to stimulate retinal bipolar cells.

**Materials and Methods:** The decreasing size of stimulation electrodes results in a higher impedance of the electrode due to the reduced surface area. This makes current-controlled stimulation unsafe as the stimulus current pulse could easily force the electrode potential to exceed the water window. Voltage-controlled stimulation has no control over the amount of charge injected into the tissue because the stimulus current is not controlled. For such a situation, the pulse-density modulated switched-capacitor based stimulation (PDM-SCS) has been engineered. The technique cyclically charges a capacitor to a predetermined voltage that is then discharged into the tissue every cycle. By pre-charging a capacitor to a predefined voltage it can be guaranteed that the electrode potential is maintained within the water window. The amount of charge injected is controlled by the size of the capacitor. The slow wave response of bipolar retinal cells to an electrical stimulus mimics the electrical behavior of a low-pass filter. The proposed PDM-SCS approach utilizes such low-pass behavior by injecting the required stimulus charge in the form of high frequency pulses in relation to the membrane properties. The injected charge and the resolution of the stimulus amplitude are controlled through the capacitor charge voltage and modulator sampling frequency.
Discussion: The PDM-SCS stimulation chip is designed, and is currently being fabricated and prepared for evaluation in clinical investigations. Acknowledgement: This work was supported by the Deutsche Forschungsgemeinschaft (DFG) funding the project (PAK 468).

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Image processing and neural stimulation methods developed for epiretinal implant systems

Objective: To develop image processing and neural stimulation methods to improve visual performance of current retina implant systems.

Materials and Methods: To overcome low spatial and temporal resolution problem, in our study, artificial retina model which has 3D two stage local-Adaptive DOG filter based spatio-temporal filtering structure (3D-ADOG) and Spatio-Temporal Electrode Mapping and Local Interleaved Stimulation (STEMLIS) methods are developed. While 3D-ADOG encodes images as like a retina and produce artificial spike activity, STEMLIS method is responsible for interaction-free stimulation of micro-electrode matrix. Performance of the methods is evaluated by real time image reconstruction methods used in DaVinci\textsuperscript{TM} digital video processor module with LCD glasses and phosphene based simulations. Beside simulation with normal seeing peoples, quantitative results are also obtained. For visual evaluation tests, 20 normal seeing peoples ages between 20 and 40 (27.9±5.64) were selected.

Results: For image reconstruction based, visually conducted contrast sensitivity, object counting, and pattern recognition tests, 3D-ADOG model respectively yielded higher scores than classical DOG based model, %11.4, %12.5, %9.8 and %73.7. For the same test set based on phosphene representation, STEMLIS method yielded higher scores than classical stimulation method as %10.5, %16.1, %14.1 respectively.

Discussion: By considering these simulation results, it has been concluded that the 3D-ADOG model and the STEMLIS method can contribute to sight restoration studies. Acknowledgement: This work was supported by a grant from TUBITAK (110E077)

Gregg J. Suaning, N.H. Lovell (Sydney/AUS)

Focal activation of retinal neurons from the supra-choroidal space

Objective: To describe stimulation paradigms to achieve low-threshold activation to effect selective stimulation of retinal ganglion cells via an electrode array implanted within the supra-choroidal space.

Materials and Methods: A stimulation paradigm that we have described as ‘quasi-monopolar’ (QMP) divides the return-path of stimulation across a ring of guard electrodes adjacent to and surrounding the stimulating electrode, and a distant monopolar return. Through acute in vivo testing in the feline, we have determined that the effect of the of guard ring electrodes is that activation is largely contained to within the ring. However, activation thresholds using this approach alone are approximately three times higher with respect to monopolar stimulation alone owing to inefficient, lateral
shunting of the electric fields. By splitting a proportion of the return current to a distant monopole, the electric field is directed towards the target neurons. The monopolar component of the return current effectively reduces the threshold of activation while the guard ring component maintains the localisation of activation. QMP further affords the possibility of delivering stimulation from multiple sites simultaneously with a significant reduction in cross-talk between stimulating sites relative to monopolar stimulation alone.

**Discussion:** The QMP stimulation paradigm provides the dual benefits of focused activation via guard-ring localisation with reduced stimulation thresholds of monopolar stimulation.

**Acknowledgement:** This research was supported by the Australian Research Council (ARC) through its Special Research Initiative (SRI) in Bionic Vision Science and Technology grant to Bionic Vision Australia (BVA).

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**Spatial Extent of the Ganglion Cells Response to Subretinal Photovoltaic Stimulation**

**Objective:** To assess the spatial extent of the response of the retinal ganglion cells (RGCs) to stimulation by subretinal photovoltaic arrays.

**Methods:** Photovoltaic arrays with pixel sizes of 140 and 70um were placed on the photoreceptor side of a rat retina, and network-mediated responses of the RGCs were recorded using a 512 electrode array. Stimulation of the individual pixels with 880nm light was used to assess the electrical receptive fields (eRFs) of the individual neurons. Stimulation with visible light was used to map the natural receptive fields (RFs) of the same neurons.

**Results:** Most of the RGCs responded to 4ms stimulation pulses with latencies in the range of 10-40ms, but some also exhibited delayed responses with latencies of 60-120ms. With 70um pixels, the eRF diameters varied from 120 to 320um for the shorter latency responses, but the delayed component could spread over a 490-560um zone. Average size of the eRFs was 270um, similar to the average size of the natural light responses – 260um. Response to pixels twice as large– 140um – was twice as wide: eRFs were 530um in diameter, on average. There was no correlation between the size of the natural RFs and eRFs in individual neurons.

**Discussion:** Similarity of the sizes of the electrical receptive fields to natural light responses, as well as the ease of implantation of the wireless arrays and good tolerance of the ocular tissues to the subretinal implant support the promise of the photovoltaic approach to restoration of sight in patients blinded by retinal degenerative diseases.

**Acknowledgements:** This study was supported by the NIH, AFOSR and BWF CASI.
Günther Zeck, F. Helmhold, M. Eickenscheidt (Tübingen/D)

Spatial sensitivity of subretinal stimulation systems evaluated by flexible microelectrode arrays

Background: Retinal implants can evoke visual percept in blind patients after successful implantation and efficient contact to the residual inner retina. Their stimulation performance with regard to spatial or temporal discrimination can be easily assessed using ex vivo retinas. Here we present how to evaluate the spatial sensitivity by using flexible microelectrode arrays which record simultaneously from multiple ganglion cells.

Methods: Whole mount retinas were interfaced in subretinal configuration to either (i) a capacitive stimulation array (Neurochip prototype; electrode size and pitch: ~50 µm) or (ii) to a retinal implant chip (Retina Implant AG, electrode size: 7 µm, pitch: 70 µm). The superfused retinal ganglion cell layer was contacted by a flexible, transparent and perforated microelectrode array comprising 16 densely spaced recording electrodes (150 µm electrode spacing). Stimulation with the capacitive electrodes is performed using monophasic constant current pulses (amplitude: 3 mA/cm²), while stimulation with the retinal implant is performed using constant voltage pulses (amplitude: 1.6V). In the latter experiments the stimulation current is monitored separately.

Results: Our protocols comprised stimulation with different electrode areas sequentially shifted by (i) 50 µm for the capacitive electrodes or (ii) by 70 µm in case of the retina implant chip. In both protocols we recorded retinal ganglion cells which change their spike pattern for minimally shifted stimulation areas. In both protocols we identify response patterns which mimic the receptive field of a retinal ganglion cell.

Conclusion: In addition to the high sensitivity to stimulus position the presented experiments demonstrate efficient stimulation with regard to stimulation strength (current amplitude or voltage amplitude respectively). This suggests that stimulation may be feasible with smaller electrodes. This work is funded by a BMBF grant (FKZ 1312038).

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Fabrication of Very Large Arrays for Retinal Stimulation

Objective: The objective of this work is to create multielectrode arrays (MEA) for epiretinal stimulation covering an area of about 100 mm². This could be the first step to an epiretinal prosthesis restoring not only the central but also the peripheral field of vision of RP patients.

Methods: Suitable shapes for the electrode arrays were designed under two main aspects, the implantability and the adaption to the curvature of the retina. The MEA is used for epiretinal stimulation and therefore has to be inserted into the eye-ball through a scleral incision, which should not exceed 5 mm in size. As the diameter of the MEA is about 10 mm it needs to be folded or rolled during the insertion and to regain its shape inside the eye without suffering from plastic deformations. When the MEA is attached to the retina it has to adapt to its curvature. To prevent the foil from wrinkling and
buckling and to ensure the electrodes have a good contact to the tissue it needs stress-relieving patterns. Several design prototypes based on polyimide were fabricated and tested in various experiments on silicone molds and in cadaver eyes. Polyimide was chosen as a base material due to its mechanical properties. Additionally it can be easily structured with standard photolithographic techniques.

**Discussion:** With globe- and star-shaped VLARS MEAs we found two designs that comply with the criteria mentioned above. Non-functional prototypes could be implanted successfully in porcine and leporine cadaver eyes and were intact also after explantation.

**Acknowledgement:** This work was supported by the Jackstaedt Foundation.

**III. Scientific Session**

**Preclinical tests - from concepts to experimental implantation**

15  T  Sandra Johnen¹, F. Meissner², I. Endler², W. Mokwa³, P. Walter¹

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**Biocompatibility of Vertically Aligned Multiwalled Carbon Nanotubes for Nano-Modification of Microelectrode Array Systems**

**Background:** To analyze the biocompatibility of distinct multiwalled carbon nanotubes (MWCNT) in order to optimize microelectrode properties related to charge transfer capacity and signal-to-noise ratio.

**Methods:** Vertically aligned MWCNT were synthesized on 4-inch silicon wafers by chemical vapor deposition and growth was achieved by nanoscale layers of iron, iron-platinum, or iron-titanium acting as catalysts. Survival, growth rate, and gene expression profile of L-929 and retinal precursor (R28) cells were estimated after direct contact as well as indirect contact, which means cultivation in cell culture medium pre-incubated with MWCNT-coated wafer pieces.

**Results:** Indirect contact had no significant influence on cell growth rates, measured in comparison to reference materials that exhibited defined levels of toxicity. Both cell types exhibited good proliferation properties on each MWCNT-coated silicon wafer. Cell viability ranged from 94.6% to 99.1%, in which better survival was shown on wafer pieces generated with the catalyst mixtures than with the iron catalyst alone. However, R28 cells exhibited a more separated growth, which may be explained by the rather hydrophobic property of the MWCNT surface, and showed a slightly decreased expression in genes associated with cell cycle regulation as well as neuronal and glial properties.

**Conclusion:** Despite the negligible differences, which are not as evident as one would expect from cytotoxic materials, all tested vertically aligned MWCNT showed good biocompatibility profiles. Therefore, MWCNT-coated microelectrode array systems provide a promising approach to electrically stimulate remaining neural cells.
Feasibility of implantation procedures of large multielectrode arrays for epiretinal stimulation

**Background:** The feasibility of implantation surgery of large epiretinal stimulators (VLARS = very large arrays retinal stimulator) shall be demonstrated. The clinical aim is to provide artificial vision with enlarged visual fields in patients with retinal dystrophies like Retinitis pigmentosa.

**Methods:** Polyimide stimulation foils with a diameter of 12.5 mm have been fabricated for implantation. Each stimulation foil contains a central field of electrodes and further electrodes for peripheral stimulation. Openings for retinal tack fixation are embedded paracentrally and in the periphery of the stimulator. Implantation is performed in pig’s eyes including lens removal, vitrectomy and the implantation via a corneal incision.

**Results:** Following lens removal by phacoemulsification and three-port vitrectomy, a decaline bubble is installed into the vitreous cavity. Via a “clear-cornea”-incision the folded stimulator is inserted into the eyeball and positioned onto the decaline bubble. Following aspiration of the decaline bubble the stimulator is lowered and positioned epiretinally at the posterior pole. The stimulator shows an overall flat contact to the retinal surface. The implantation is finished by fixation using retinal tacks.

**Conclusion:** Our experiments demonstrate the feasibility of implantation surgery of large electrode arrays for retinal dystrophies. Long term implantation for biocompatibility testing as well as stimulation experiments for the generation of cortical activation in animal experiments will follow.

Photovoltaic Retinal Prosthesis: evaluation in-vivo

**Background:** In the photovoltaic approach to retinal prosthesis the camera-captured images are projected onto the retina using pulsed near-infrared (NIR) light. Each pixel in the subretinal implant converts pulsed light into local electric current to stimulate the nearby inner retinal neurons. This study characterized the cortical responses to photovoltaic stimulation and compared them with visual evoked potentials elicited by visible light.

**Methods:** Subretinal photodiode arrays with pixel sizes of 70 and 140um were implanted in the subretinal space of rats with normal (WT) and degenerate (RCS) retina. Cortical responses (VEP) to pulsed NIR (915nm) and visible (635nm) light stimulation were recorded over a 6 month follow-up period. Stimuli were modulated by pulse duration, peak irradiance and repetition rate.

**Results:** Stimulation thresholds with 10 ms pulses were 0.5mW/mm2 for
70um pixels and 0.25 mW/mm² for 140um pixels. Latency of the visible light-induced VEP decreased with increasing irradiance, unlike the latency of eVEP, which was significantly shorter, and did not vary with NIR light irradiance. In both, WT and RCS rats the eVEP amplitude increased with peak irradiance and pulse duration, and decreased with increasing frequency in the range of 2-20Hz, similar to the visible light response. However, from 20 to 40Hz the VEP continued to decrease, while the eVEP did not change as much.

**Conclusions:** Robust cortical responses to photovoltaic subretinal stimulation and similarity of the eVEP modulation by NIR irradiance, pulse duration and frequency to VEP modulation by visible light suggest similarity in processing of the retinal responses elicited by both types of stimuli at the visual cortex. The small size and lack of wires makes photovoltaic arrays easy to implant and well tolerated in the subretinal space. Photovoltaic retinal prostheses offer a promising approach to restoration of sight in patients blinded by retinal degenerative diseases.

**Feasibility of 2nd Generation STS Retinal Prosthesis in dogs**

**Background:** We have demonstrated that suprachoroidal transretinal stimulation (STS) allowed 2 patients with advanced retinitis pigmentosa resolve to white bar targets. We have developed a 2nd generation STS system with a 49 channel electrode array, and the purpose of this study was to determine the feasibility of this new electrode array to be used as a retinal prosthesis.

**Methods:** To test the feasibility, we implanted an internal coil, a decoder, a multiplexer, and the 49 channel platinum electrode array in 3 dogs. The stimulating electrodes were implanted in the upper-temporal quadrant (dog 1) or lower temporal quadrant (dog 2, 3). The return electrode was passed through the pars plana and implanted in the lower temporal (dog 1) or the upper nasal (dog 2,3) quadrant of the vitreous. The internal coil and the decoder were implanted under the fascia of the temporal muscle. Wires from the multiplexer and the return electrode were connected to the decoder. At the end of the surgery, internal devices were examined by connecting the external coil and delivering electrical pulses. The surface of the electrodes was processed by a femto-second laser to increase the charge injection capability. The electrical stimulating pulses consisted of cathodic-first biphasic pulses (duration, 0.5 msec; frequency, 20 Hz; interpulse delay, 0.5 ms; number of pulses, 20) and they were applied sequentially to each electrode with a delay of 0.45 ms.

**Results:** All electrodes were functioning at the end of surgery in 3 dogs. Six months after the surgery, the fundus photographs and fluorescein angiograms showed no retinal damage in 3 dogs. Corneal artifacts elicited by the electrode array were recorded indicating that the electrodes were functioning.
**Conclusion:** Our results indicate that the 2nd generation STS retinal prosthesis is feasible and can be considered for clinical use.

**Dov Weinberger**¹, R. Gefen², D.R. Prag² (¹Petach Tikva/IL, ²Herzeliya/IL)

*In-vivo evaluation of penetrating electrode array implantation technique for artificial retina prosthesis*

**Purpose:** To develop a surgical technique for epiretinal implantation and attachment of retinal prosthetic devices, while considering procedure time, patient recovery, and precision of implantation.

**Methods:** Nano-Retina dummy implant made of silicon and glass was used to develop the surgical procedure in the domestic pig. Anterior chamber approach through the limbus and a pars-plana approach were tested. Animal behavior, fundus examination and histology were used to evaluate long-term retinal response.

**Results:** The anterior chamber approach was found to be preferable to the pars-plana approach due to the fairly large incision that was required for insertion of this relatively small implant. The procedure begins in standard anterior capsulotomy, lens aspiration and posterior capsulotomy. Partial pars-plana 23G vitrectomy is then performed and the implant is inserted through the anterior chamber via the opening in the posterior capsule, followed by in the bag intraocular lens implantation. The remaining vitreous cushions the implant and is gradually removed to place the implant gently on the retina. The surgery was completed within one hour. Chronic implantations to evaluate long-term reaction of the eye to the implant will be described as well as different modes of attachment of the implant to the retina.

**Conclusions:** Implantation surgery through the limbus, an expansion of the commonly performed cataract surgery followed by lens implantation, was found to be suitable and efficient for epiretinal implantations of retinal prosthesis. Furthermore, patients who undergo vitreal procedures generally develop a cataract within months and would require lens replacement. This procedure circumvents this additional surgery.

**IV. Scientific Session**

**Clinical tests - from concepts to products**

**Takeshi Morimoto**¹, T. Endo², H. Kanda¹, K. Nishida², T. Fujikado¹ (¹Osaka/JP, ²Suita/JP)

*Evaluation of residual retinal preservation by using transcorneal electrical stimulation and optical coherence tomography in patients with advanced retinitis pigmentosa, candidates for retinal prosthesis*

**Purpose:** The success of retinal prosthesis to restore vision depends on the presence of physiologically intact retinal ganglion cells that can transmit visual signals to the brain. Therefore it is important to properly evaluate the degree of retinal integrity for patient selection. The purpose of study to investigate the relationship between the retinal thickness by optical coherence tomography (OCT) and the threshold current to evoke phosphene by transcorneal electrical stimulation (TES) in patients with advanced retinitis pigmentosa (RP).
Methods: Forty four eyes of 25 patients with RP (average age, 64.2 years) were examined. The best-corrected visual acuity (BCVA) ranged from 0 to HM (median, LP). Retinal thickness (RT) was measured by macular cube scan (512×128) of Cirrus HD-OCT. Phosphene threshold was obtained when the subject can reliably identify a visual sensation at the center of visual field during TES (10ms/phase, 20Hz, 20 pulses).

Results: The central phophene was elicited in 25 eyes but was not elicited with current less than 2 mA in 19 eyes. There was no significant difference in BCVA between in a group with central phosphene and in that without central phosphene. The average RTs at three areas (center, central subfield, Maximum subfield) were significantly thicker in a group with central phosphene than that without central phosphene (center: 213 ±76 um vs 128 ± 65 um, P<0.05;central subfield: 271 ± 50 um vs 179 ± 81um, P<0.05; Maximum subfield: 252 ±34 um vs 184 ± 67 um, P<0.05). But no significant correlation was observed between RTs and thresholds of phosphene.

Conclusions: OCT provides an useful information to select a candidate for a retinal prosthesis, but the RTs did not proportionally correlate with the threshold of phosphene. It is necessary to examine patients by both OCT and TES in order to select patients suitable for a retinal prosthesis.

Matthias Keserü, G. Richard (Hamburg/D)

Chances and limitations of visual prosthetics - our first experiences with the Argus II epiretinal prosthesis

Retinal implant technology has improved over the last years, gaining advantages and possibilities in visual rehabilitation for patients with retinal degenerative diseases. Several study groups have already reported of succesful promotion of visual sensations by electrical stimulation of the human visual system. The Argus II epiretinal prosthesis is the first electronic device approved for partial restoration of vision in patients with retinitis pigmentosa. Nevertheless the anatomical, physiological and technical circumstances are setting boundaries for prosthetic visual restoration. We want to show our first experiences with the Argus II epiretinal prosthesis and want to rule out the possibilities and limitations of visual function by epiretinal stimulation.

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¹(Tuebingen/D. ²Retina Implant AG, Reutlingen/D. ³Stuttgart/D. ⁴Dresden/D)

Subretinal implant Alpha IMS mediates useful vision in blinding photoreceptor diseases

Objective: To restore visual functions by a photosensitive microchip with 1500 pixels (Alpha IMS from Retina Implant AG, Reutlingen, Germany, having received recently CE mark for commercial use in Europe).

Material and Methods: Alpha IMS implants with wireless power and signal transmission were meanwhile placed into the subretinal space of 25 patients blind from retinal dystrophy in order to restore some visual functions; brightness and contrast perception can be controlled by the patient.

Results: Here we report on the first module of the multicenter trial on experiences with implant surgery in 9 patients. All the subjects had...
The successful implantation of the chip. All were able to perceive light after implantation of the photodiode chip. The visual experiences ranged from perception of light where there was none before surgery, to the ability to see individual letters 4 cm high at a working distance of 40 cm. Motion detection was possible up to angular speed up to 35 deg/s, grating acuity up to 3.3 cpd. In some cases visual acuity measurement with Landolt C-rings was possible up to Snellen visual acuity of 20/546. Additionally, the identification, localization and discrimination of objects improved significantly in most patients. In repeated tests over a nine month period, several subjects were able to read letters spontaneously, controlled in four alternative forced choice tests. Control tests were performed each time with the implant’s power source switched off.

**Discussion:** The study has shown proof of concept that a photodiode chip placed in the subretinal space can provide useful vision for many subjects. Selection of patients based on experiences with preoperative OCT analysis, fluorescence angiography and autofluorescence helps to identify patients optimally suited for subretinal electronic implants.

**Acknowledgement:** The clinical trial (www.clinicaltrials.gov, NCT01024803) was supported by Retina Implant AG, Reutlingen, Germany

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**Detection of human faces by blind patients implanted with the Argus® II Retinal Prosthesis System**

**Purpose:** To investigate whether Argus II subjects can locate human faces with their systems using a facial detection algorithm and whether detection speed improves when field of view that is mapped onto the Argus II implant is changed (i.e. demagnified).

**Methods:** To date, more than 50 patients blinded by outer retinal dystrophies received an Argus II epi-retinal prosthesis (Second Sight, Sylmar, CA). In normal use, a micro camera mounted on a pair of glasses gathers visual information. The video is subsampled to match the field of view of the implanted array and processed into 60 pixels that characterize the average brightness of the scene at each electrode location. In the current study, the image of the scene acquired by the video camera was processed using a face detection algorithm, resulting in a visual percept only where a human face was detected by the processor. A printed image of a face at normal size was placed at random location on a wall at a distance of 3 meters. A distractor image with equivalent size and brightness was also placed on the wall at the same height. The subject was required to search for the face. In some trials, the image processing algorithm captured a field of view that matched the field-of-view of the implanted array (20 degrees diagonally) while in some trials the entire field-of-view of the camera (53 degrees) was captured and...
“zoomed out” to fit the array. In a second experiment the blind subject was engaged in a conversation with a sighted person, who either faced the subject or turned away at some point during the conversation. The blind subject reported whenever he was unable to detect the location of the face.

**Results:** The patients tested were able to find the face with both magnifications. The time to find the target was significantly shorter when using the wider field-of-view. In the “real conversation” task, the blind subjects were able to recognize within a few seconds when the other person turned away.

**Conclusions:** Face detection in real world, i.e. at 2-3 m distance is a challenging task with a retinal implant. Using a device that takes advantage of external image processing, we can provide face detection functionality to blind patients. This feasibility study demonstrated that image processing algorithms can enable patients to perform daily tasks that are not limited by the resolution or the sensitivity of the array.

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**24 T**

Gislin Dagnelie$^1$, H.C. Stronks$^2$, M.P. Barry$^1$ ($^1$Baltimore/USA. $^2$Canberra/Aus)

*Use of the electrically elicited VEP (EVEP) and ERG (EERG) to probe retinal processing in Argus II recipients*

**Purpose:** The electroretinogram (ERG) and Visually Evoked Potential (VEP) are widely used in clinical diagnostic testing to examine the function of the retina and higher visual pathways, respectively. In this study, we examined whether electrical stimulation of the retina with an Argus II implant would lead to recordable responses at the cornea (EERG) and occipital scalp (EVEP).

**Methods:** Three participants in the Argus II clinical trial volunteered for these experiments. EERG recordings used bipolar Burian-Allen electrodes, since in proximity of the implant electronics the stimulus artifacts picked up by monopolar (Jet or DTL) electrodes precluded recovery of the underlying response activity. For the EVEP, where the recording electrodes were much farther from the implant, standard scalp recordings could be used, with a high mid-frontal reference electrode. To allow stimulus artifacts to die down and to reduce premature adaptation to prolonged stimulation, stimulus pulses were separated by at least 2.5 s, and each recording lasted 500 s. Depending on stimulus amplitude, 4 – 12 such recordings were combined to obtain an averaged waveform.

**Results:** Reproducible EVEP waveforms, with a plausible dependence on stimulus attributes, could be recorded in all 3 participants, whereas this was not the case for EERG responses. Even for the EVEP, response amplitudes and waveforms are highly variable and not significant when patterned stimulation is applied to a subset of electrodes.

**Conclusions:** We have demonstrated that EVEPs can be used to examine properties of the visual pathways. The EERG, on the other hand, cannot be recorded reliably from the ocular surface. Recordings of retinal signals from the implant electrodes, immediately following stimulation at those same or neighboring electrodes, will be required to obtain reliable EERGs. High-quality reverse telemetry will be an essential tool for such recordings to become possible.
Comparison of the EPIRET III Prototype and the ARGUS II System after implantation in humans

Objective: To compare two different epiretinal stimulation implants after implantation of the EPIRET III prototype and the ARGUS II system in patients with retinitis pigmentosa.

Materials and Methods: Six blind individuals with retinitis pigmentosa underwent the implantation of an EPIRET III prototype in the context of a phase I/IIa trial as proof of concept in man with explantation after 4 weeks. 5 other RP patients received an ARGUS II system as permanent therapeutical device with a follow-up of 6 months. Two of these patients received the EPIRET device in one eye and the ARGUS II later on in the other. The EPIRET III prototype is a completely intraocular device which was test under laboratory conditions with an experimental signal transfer and no camera device. The ARGUS II system is an epiretinal stimulator with an extraocular power supply that is used with a camera and a video processor unit. Different features of the implantation procedures and the stimulation properties such as stimulation thresholds were compared.

Results: The implantation of the EPIRET III device took 2 hours, the implantation of the ARGUS II device 2.0 – 4 hours. One patient complained of chronic periocular pain after implantation of the ARGUS device, another patient had a sterile hypopion after EPIRET III implantation. The intraindividual comparison of stimulation thresholds in the binocular patients yielded that the EPIRET device required amplitudes of 10 and 6 µA with charge densities of 56,81 and 15,51 µC/cm2 at a stimulation duration of 446 ms, whereas the ARGUS device required amplitudes of 473,66 and 373 µA with charge densities of 737,68 and 570,75 µC/cm2, respectively, at a duration of 450 ms.

Discussion: Possible explanations for the lower thresholds in the EPIRET device maybe a closer contact due to the fixation with 2 tacks instead of 1, the 3D configuration of the EPIRET electrodes or the coating with IrOxact and a resulting high surface magnification.

Argus® II Retinal Implant: long-term study reliability

Purpose: Retinal prostheses are susceptible to damage by body fluids over time. Long-term reliability of retinal prostheses requires hermetic packaging to protect the electronic circuitry of the implant from the harsh environment of the human body and a robust high-density electrode array for safe chronic stimulation. In addition to lifetime testing under normal use conditions, accelerated lifetime testing has been widely used to predict the implants’ life and to better understand their failure modes.

Methods: Lifetime testing of the Argus II implant has been conducted at the component, subsystem and final device levels. Long-term stability of the implants is assessed in vitro through active soak tests under constant pulse stimulation. The implants are tested in buffered saline at body temperature, or elevated temperatures for accelerated tests. The implants are attached to
a silicone eye model to simulate the actual implanted condition. In some tests, a motor moves the entire eye model to simulate micromotion of a human eye. The device functionality, visual appearance, and material changes are monitored through the course of the lifetime test.

**Results:** Electrode material lifetime has reached 7 years in real-time testing under constant pulse stimulation and predicted equivalent of over 50 years of use in accelerated testing. Thin-film polymer electrode array insulation has reached 7 years in real-time testing and an equivalent lifetime of over 26 years in accelerated testing. Finished implants have reached more than 10 year lifetime in accelerated testing. These bench-test results are supported by clinical trial data: 30 subjects have been implanted an average of 4.2 years (range 3.3 to 5.5, excluding one explant at 18 months). Cumulatively, this represents 125 patient-years with only one device failure at 4 years post-implant.

**Conclusions:** The Argus II Retinal Implant has been tested at the component and system levels for long-term reliability. Thin-film electrode arrays withstood aggressive constant pulse stimulation and provided long-term safe stimulation without corrosion or material degradation. The hermetic package demonstrated the functional lifetime of the implant by preventing the moisture level accumulated inside the device. Lifetime tests support long-term reliability of Argus II Retinal Implants. Such long-term reliability is of paramount concern with respect to regulatory approval, and clinical utility, safety, and adoption.

Lauren N. Ayton¹, C.D. Luu¹, P.J. Allen¹, N.L. Opie¹, J. Villalobos², C.E. Williams², R.H. Guymer¹, on behalf of the Bionic Vision Australia consortium (¹Centre for Eye Research Australia, The University of Melbourne, Royal Victorian Eye and Ear Hospital, East Melbourne/AUS. ²The Bionics Institute, East Melbourne/AUS)

**Stability of a Suprachoroidal Visual Prosthesis**

**Background:** In 2012, Bionic Vision Australia implanted three patients with end-stage retinitis pigmentosa with a prototype suprachoroidal visual prosthesis implant. The suprachoroidal implant location was chosen, in part, for the hypothesised improved device stability. This paper will detail the initial device stability results during twelve months from implantation.

**Methods:** The implanted prototype device consisted of a silicone and platinum 24-channel array, which was connected via a helical lead wire to a percutaneous connector behind the ear. Intraocular array position was monitored over a twelve-month period with weekly fundus photography and optical coherence tomography (OCT). Lead wire and percutaneous connector stability were monitored using monthly X-ray and 6-monthly computerized tomography (CT) imaging. Device position was compared to anatomical landmarks to assess stability over time.

**Results:** From image analysis, both the intraocular array and extraocular connections remained in a stable position over twelve months. There was no damage to the devices and all electrodes remained functional over the 12 month follow up.

**Conclusion:** The initial twelve-month data show that the suprachoroidal implant location allows excellent device stability. As device efficacy is
dependent on a stable electrode-tissue interface, suprachoroidal implantation may be a desirable option for visual prostheses.

V. Scientific Session
Clinical tests - rehabilitation

28 L Gislin Dagnelie¹, D. Geruschat² (¹Baltimore/USA, ²Elkins Park/USA)
Update on the Development of a Prosthetic Low Vision Rehabilitation (PLoVR) curriculum

Purpose: Low vision specialists are used to helping patients with severe vision loss make the best possible use of their remaining sight. Artificial vision may pose entirely new challenges to low vision care providers, since restored vision may be very different from native vision.

Methods: The NEI-sponsored PLoVR study aims to improve our understanding of ultra-low and artificial vision, and adapt the materials and methods used in low vision care to this new patient population. We have developed a questionnaire to probe the visual ability of patients with these vision levels, and are calibrating the survey through Rasch analysis. In addition, the PLoVR study designs new activities to be used for both rehabilitation and visual performance evaluation.

Results: Of 100 respondents answering the 149 question survey in the initial calibration round, only 6 were recipients of retinal implants, and none were gene therapy recipients. Nonetheless, the results allowed us to calibrate the survey items along a visual difficulty scale, that should apply to patients with these and other therapeutic modalities. As more patients are being treated with these modalities, the calibrated survey will allow mapping their progress during rehabilitation, and on-going Rasch analysis will further improve the quality of the instrument.

Conclusions: Low vision rehabilitation specialists are already working with retinal implant recipients, and recipients of other treatments will soon follow. A generalized approach to the rehabilitation of individuals with ultra-low vision, based on the results of the PLoVR study, will be the basis for the coming expansion of this field.

29 T Stefania Guerra¹, F. Anaflous¹, J. Dorn², D. Geruschat³, R. Greenberg² (¹Second Sight Medical Products, Sàrl, Lausanne/CH. ²Second Sight Medical Products, Inc, Sylmar/USA. ³The Maryland School for the Blind, Baltimore/USA)
Elaborating a Rehabilitation Curriculum for Argus® II Retinal Prosthesis System Users

Purpose: The purpose of this work was to develop an instructional curriculum for Argus® II Retinal Prosthesis System (Argus II) patients who have undergone successful implantation of the system in a commercial setting. In the clinical trial that supported approval of Argus II for commercial use in Europe, variability in functional outcomes was observed between subjects. Some of this variability was attributed to differences in subjects’ ability to integrate the input of the technology into their lives. We developed an instructional curriculum specifically designed to teach patients the
foundational skills that are required to maximize the benefits of the Argus II technology.

**Methods:** During the clinical trial, we evaluated Argus II subjects’ functional vision with and without the System in real-world tasks. Based upon these experiences, we identified critical skills needed to successfully integrate the Argus II into users’ everyday lives within the context of the foundational blindness skills they already possess. Some of these skills are similar to other low vision rehabilitation techniques and some are unique to prosthetic vision. We then developed a curriculum and instructional kit to teach these skills and techniques to new patients. **Results:** These experiences resulted in a curriculum that serves as a guide for the therapists who are providing the rehabilitation services and an instructional kit that provides standardized training tools. The curriculum follows commonly accepted low vision rehabilitation principles of visual skill acquisition by isolating skills, using materials that are designed to support the development of these skills, and finally strategies for implementing the technology into the homes and lifestyles of the patient. For example, patients and caregivers will learn the importance of illumination and contrast, how and why to modify the home environment to maximize visibility, how to effective use the Argus II System’s different image processing filters for different environments, and what types of activities can be practiced at home.

**Conclusions:** The purpose of this work is to support patients so they can maximize the benefit of the Argus II System. We believe that applying standard low vision rehabilitation principles to the development of visual skills with the Argus II System will offer the best opportunity for patients to optimize the benefits from this technology.

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**Michael Scott Evans**¹,², Q.C. Vuong¹, P. Degenaar², R. Cheong-Leen³, S. George⁴ (¹Newcastle University, Institute of Neuroscience, Newcastle/UK. ²Newcastle University, School of EEE, Newcastle/UK. ³Imperial College, Department of Medicine, London/UK. ⁴Imperial College Healthcare NHS Trust, Western Eye Hospital, London/UK)

**Investigating assistive functions for visual prosthesis with low-vision patients**

**Objective:** Visual prostheses have returned poor visual acuity. This is akin to patients with macular degeneration (AMD). We therefore use this cohort to study visual assistive functions for visual prosthesis. Here we investigated whether an auditory feedback system could facilitate face identification.

**Materials and Methods:** Sixteen AMD patients were recruited from Western Eye Hospital, London. The patients were tested with a face discrimination task, in which they reported whether two sequentially presented faces were the same or different. We measured how accurately and quickly they responded on each trial. In one block, we provided auditory feedback on whether the faces matched or not and in another block, there was no auditory feedback. The faces were blurred and contrast-reduced to different levels in order to simulate different viewing distances and lighting conditions.

**Results:** We found that patients’ accuracy was systematically affected by blurring and contrast reduction but not by auditory feedback. Patients, however, responded more quickly on feedback blocks.

**Conclusion:** An auditory assistive function can facilitate face identification,
possibly by providing an alerting signal, without adversely affecting accuracy. Our study further suggests that visual prostheses which incorporate face-recognition technology also need tuning according to user requirements. The ultimate purpose of our studies is to provide these parameters (e.g., at what viewing distance would the users begin to rely on assistive functions or at what accuracy level would the users tolerate assistive functions).

Acknowledgement: This work was funded by the BRC and Newcastle EEE.


Safety profile in the Argus® II Retinal Prosthesis System post-market patients

Purpose: The Argus II Retinal Prosthesis System (Argus II) is the first and only artificial retina widely approved for market use (2011 CE mark in Europe, 2013 US FDA approval). In the commercial setting, it has since been implanted in 29 patients blinded by Retinitis Pigmentosa in 9 surgical centers in Italy, Germany, France, Netherlands, Saudi Arabia, and the UK. A post-market surveillance study has been started with the purpose to evaluate the safety profile of the approved device during commercial use compared to that observed in the investigational clinical study.

Methods: Safety data in the post-market setting has been collected from the day of surgery through August 2013, covering on average 10.2 months (median 9.2 months, range from 0.6 to 22 months) of exposure. The demographic distribution is: 11 female and 18 male patients, average age 52.9 years (range 31.0 - 74.0 years). The device was implanted OD in 17 patients and OS in 12 patients.

Results: Two of the 29 subjects have experienced serious adverse events that required a surgical procedure to treat. The first patient had an exposed suture led to conjunctival erosion which required repair. The second patient had hypotony that was treated with additional sutures and injection of saline. In addition, there were 16 non-serious adverse events (AEs) related to the surgical procedure: anterior chamber inflammation (1), fainting (2), conjunctival erosion (1), conjunctival irritation (1), high IOP (2), nausea/vomiting (3) experienced by 9 patients. These events were as follows: anterior chamber inflammation (1), fainting (2), hypotony (1), misshapen pupil (1), retinal tear (1), slight conjunctival injection (1), and syncope (1). There were also 6 non-serious, device-related events: decrease in light perception (1), headache (1), macular edema (1), ocular pain (1), revision of array placement (1), and vertigo (1). As was the case in the clinical trial, the majority of AEs (68%) occurred within the first month of implant, 14% occurred between 1-3 months, and the remainder of the events occurred between 6-12 months.

Conclusions: The first group of Argus II patients using the commercially available device demonstrates a safety profile that is, at 10 months post implantation, markedly better than that observed in the developmental phase of Argus II.
VI. Scientific Session
New ideas -
from products back to thoughts - thinking the future

32 L Jong-Mo Seo\textsuperscript{1,2}, H. Chung\textsuperscript{1}, S.J. Kim\textsuperscript{2}, D.I. Cho\textsuperscript{2}, Y.S. Goo\textsuperscript{3}, K.H. Kim\textsuperscript{4}, H.H. Koh\textsuperscript{5}, (\textsuperscript{1}Electrical Engineering and Computer Sciences, Seoul/ROK.\textsuperscript{2}Ophthalmology, Seoul National University Hospital, Seoul/ROK.\textsuperscript{3}Physiology, Chungbuk National University, Cheongju/ROK.\textsuperscript{4}Biomedical Engineering, Yonsei University, Seoul/ROK.\textsuperscript{5}Electrical Engineering, Chungnam National University, Daejeon/ROK)

Updates of Seoul Artificial Retinal Project

Seoul Artificial Retina Project started research in the year 2000, and tried preclinical experiments of subretinal, epiretinal and suprachoroidal stimulation. In this presentation, overview of the Korean artificial retina project will be introduced. Polyimide and liquid crystal polymer (LCP)-based gold electrodes were fabricated and tested in suprachoroidal, subretinal, and epiretinal conditions in rabbit eyes, and LCP was chosen as a base material for the artificial retina system. Monolithic, one-package system was designed and functionally tested ex vivo. In vivo experiments were done and the design of the package was revised. High-density electrode arrays are under investigation and stimulation parameters are being optimized by ex vivo experiments with multichannel electrode array recording.

33 T Peter Walter (Aachen/D)
Towards bidirectional retinal stimulators

Towards bidirectional retinal stimulators Peter Walter, Department of Ophthalmology, RWTH Aachen University, Germany Objective. To describe the concept of bidirectional retinal stimulators for improving the efficacy of prosthetic devices for the visual system.

Materials and Methods: Limitations of current available retinal stimulators and the underlying concepts were analyzed. Recordings of spontaneous local electrical activity were performed in several rodent models of Retinitis pigmentosa. Stimulation experiments were performed to test the hypothesis if the pattern of intrinsic retinal activity contribute to the likelihood of successful retinal stimulation.

Results: Different types of intrinsic activity can be found in the degenerated retina. The type of intrinsic activity effects the efficacy of stimulation considerably. Based on these findings a concept of bidirectional retinal stimulators is introduced.

Discussion: To increase the efficacy of successful retinal stimulation a bidirectional approach to retinal stimulation is suggested where implanted devices are equipped with signal recording and data analysis power. Thus, information on intrinsic retinal activity and the responsiveness to test stimuli can be used to automatically adjust the stimulation parameters and the pulse sequences.

Acknowledgements: This work was supported by DFG grant PAK 469/1, WA 1472/6.1, and a grant of the Hans Lamers Foundation, Jülich, Germany.
**Stefan Lück, W. Mokwa** (Institute of Materials in Electrical Engineering 1, RWTH Aachen, Aachen/D)

*Development of penetrating 3-D multi electrode arrays for stimulation of neurons and recording of neuronal activity in the retina*

**Objective:** In the present paper the development of a three dimensional micro electrode array with an iridium oxide coating is described. The electrode arrays are optimized for insertion into retinal tissue. The array allows to stimulate neurons or to record neuronal activity and by this to acquire spatially resolved data. In addition local changes of pH values can be measured with the electrodes, too.

**Materials and Methods:** A fork like structure serves as a carrier for the electrodes. These structures have four shafts with a length of up to 1mm, a width of 50 μm to 100 μm and a thickness of 20 μm, which can penetrate the retina. Four electrodes with sizes varying from 100 square micrometers to 1600 square micrometers are placed on every shaft. The shape of the carriers is etched into an oxidized silicon wafer by reactive ion etching. The carriers are separated from the wafer by backside etching. Signal lines are micro structured sputtered gold films. The electrodes are made by micro electroplating of gold and then coated with iridium oxide. Polyimide serves as a protection layer. To arrange the electrodes in a 3-D array the structures are glued together to a stack. The shafts and their tips were optimized to allow penetration and to minimize the damage to the retina and to be still stable enough to endure the mechanical stress during implantation. Because of the small width of the shafts, the electrode size is limited. The small size leads to high impedance. Measurements show that the electrode impedance is significantly reduced by coating with iridium oxide due to its electro chemical behavior and its porosity.

**Acknowledgment:** This work is funded by the German Research Foundation (DFG) within the research project “BiMEAs”.

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*Biocompatibility of Biochemically Modified Surfaces as a Fixation Concept for Epiretinal Stimulator Arrays*

**Background:** To develop an alternative fixation procedure for epiretinal stimulators as an alternative to the conventional fixation using retinal tacks.

**Methods:** Polyimide microstructures were coated with different protein configurations by immobilizing laminin peptide composites onto the surface. Implantation was performed in rabbits including vitrectomy and the positioning of the structures onto the retinal surface. After an observation period of three months the eyes were enucleated for histopathological examination.

**Results:** Using one additional retinal tack at one edge of the microstructures led to tight connection of the entire dummy microstructures at the posterior pole of the rabbits’ eyes. In cases where the positioning was performed
without an additional tack fixation the dummy structures did not remain at the posterior pole. In one case with additional tack fixation the microstructure showed tight contact although the tack was not detectable at the fixation site during the follow-up examinations.

**Conclusions:** Our first results of in-vivo implantation show that basically a tight contact of the modified microstructures with the retinal surface could be achieved. However, the necessity of a temporary additional tack fixation implies that a certain period of time needs to be bypassed until the biochemical fixation takes effect completely. Moreover, experiments in animal models which are more similar to the human eye could be helpful to investigate the relevance of this problem while the design of an entirely implanted prosthesis including the transscleral fixation of the receiver and the built-in stress of the stimulator cable may provide a certain temporary fixation.

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**The Cost-Effectiveness of the Argus II Retinal Prosthesis System in Retinitis Pigmentosa Patients**

**Objective:** To assess the cost-effectiveness of the Argus II Retinal Prosthesis System (Argus II) in Retinitis Pigmentosa (RP) patients. **Design:** Decision analysis model based-comparison of long term costs and health outcomes of Argus II implantation versus usual care (i.e. nursing care and rehabilitation) in RP patients. **Participants:** A hypothetical cohort of 1000 RP patients aged 46 years followed up over a (lifetime) 25-year time horizon. **Method:** A multi-state transition Markov model was developed to determine the cost-effectiveness of Argus II versus usual care in RP from the perspective of healthcare payer. Health outcomes were expressed as quality adjusted life years (QALYs) and direct healthcare costs expressed in 2012 €. Results are reported as incremental cost per ratios (ICERs) with outcomes and costs discounted at an annual rate of 3.5%.

**Results:** The ICER for Argus II was €14,603/QALY. Taking into account the uncertainty in model inputs the ICER was €14,482/QALY in the probabilistic analysis. In the scenarios of an assumption of no reduction on cost across model visual acuity states or a model time horizon as short as 10 years the ICER increased to €31,890/QALY and €49,769/QALY respectively. **Conclusion:** This economic evaluation shows that Argus II is a cost-effective intervention compared to usual care of the RP patients. The lifetime analysis ICER for Argus II falls below the published societal willingness to pay of EuroZone countries.