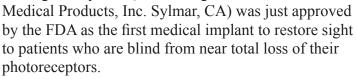
Artificial Sight: Restoration of Sight through Use of Argus II, a Bioelectronic Retinal Implant

Mark S. Humayun, M.D., Ph.D., Cornelius Pings Professor of Biomedical Sciences, Professor of Ophthalmology, Biomedical Engineering, Cell and Neurobiology, University of Southern California

ore than 1 million Americans are legally blind and another 10% cannot detect light .¹ With increased mean lifespan, the frequency of age-related eye disease will double in the next 30 years. ² A significant percentage of the non-treatable blindness stems

the non-treatable blindness stems from loss of photoreceptors (the rods and cones) ^{3,4} Once photoreceptors are lost, restoring useful vision to blind patients has been impossible. ⁵

However, after nearly a century of research into the use of electrical stimulation to restore sight, the Argus II system (Second Sight



NON-RETINAL VISUAL PROSTHESES

The concept of artificial vision was first tested in 1929 when electrical stimulation of the visual cortex resulted in a blind patient seeing a spot of light (phosphene). ⁶ More than 30 years later, Giles Brindley's implantation of an 80-electrode device onto the visual cortex of a blind patient renewed the possibilities of artificial vision restoration. ⁷⁻¹⁴ But, this goal of developing a visual cortical implant to restore vision remains elusive. ^{12,13, 15-27}

RETINAL PROSTHESES

Analogous to the cochlear implants for some forms of deafness, retinal prostheses propose to restore useful vision by converting visual information into patterns of electrical stimulation that would excite the remaining inner retinal neurons after photoreceptor loss in diseases such as retinitis pigmentosa (RP) and age-related macular degeneration (AMD). However, knowing that the retina has more than 100 million photoreceptors while the cochlea has only 15,000 hair

cells, the retinal implant is obviously a much more complicated challenge. First, there must be enough viable retinal cells remaining to initiate a neural signal. Post mortem studies on patients' eyes with end-stage RP and AMD have revealed that that plentiful numbers of non-photoreceptor neurons in the retina do survive the disease process. Although neurons in the retina survive despite photoreceptor loss, there is significant reorganization of the remaining neural network.⁴⁴

In spite of these well-documented changes in the inner retina after photoreceptor loss, when handheld electrodes were inserted in the eye of blind test subjects in an operating room, the test subject detected small spots of light when the electrodes were activated and the apparent location of the spot of light in general corresponded with the retinal area stimulated. These critical experimental findings led directly to the development of chronic retinal implant systems.

Two approaches have been evaluated thus far —subretinal implants (microphotodiode arrays inserted between the bipolar cell layer and retinal pigment epithelium) and epiretinal prostheses, in which visual information from devices like cameras provide the patterns of stimulation to the residual retinal neuronal networks. The implantation of a subretinal prosthesis, as well as maintaining its electronic functionality over long-term, is much more difficult than the Argus II epiretinal prosthesis. As of now, no subretinal implants have been successful to be approved as medical implants. 47-52.

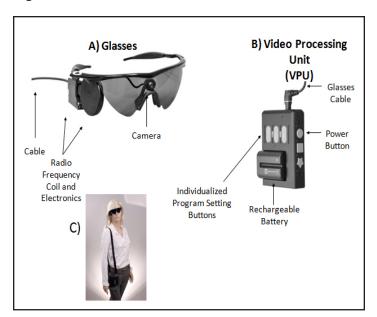
ARGUS II- EPIRETINAL PROSTHESIS

Epiretinal implants vary in terms of how much of the required electronic circuitry is contained in the intraocular device and how they are connected to the extraocular elements (induction coils, penetrating wires, or lasers).

The ARGUS TM II System (figure 1-2) is a two system implant in which the wearable and implantable units communicate wirelessly. The wearable

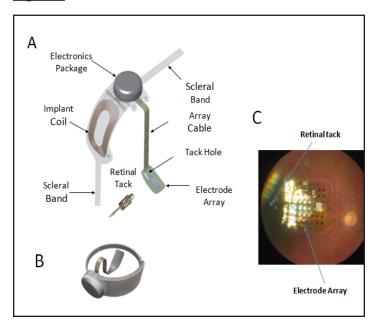
components include a miniature camera in the glasses from which information goes to a belt-worn pocket size video processing unit (VPU) with rechargeable battery. The VPU encodes the information and both power and data are then sent back to the glasses and then wirelessly (via a near field inductive link) sent to the implanted components. The implanted components consist of a receiver coil which then send the information to an implanted electronic chip inside a hermetic metal can. The implanted chip then decodes and routes controlled pulses via an integrated flexible cable with electrodes to excite retinal neurons. The electrode array is 6mmx5.5mmx0.5mm and when implanted in the center of the retina (i.e., macula) its diagonal dimension spans the central 20 degrees of visual field. All components of the Argus II fit inside the eye socket (orbit) and only the integrated cable with electrodes are placed inside the eye with the rest of the device sutured to the eye wall (sclera) and covered by the conjunctiva.

Figure 1:



Argus II Wearable components: (A) Glasses with camera and inductive (radio frequency) coil and associated electronics. (B) Video processing unit (VPU) with rechargeable battery. The VPU connects to the glasses via a cable and encodes the camera input and sends it back to the coil to be transmitted wirelessly to the implanted components. (C) Example of how the system can be worn with VPU using a shoulder sling. Alternatively VPU can be worn on a waist belt or put into a pocket.

Figure 2:



Argus II implantable components. (A) shows the device expanded and shows the various components. (B) Shows the device as it would be when wrapped around the eye; note the electrode array would be inserted through the eye wall (sclera). The entire implant is under the conjunctiva so it is not visible or exposed reducing the chances of infection. (C) Picture of the retina showing the electrode array places in the central retina (macula) in a subject with RP.

(Credit: Mark Humayun and Second Sight Medical Products)

The Argus II safety and efficacy data from an international study of 30 patients with a cumulative follow up of approximately 100 years was submitted to the European and US regulatory bodies, leading to approval in Europe in 2011 and FDA approval in the US in 2013. All subjects were able to perceive light during electrical stimulation and 27 out of 28 subjects (96%) performed better in localizing the object with System ON versus OFF. Seven subjects have been able to reliably score on the visual acuity scale with the System ON. The best result to date is 1.8 logMAR (equivalent to Snellen 20/1262). 70 When letter reading was tested in 30 subjects, six could identify any letter of the alphabet at a 63.5% success rate (vs. 9.5% with the system off). Some subjects were able to put the letters together into words and read sentences. 62

Conjunctival erosion remained the most common adverse event and was seen in 3 patients but in the other patients the defect was small and either self-repaired or was easily repaired with a few sutures. Details of all the adverse events as well as the benefits

from the Argus II are provided in the reference listed 71

CONCLUSIONS

Currently, the Argus II is the only approved visual prosthesis. It is approved in Europe and in the US. It is intended for patients with severe visual loss from photoreceptor loss. It does require a major operation and there are associated risks with the procedure, but the benefits were deemed to outweigh the risks by the US and European regulatory bodies, leading to its approval as a medical implant. The approval of the Argus II is a major milestone in the field of artificial vision and provides a treatment option for patients for whom there was no near-term foreseeable treatment.

The development of retinal prostheses to generate artificial vision for the blind is indeed a complex, long-term, expensive, and interdisciplinary undertaking, but it does now provide the much awaited "good news" for many blind patients.

DISCLOSURES

Mark Humayun, M.D., Ph.D. has equity in, is a patent holder for, receives royalties from, and is a consultant to Second Sight Medical Products, Inc.

REFERENCES

- Ross RD. Is perception of light useful to the blind patient? (Editorial and Comments). Arch Ophthalmol 1998; 116: 236-238.
- 2. Humayun MS, de Juan E Jr. Artificial vision. Eye. 1998; 12 (Pt 3b): 605-7.
- **3.** Bunker, C.H., et al., Prevalence of retinitis pigmentosa in Maine. American Journal of Ophthalmology., 1984. 97(3): p. 357-65.
- Curcio, C.A., N.E. Medeiros, and C.L. Millican, Photoreceptor loss in age-related macular degeneration. Investigative Ophthalmology & Visual Science., 1996. 37(7): p. 1236-49.
- **5.** del Cerro M, Gash DM, Rao GN, et al. Retinal transplants into the anterior chamber of the rat eye. Neuroscience 21: 707-23, 1987.
- 6. Foerster, O., Beitrage zur pathophysiologie der sehbahn und der spehsphare. J Psychol Neurol, 1929. 39: p. 435-463. Brindley, G., The number of information channels needed for efficient reading. J Physiol, 1965. 177: p. 44.
- 7. Brindley G, R.D., Implanted stimulators of the visual

- cortex as visual prosthetic devices. Trans Am Acad Ophthalmol Otolaryngol, 1974(78): p. 741-45.
- 8. Brindley, G.S., Sensations produced by electrical stimulation of the occipital poles of the cerebral hemispheres, and their use in constructing visual prostheses. Annals of the Royal College of Surgeons of England., 1970. 47(2): p. 106-8.
- Brindley, G.S. and W.S. Lewin, The sensations produced by electrical stimulation of the visual cortex. Journal of Physiology., 1968. 196(2): p. 479-93.
- **10.** Brindley, G.S. and W.S. Lewin, The visual sensations produced by electrical stimulation of the medial occipital cortex. Journal of Physiology., 1968. 194(2): p. 54-5P.
- **11.** Dobelle, W.H. and M.G. Mladejovsky, Phosphenes produced by electrical stimulation of human occipital cortex, and their application to the development of a prosthesis for the blind. Journal of Physiology., 1974. 243(2): p. 553-76.
- **12.** Dobelle, W.H., et al., "Braille" reading by a blind volunteer by visual cortex stimulation. Nature., 1976. 259(5539): p. 111-2.
- **13.** Dobelle, W.H., et al., Artificial vision for the blind by electrical stimulation of the visual cortex. Neurosurgery., 1979. 5(4): p. 521-7.
- **14.** Dobelle, W.H., Artificial vision for the blind by connecting a television camera to the visual cortex. ASAIO Journal., 2000. 46(1): p. 3-9.
- **15.** Pollen, D.A., Responses of single neurons to electrical stimulation of the surface of the visual cortex. Brain, Behavior & Evolution., 1977. 14(1-2): p. 67-86.
- **16.** Schmidt, E.M., et al., Feasibility of a visual prosthesis for the blind based on intracortical microstimulation of the visual cortex. Brain., 1996. 119(Pt 2): p. 507-22.
- **17.** Maynard, E.M., Visual prostheses. Annual Review of Biomedical Engineering., 2001. 3: p. 145-68.
- 18. Bak, M., et al., Visual sensations produced by intracortical microstimulation of the human occipital cortex. Medical & Biological Engineering & Computing., 1990. 28(3): p. 257-9.
- 19. Maynard, E.M., C.T. Nordhausen, and R.A. Normann, The Utah intracortical Electrode Array: a recording structure for potential brain-computer interfaces. Electroencephalography & Clinical Neurophysiology., 1997. 102(3): p. 228-39.
- **20.** Uematsu, S., et al., Electrical stimulation of the cerebral visual system in man. Confinia Neurologica., 1974. 36(2): p. 113-24.

- 21. Rousche, P.J. and R.A. Normann, Chronic intracortical microstimulation (ICMS) of cat sensory cortex using the Utah Intracortical Electrode Array. IEEE Transactions on Rehabilitation Engineering., 1999. 7(1): p. 56-68.
- **22.** McCreery, D.B., et al., A characterization of the effects on neuronal excitability due to prolonged microstimulation with chronically implanted microelectrodes. IEEE Transactions on Biomedical Engineering., 1997. 44(10): p. 931-9.
- **23.** Agnew, W.F., et al., Histopathologic evaluation of prolonged intracortical electrical stimulation. Experimental Neurology., 1986. 92(1): p. 162-85.
- **24.** Weiland, J.D. and D.J. Anderson, Chronic neural stimulation with thin-film, iridium oxide electrodes. IEEE Transactions on Biomedical Engineering., 2000. 47(7): p. 911-8.
- Normann, R.A., et al., A neural interface for a cortical vision prosthesis. Vision Research., 1999. 39(15): p. 2577-87.
- **26.** Margalit, E., et al., Retinal prosthesis for the blind. Survey of Ophthalmology., 2002. 47(4): p. 335-56.
- **27.** Veraart, C., et al., Visual sensations produced by optic nerve stimulation using an implanted self-sizing spiral cuff electrode. Brain Research., 1998. 813(1): p. 181-6.
- **28.** Naples, G.G., et al., A spiral nerve cuff electrode for peripheral nerve stimulation.[comment]. IEEE Transactions on Biomedical Engineering., 1988. 35(11): p. 905-16.
- **29.** Sweeney, J.D. and J.T. Mortimer, An asymmetric two electrode cuff for generation of unidirectionally propagated action potentials. IEEE Transactions on Biomedical Engineering., 1986, 33(6): p. 541-9.
- **30.** Ungar, I.J., J.T. Mortimer, and J.D. Sweeney, Generation of unidirectionally propagating action potentials using a monopolar electrode cuff. Annals of Biomedical Engineering., 1986. 14(5): p. 437-50.
- **31.** Buckett, J.R., et al., A flexible, portable system for neuromuscular stimulation in the paralyzed upper extremity. IEEE Transactions on Biomedical Engineering., 1988. 35(11): p. 897-904.
- **32.** Delbeke, J., M. Oozeer, and C. Veraart, Position, size and luminosity of phosphenes generated by direct optic nerve stimulation. Vision Research., 2003. 43(9): p. 1091-102.
- **33.** Cuoco, F.A., Jr. and D.M. Durand, Measurement of external pressures generated by nerve cuff electrodes. IEEE Transactions on Rehabilitation Engineering., 2000. 8(1): p. 35-41.
- 34. Branner, A. and R.A. Normann, A multielectrode

- array for intrafascicular recording and stimulation in sciatic nerve of cats. Brain Research Bulletin., 2000. 51(4): p. 293-306.
- **35.** Veraart C, Wanet-Defalque MC, Gerard B, et al. Pattern recognition with the optic nerve visual prosthesis. Artif Organs. 2003 Nov; 27(11): 996-1004.
- **36.** del Cerro, M., et al., Retinal transplants into the anterior chamber of the rat eye. Neuroscience., 1987. 21(3): p. 707-23.
- **37.** Humayun, M.S., et al., Morphometric analysis of the extramacular retina from postmortem eyes with retinitis pigmentosa. Investigative Ophthalmology & Visual Science., 1999. 40(1): p. 143-8.
- **38.** Santos, A., et al., Preservation of the inner retina in retinitis pigmentosa. A morphometric analysis. Archives of Ophthalmology., 1997. 115(4): p. 511-5.
- Stone, J.L., et al., Morphometric analysis of macular photoreceptors and ganglion cells in retinas with retinitis pigmentosa. Archives of Ophthalmology., 1992. 110(11): p. 1634-9.
- **40.** Kim, S.Y., et al., Morphometric analysis of the macula in eyes with geographic atrophy due to agerelated macular degeneration. Retina., 2002. 22(4): p. 464-70.
- **41.** Kim, S.Y., et al., Morphometric analysis of the macula in eyes with disciform age-related macular degeneration. Retina., 2002. 22(4): p. 471-7.
- **42.** Marc RE. (2003). Neural remodeling in retinal degeneration. *Prog Retin Eye Res* 22, 607.
- **43.** Varela C, Igartua I, De La Rosa EJ & De La Villa P. (2003). Functional modifications in rod bipolar cells in a mouse model of retinitis pigmentosa. *Vision Res* 43, 879-885.
- **44.** Rizzo JF 3rd, Wyatt J, Loewenstein J, et al. Methods and perceptual thresholds for short-term electrical stimulation of human retina with microelectrode arrays. Invest Ophthalmol Vis Sci. 2003 Dec; 44(12): 5355-61.
- **45.** Rizzo JF 3rd, Wyatt J, Loewenstein J, et al. Perceptual efficacy of electrical stimulation of human retina with a microelectrode array during short-term surgical trials. Invest Ophthalmol Vis Sci. 2003 Dec; 44(12): 5362-9.
- **46.** Zrenner et al. Subretinal electronic chips allow blind patients to read letters and combine them to words. *Proc. R. Soc. B* published online 3 November 2010
- **47.** Zrenner et al. Details on the Technology of the Subretinal Implant, Clinical Study Design, Results and Spontaneous Reports of Patients including nine Movie Clips on performance. Electronic

- Supplementary Material to the publication of E. Zrenner et al.: Subretinal electronic chips allow blind patients to read letters and combine them to words. Proc.R.Soc.B (2010) at URL: http://rspb.royalsocietypublishing.org/lookup/doi/10.1098/rspb.2010.1747
- **48.** 92-Kusnyerik, A. et al. 2008 Preoperative 3D Planning of Implantation of a subretinal Prosthesis Using MRI Data. *Invest Ophthalmol Vis Sci* 49:E-Abstract 3025
- **49.** Besch D. Extraocular surgery for implantation of an active subretinal visual prosthesis with external connections: feasibility and outcome in seven patients. Br J Ophthalmol. 2008 Oct;92(10):1361-1368
- **50.** Zrenner E. Subretinal electronic chips allow blind patients to read letters and combine them to words. Proc Biol Sci. 2011 May;278(1711):1489-1497
- 51. Zrenner et al., Improvement of visual orientation and daily skills mediated by subretinal electronic implant alpha IMS in previously blind RP patients, ARVO Meeting 2011 457/D1104
- 52. Shire, Douglas B. et al. "In vivo operation of the Boston 15-channel wireless sub retinal visual prosthesis." Human Vision and Electronic Imaging XV. Ed. Bernice E. Rogowitz & Thrasyvoulos N. Pappas. San Jose, California, USA: SPIE, 2010. 752705-8. http://dx.doi.org/10.1117/12.846745 ©2010 SPIE
- 53. Ciavatta VT et al. Retinal expression of Fgf2 in RCS rats with subretinal microphotodiode array. MTInvest Ophthalmol Vis Sci. 2009 Oct;50(10):4523-4530
- **54.** Palanker D, Vankov A, Huie P and Baccus S. Design of a high-resolution optoelectronic retinal prosthesis. J Neural Eng. 2005;2:105-120
- **55.** John S. Pollack. Evaluation of the Artificial Silicon Retina™ Device for the Treatment of Vision Loss from Retinitis Pigmentosa. ASRS presentation 2006
- 56. A.Y. Chow. Long-Term Neurotrophic Rescue of Visual Acuity in Artificial Silicon Retina Chip Implanted Retinitis Pigmentosa Patients. Invest. Ophthalmol. Vis. Sci. 2010; 51: E-Abstract 2021
- **57.** Peyman, G., et al., Subretinal semiconductor microphotodiode array. Ophthalmic Surgery & Lasers., 1998. 29(3): p. 234-41
- **58.** Chow AY, P.G., Pollack JS, et al, Safety, feasibility and efficacy of subretinal artificial silicon retina prosthesis for the treatment of patients with retinitis pigmentosa [abstract]. Invest Ophthalmol Vis Sci,

- 2002. 43(E-abstract 2849)
- 59. Chow AY et al. Subretinal implantation of semiconductor-based photodiodes: durability of novel implant designs. J Rehabil Res Dev. 2002 May-Jun;39(3):313-21
- **60.** Schwahn HN et al. Studies on the feasibility of a subretinal visual prosthesis: data from Yucatan micropig and rabbit. Graefes Arch Clin Exp Ophthalmol. 2001 Dec;239(12):961-7
- **61.** Humayun MS. Interim Performance Results from the Second Sight® Argus[™] II Retinal Prosthesis Study. Arvo Abstract 2594, 2011
- **62.** Richard G. Long-Term Stability of Stimulation Thresholds Obtained From a Human Patient With a Prototype of an Epiretinal Retina Prosthesis Invest Ophthalmol Vis Sci E-Abstract 4580 2009
- **63.** Richard G. Chronic epiretinal chip implant in blind patients with retinitis pigmentosa: long-term clinical results *Invest. Ophthalmol. Vis. Sci.* 48 2007 E-Abstract 666
- 64. Roessler et al.Implantation and Explantation of a Wireless Epiretinal Retina Implant Device: Observations during the EPIRET3 Prospective Clinical Trial. Investigative Ophthalmology & Visual Science, June 2009, Vol. 50, No. 6
- **65.** Klauke S. Stimulation with a wireless intraocular epiretinal implant elicits visual percepts in blind humans. Invest Ophthalmol Vis Sci. 2011 Jan;52(1):449-455
- 66. Roessler G. Implantation and explantation of a wireless epiretinal retina implant device: observations during the EPIRET3 prospective clinical trial. Invest Ophthalmol Vis Sci. 2009 Jun;50(6):3003-3008
- **67.** Tusa et al.The retinotopic organization of area 17 (striate cortex) in the cat. The Journal of Comparative Neurology Volume 177, Issue 2, pages 213–235, 15 January 1978
- **68.** Ahuja AK et al. Blind subjects implanted with the Argus II retinal prosthesis are able to improve performance in a spatial-motor task. Br J Ophth. 2011 Apr;95(4):539-543
- **69.** Humayun, M. S and Argus II Study Group. Interim performance results from the second sight(R) ArgusTM II retinal prosthesis study. 2010 *Invest. Ophthalmol. Vis. Sci.* 51, 2022. [ARVO e-abstract]
- 70. da Cruz, L. and Argus II Study Group. (2010). Patients blinded by outer retinal dystrophies are able to identify letters using the ArgusTM II retinal prosthesis system. *Invest. Ophthalmol. Vis. Sci.* 51, 2023. [ARVO e-abstract]

71. Humayun MS. Oral presentation, American Society

of Retina Specialists, 2009.