ARTIFICIAL VISION:
CREATING VISUAL FUNCTION

P. E. Stanga
Consultant Ophthalmologist and Vitreoretinal Surgeon
Professor of Ophthalmology and Retinal Regeneration
Director, Manchester Vision Regeneration (MVR) Lab

Manchester Royal Eye Hospital, NIHR/Wellcome Trust Manchester CRF & University of Manchester
• Allergan Plc.
• Bausch & Lomb Inc.
  • Bayer AG
  • ExcelLens Inc.
  • Novartis AG
  • Optos Plc.
• Second Sight Medical Products, Inc.
  • Thrombogenics Inc.
  • Topcon Corp.
What do we mean by Artificial Vision?

- Artificial Vision is Visual Function acquired by means of an epi or sub retinal microelectronic device.

- Arrays of electrodes and amplifiers convert light into signals that stimulate bipolar cells to elicit an “electrical activity” that is interpreted as vision.
What is the Need of an Artificial Vision Prosthesis?
Retinal Diseases Affect Different Layers
Retinal Diseases Affect Different Layers

Outer Retinal & RPE Diseases
What regions of the Visual Pathway can we stimulate?

- Ocular Prosthesis
- Optic Nerve Prosthesis
- Cortical Prosthesis
Dobelle Institute Cortical Prosthesis Patient
Why the Epiretinal approach?

[…] It is doubtful whether, after replacement of photoreceptors with a subretinal implant, the signals will reach the ganglion cells following the normal pathway, since a photoreceptor degeneration also causes a degeneration of the inner retinal layers.

Therefore, some research groups prefer a direct stimulation of ganglion cells by epiretinally localized stimulator electrodes.

From a surgical point of view, “standard” methods of vitreoretinal surgery can be utilized to a certain extent, and, compared to subretinal implantation, no retinal detachment has to be performed.
Argus™ II Epiretinal Prosthesis

- Equivalent to visual field of 20°
- Each electrode individually programmable
- Provides significant user control over image processing
- Upgradable hardware and software

System used outside the clinic by every subject
Argus™ II Epiretinal Prosthesis
# Second Sight Argus II Study Group

<table>
<thead>
<tr>
<th>Site</th>
<th>Investigators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moorfields Eye Hospital (London, UK)</td>
<td>Lyndon da Cruz(^F), Andrew Webster(^F)</td>
</tr>
<tr>
<td>Johns Hopkins Hospital (Baltimore, MD)</td>
<td>Gislin Dagnelie(^F), James Handa(^F)</td>
</tr>
<tr>
<td>Quinze-Vingts (Paris, France)</td>
<td>José-Alain Sahel(^F), Saddek Mohand-Said(^F), Pierre-Olivier Barale(^F), Sarah Scheer(^F)</td>
</tr>
<tr>
<td>Manchester Royal Eye Hospital (Manchester, UK)</td>
<td>Paulo Stanga(^F), Susmito Biswas(^F)</td>
</tr>
<tr>
<td>Puerto de Hierro (Guadalajara, Mexico)</td>
<td>Arturo Santos(^F), Enrique Roig(^F)</td>
</tr>
<tr>
<td>Doheny Eye Institute (Los Angeles, CA)</td>
<td>Amani Fawzi(^F), Dean Eliott(^F), Mark Humayun(^F)(^IPC), Rajat Agrawal(^F)(^C)</td>
</tr>
<tr>
<td>UC San Francisco (San Francisco, CA)</td>
<td>Jacque Duncan(^F), Eugene de Juan(^F)(^IPC)</td>
</tr>
<tr>
<td>Retina Foundation of the Southwest (Dallas, TX)</td>
<td>David Birch(^F), Eugene Filley(^F), Rand Spencer(^F)</td>
</tr>
<tr>
<td>Hôpitaux Universitaires de Genève (Geneva, Switzerland)</td>
<td>Farhad Hafezi(^F), Joel Salzmann(^F), Marco Pelizzone(^F), Jorg Sommerhalder(^F), Angelica Perez-Fornos(^F)</td>
</tr>
<tr>
<td>Scheie Eye Institute (Philadelphia, PA)</td>
<td>Artur Cideciyan(^F), Samuel Jacobson(^F)</td>
</tr>
<tr>
<td>Wills Eye Hospital (Philadelphia, PA)</td>
<td>Gary Brown(^F), Allen Ho(^F), Carl Regillo(^F), Julia Haller(^F)</td>
</tr>
<tr>
<td>Columbia University (New York, NY)</td>
<td>Lucian del Priore(^F)</td>
</tr>
<tr>
<td>Lighthouse International (New York, NY)</td>
<td>Aries Arditi(^F)</td>
</tr>
</tbody>
</table>

Funding/Support: National Institutes of Health Grant EY12893 and Second Sight Medical Products, Inc.
Intended Patient Population

- Patients with **severe to profound outer retinal degeneration (Retinitis Pigmentosa)**
  - Rare group of diseases which causes slow death of photoreceptors in retina
  - Disease results in irreversible blindness
  - Currently, no other proven treatments are available for this population of patients
6 Month Results published in April 2012 Ophthalmology

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Clinical Trial: www.clinicaltrials.gov NCT00407602

NIH Grant: EY012893

Contact: Prof. P. E. Stanga
Professor of Ophthalmology & Retinal Regeneration
Consultant Ophthalmologist & Vitreoretinal Surgeon
Director, Manchester Vision Regeneration (MVR) Lab

p.stanga@retinaspecialist.co.uk

Study Design

Argus II Update – Clinical Trial

• Prospective, single-arm, non-randomized trial
• Multi-center
• 5-year follow-up per subject (optional extension to 10 years)

• Indicated population: Subjects with severe to profound outer retinal degeneration (i.e., remaining visual acuity worse than 2.3 logMAR in both eyes)

http://clinicaltrials.gov/show/NCT00407602
### Demographics and Implant Surgery

<table>
<thead>
<tr>
<th>Subject</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects (n)</td>
<td>30</td>
</tr>
<tr>
<td>Age at Time of Implant (years)</td>
<td>58 ± 10 (range 28 – 77)</td>
</tr>
<tr>
<td>Females : Males</td>
<td>9 : 21</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
</tr>
<tr>
<td>Retinitis pigmentosa</td>
<td>97% (n=29)</td>
</tr>
<tr>
<td>Choroideremia</td>
<td>3% (n=1)</td>
</tr>
<tr>
<td>Baseline Vision</td>
<td></td>
</tr>
<tr>
<td>Bare light perception*</td>
<td>97% (n=29)</td>
</tr>
<tr>
<td>No light perception</td>
<td>3% (n=1)</td>
</tr>
<tr>
<td>Median Surgery Time (hours)</td>
<td>4:04 (range 1:53 – 8:32)</td>
</tr>
</tbody>
</table>

* Defined as vision worse than 2.9 logMAR and the ability to detect a photographic flash
Surgical Technique

RETINAL CHIP

P STANGA

Manchester Royal Eye Hospital
# Implant Duration & Long-Term Reliability

Data as of March 19, 2014

<table>
<thead>
<tr>
<th>Subjects (n)</th>
<th>30</th>
</tr>
</thead>
<tbody>
<tr>
<td># Years Implanted (Avg.)</td>
<td>5.4 (range 1.2– 6.8)</td>
</tr>
<tr>
<td>Cumulative Implant Time</td>
<td>161 subject-years</td>
</tr>
</tbody>
</table>

| # Subjects with device explant | 3                           |
| # Subjects with device failure | 2                           |
| Range of implant functionality to date (not including explants) | 3.9 – 6.8+ years |
# Device- or Surgery-Related Serious Adverse Events

<table>
<thead>
<tr>
<th>Complication</th>
<th>Scleral Fixated IOL</th>
<th>PPV RD</th>
<th>Retinal Tack</th>
<th>Glaucoma Drainage Devices</th>
<th>Argus II Subjects (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjunctival Erosion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5%&lt;sup&gt;a&lt;/sup&gt; 16%&lt;sup&gt;b&lt;/sup&gt; 10.0%</td>
</tr>
<tr>
<td>Endophthalmitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1%&lt;sup&gt;a&lt;/sup&gt; 5%&lt;sup&gt;c&lt;/sup&gt; 10.0%</td>
</tr>
<tr>
<td>Hypotony</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10%&lt;sup&gt;a&lt;/sup&gt; 10.0%</td>
</tr>
<tr>
<td>Iatrogenic Retinal Tear/Detachment</td>
<td>8.5%&lt;sup&gt;d&lt;/sup&gt; 9.5%&lt;sup&gt;e&lt;/sup&gt;</td>
<td>17.6%&lt;sup&gt;f&lt;/sup&gt; 17.8%&lt;sup&gt;g&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>10.0%</td>
</tr>
<tr>
<td>Wound Dehiscence</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11%&lt;sup&gt;a&lt;/sup&gt; 10.0%</td>
</tr>
<tr>
<td>Dislodged Tack</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>5.3%&lt;sup&gt;h&lt;/sup&gt; 6.7%</td>
</tr>
</tbody>
</table>

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Key Question: What can be achieved by the patient?
Benefit

Visual Function

- Object Localization
- Motion Discrimination
- Visual Acuity Testing
- Letter Reading

Functional Vision and Quality of Life

- Orientation and Mobility
- Functional Low Vision Observer-Rated Assessment (FLORA)
Visual Function Benefit

- **Mean Accuracy (pixels)**
  - System OFF
  - System ON

- **Mean Response Error (degrees)**
  - System OFF
  - System ON

- **Percent of subjects with acuity < 2.9 logMAR**
  - Baseline
  - 1 Year
  - 2 Years
  - 3 Years
  - 4 Years
  - 5 Years

- **Average Success Rate**
  - System OFF
  - System ON

**Course is 20’ x 10’**
Orientation & Mobility Tasks: “in real life” and requiring accuracy...
Orientation & Mobility Tasks: “in real life”
Initial Word Recognition Results With the Argus™ II Retinal Prosthesis

P.E. Stanga¹, B. Coley², F. Merlini², S. Biswas¹, G. Turner¹, R. Greenberg²

¹Retinal Dept., Manchester Royal Eye Hospital and University of Manchester, Manchester, United Kingdom; ²Second Sight Medical Products Inc., Sylmar, California, USA

Background:
The feasibility of using a retinal prosthesis to restore partial sight to people blinded by outer retinal degenerative diseases is currently being investigated. Diseases such as Retinitis Pigmentosa (RP) destroy photoreceptors but leave a significant percentage of inner-retinal cells (ganglion and bipolar cells) intact and functional. Direct electrical stimulation of inner-retinal cells via an implanted array of electrodes may provide rudimentary vision.

The Argus™ II retinal prosthesis system consists of:
- An array of 60 independently-controlled electrodes implanted apically to an intimate coil to wirelessly relay data and power to extra-cocular driver circuitry.
- An external video processing unit (VPW)
- A miniature video camera mounted on a pair of glasses

1. Camera: acquires a video signal in real-time
2. VPW: digitizes images, applies image-processing filters, and down-samples the resolution to a 6 x 10 grid

The 60 pixel image is mapped to stimulation amplitudes on the corresponding electrodes using look-up tables that have been customized for each subject.

The electronics are sutured epiperiorally and then after a vitrectomy surgery the electrode array is inserted through the pars plana and tacked to the retina in the macular region.

Conceptual view of external and internal ocular sections (Argus II)

Argus II epipillary prosthesis "tacked" onto right macula

Close-up of Argus II glaucoma with epipillary camera (solid white arrow) and optic-frequency board & telemetry cells (fellow white arrow)

Purpose:
We present the results of the first subject who could achieve short word recognition out of a total of 32 subjects participating in the International Argus II Retinal Prosthesis Trial (Second Sight Medical Products Inc, Sylmar, CA, USA).

Methods:
Subjects were blind with bare light perception due to retinitis pigmentosa and were tested as follows using a computer monitor. Two, three, and four letter words were displayed in 477, 379 and 301 point Century Gothic font in white letters on a computer screen on a black background using PowerPoint, viewed 12" away. An open set of words were used and were displayed in a random order. Subjects were asked to recognize high contrast short words by identifying each letter at a time, and then say which word these spelled. (See Appendix)

Results:
Subject 52-001 was the first subject to undergo word recognition testing in the trial. Within minutes of commencing the test, he could identify at least three of the five words. We observed a significant difference between the device off, the device on scrambled VCF and the device on home use VCF. There was no impact of the residual vision. (See Table showing First Session Results).

Conclusions:
This subject, implanted with the Argus II device, has demonstrated the feasibility of identifying high contrast letters and mentally constructing short words. The subject's performance is significantly better with the device on home use VCF compared to the device off and the device on scrambled VCF. Since the subject did not know in advance which words would be presented, we believe he achieved the word recognition task. Further subjects will be tested in the near future.
Letter Identification Test: What the patient sees...
MVR Lab Reading Test: the next frontier...
Orientation & Mobility Tasks: “most important skill for a hospital patient...”
<table>
<thead>
<tr>
<th>Task Description</th>
<th>Argus II System ON</th>
<th>Argus II System OFF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects performing the task</td>
<td>Subjects performing the task</td>
<td></td>
</tr>
<tr>
<td>Independently cross of residential streets following a crosswalk</td>
<td>19</td>
<td>18</td>
</tr>
<tr>
<td>Avoid obstacles while walking</td>
<td>25</td>
<td>24</td>
</tr>
<tr>
<td>Estimate the size of an obstacle</td>
<td>24</td>
<td>22</td>
</tr>
<tr>
<td>Avoid low-hanging branches, plants, head-high shelves, etc.</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Detect curbs</td>
<td>23</td>
<td>21</td>
</tr>
<tr>
<td>Visually locate a place setting on a dining table</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>Sort light from dark laundry</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td>Travel within home independently</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>Identify ordinary objects at various distances</td>
<td>24</td>
<td>23</td>
</tr>
</tbody>
</table>

Percent Possible: 57.9% for Argus II System ON; 22.2% for Argus II System OFF; 72.0% for Argus II System ON; 29.2% for Argus II System OFF; 58.3% for Argus II System ON; 4.5% for Argus II System OFF; 53.3% for Argus II System ON; 6.7% for Argus II System OFF; 82.6% for Argus II System ON; 19.0% for Argus II System OFF; 83.3% for Argus II System ON; 4.2% for Argus II System OFF; 77.8% for Argus II System ON; 5.9% for Argus II System OFF; 92.3% for Argus II System ON; 88.5% for Argus II System OFF; 70.8% for Argus II System ON; 21.7% for Argus II System OFF.
FLORA Results 12M

n=26 subjects*

<table>
<thead>
<tr>
<th>Large Positive effect</th>
<th>Mild positive effect</th>
<th>Prior positive effect</th>
<th>Neutral effect</th>
<th>Negative effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>9 (35%)</td>
<td>7 (27%)</td>
<td>4 (15%)</td>
<td>6 (23%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

Positive Effect

20 (77%)

No positive effect

6 (23%)

*4 subjects did not participate in the FLORA.

Functional Low-Vision Observer-Rated Assessment (FLORA) n=23

Between Y1 and Y3:
- 4/10 improved
- 5/10 same
- 1/10 declined
Is it possible to achieve Artificial “Colour” Vision?

(ARVO 2011 & 2012)
Purpose

To test if subjects blinded by outer retinal dystrophies can consistently perceive different coloured phosphenes at the same time with the **Argus II Retinal Prosthesis System**.

Previous colour work:

Stanga et al. Subjects blinded by outer retinal dystrophies are able to perceive color using the Argus II Retinal Prosthesis System. ARVO Poster 2011
Methods & Results

- **Four blind subjects**

- Different pairs of electrodes were directly and simultaneously stimulated with trains of cathodic-anodic pulses at different frequencies and intensities:
  - Direct stimulation
  - Frequencies (F) = 5, 20, 60 and 120 Hz
  - Duration: 1s
  - Intensities (I)
  - Pulse Width (PW) = 0.45ms
  - Inter-Phase gap = 0ms

- Subjects reported the colour(s) they perceived after each stimulation

- **Seven different colour combinations** were perceived by the combined subjects, though not all subjects saw all colors

- One subject (of the four) only saw white phosphenes
Conclusion

• Were able to perceive simultaneous colors with electrical stimulation
• First time have been shown to see two colours at once
• These data, as well as data from planned future studies, could someday lead to use of colour in visual prostheses
Benefits of the Argus II System

Self-Reported Daily Use of Argus II

<table>
<thead>
<tr>
<th>Locating or Identifying Objects</th>
<th>Orientation and Mobility</th>
<th>Detecting Light</th>
<th>Household Tasks</th>
<th>Reading</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Can find utensils on a table, coffee pot</td>
<td>• Can find doors, windows, elevators; avoid hitting doorframes</td>
<td>• Can detect lights on a Christmas tree and fireworks</td>
<td>• Can sort out dark and light coloured laundry</td>
<td>• Can identify credit card size letters</td>
</tr>
<tr>
<td>• Can locate parked and moving cars</td>
<td>• Can localize position of someone’s head while talking to them</td>
<td>• Can locate a full or quarter moon.</td>
<td>• Can detect when people come up to desk at work</td>
<td>• Can read magazine headlines</td>
</tr>
<tr>
<td>• Can locate bus stop poles and flag poles</td>
<td>• Can get around new places especially if lighting is correct</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Can follow a cross-walk across a street</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The Argus II System can improve the patient’s orientation and mobility, activities of daily living and well-being.
Conclusions

• The clinical trial demonstrated that Argus II can reliably withstand long-term implant (> 5 years) in a significant number of subjects (160+ subject-years) with an acceptable safety profile.

• Using the system, blind subjects showed improved performance on visual tasks, and results have been sustained for over 5 years.

• Subjects report using Argus II in their daily lives and the System has a positive impact on their well-being.

What should be next: after detection of motion & direction, letter identification, reading words and colour vision?
Face Detection using the Argus® II Retinal Prosthesis System (ARVO 2013)

P. E. Stanga
Professor of Ophthalmology & Retinal Regeneration
Consultant Ophthalmologist & Vitreoretinal Surgeon
Director, Manchester Vision Regeneration (MVR) Lab

Manchester Royal Eye Hospital and University of Manchester, United Kingdom

p.stanga@retinaspecialist.co.uk

Sahel JA (F), Mohand-Said S (F), da Cruz L (F), Caspi A (E), Merlini F (E), Greenberg R (E, I, P)
1UMR-S 968, Institut de la Vision, Paris, France; 2Retinal Dept., Moorfields Eye Hospital, London, United Kingdom; 3Second Sight Medical Products , Sylmar, California, USA
Can we detect faces with a retinal prosthesis?

Face Recognition and Detection of Facial Expression are important components of effective interpersonal communication.

However, Face Detection/Localisation is first necessary to achieve this.
Many Argus II users have difficulty distinguishing faces from other similarly sized and shaped objects. Yet face detection is often socially important to them.

The solution: use external video processing to detect a face and stimulate only where it appears.
Experiment 1

Patients implanted with the Argus II retinal prosthesis searched for human a face at a distance of 2 meters.
In normal mode with the face detection filter on, the Argus II samples a portion of the image that matches the field-of-view of the array (yellow rectangle). This creates a one-to-one relationship between the real world and the retinal representation. However, only the image of the face within the array field of view is used for stimulation.
Results – Experiment 1

Faces were detected and localized in 100% of the trials.

Response Time in each condition was:

<table>
<thead>
<tr>
<th>Patient ID</th>
<th>Wide FOV (53 deg)</th>
<th>Normal FOV (20 deg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>38 ± 4</td>
<td>53 ± 12</td>
</tr>
<tr>
<td>2</td>
<td>20 ± 2</td>
<td>42 ± 5</td>
</tr>
<tr>
<td>3</td>
<td>5 ± 1</td>
<td>11 ± 3</td>
</tr>
<tr>
<td>4</td>
<td>12 ± 2</td>
<td>22 ± 4</td>
</tr>
</tbody>
</table>

The times are given in seconds ± SE

10 trials for each subject in each condition (after 10 practice trials)

**Conclusion:** face localization is feasible. Using a wide field of view, detection times were reduced by 1.4 – 2.2x
Results – experiment 2

Subjects detected loss of eye contact on 100% of trials

<table>
<thead>
<tr>
<th></th>
<th>Subject 1</th>
<th>Subject 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Response Time</td>
<td>5.2</td>
<td>6.4</td>
</tr>
<tr>
<td>Standard Error</td>
<td>0.9</td>
<td>0.7</td>
</tr>
</tbody>
</table>
Conclusions

Image processing algorithms enable patients to perform daily tasks that are not limited by the resolution or the sensitivity of the array.

Using external image processing, face detection can be as easy as light localization for Argus II System users.
Subject comments

The psychological and social aspect concerning the interaction with others

The interest in this tool for the blind population whose careers require customer contact
What’s next at MREH/MVR Lab (2014-16):

Manchester Argus II Trial in GA-AMD  
MREH only site

Two (2)  
Retinitis Pigmentosa patients
With thanks to:

Manchester Vision Regeneration (MVR) Lab at NIHR/Wellcome Trust CRF

**Director**
- Prof Paulo Stanga

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- Danielle Ridyard

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- Dr Salvador Pastor Idoate
- Dr Claudia Quijano

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- Iain McLean
- Kate Barugh
- Fiona Crawford
- Iain Venables

**MREH Consultants**
- Mr Susmito Biswas
- Mr George Turner
- Mr Steve Charles
- Prof Paul Bishop
- Prof Graeme Black
- Prof David Henson

paulo.stanga@cmft.nhs.uk
danielle.ridyard@cmft.nhs.uk
Steve Austin's **bionic left eye:**

- 20.2:1 zoom lens
- normal vision
- infrared filter for night vision
- targeting device for his throwing arm
Testimonial from an MREH patient

Subject 52-00x