RESTORATION OF SIGHT: ARGUS II RETINAL PROSTHESIS

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Foundation Fighting Blindness Vision Walk Organizing Reception
January 6, 2014
Foundation Fighting Blindness

- Established in 1971 by a group of families devoted to raising money to cure blinding retinal degenerative diseases.
- The FFB has raised over $500 million
- FFB funded research has identified over 200 disease causing genes.
- FFB Funded treatments include the Argus II Retinal Prosthesis and genetic therapies
Foundation Fighting Blindness

- The FFB continues to fund ongoing and new research:
  - $14 million in grants to over 100 projects – from the basic research to clinical trials
- Even 10 years ago, there was no treatment for blinding retinal degenerative diseases.
  - Today, some patients are candidates for vision restoring therapies...and more are developed every year
- The FFB funds diverse research to this end.
Argus II Retinal Prosthesis

- What is the Argus II?
- Advances leading up to development of the Argus II
- Overview of visual anatomy
- How the Argus II works
- FDA approval
- Who is eligible for the Argus II?
- Where can I get the Argus II?
What is the Argus II

- The “Bionic Eye” (2.0)
- A prosthesis that stimulates the retina when eye’s light-sensing cells no longer work.
- The first FDA approved retinal prosthesis
- A camera reacts to light and sends a signal to an array of 60 electrodes surgically implanted on the retina.
- More on this later…
Eyeglasses with camera

Video processing unit

Electrode array

Electronics

Wireless receiver

http://www.ianfyfe.co.uk/wordpress/wp-content/uploads/2011/06/Argus-II-system.jpg
http://wordlesstech.com/2013/02/17/first-bionic-eye-receives-fda-approval/
History of the Argus II

- 1929: Electrical stimulation of the vision centers in the brain causes blind patients to see flashes of light (phosphenes).
- 1968: Brindley and Lewin implant an 80 electrode array in the visual cortex of a blind patient and produce phosphenes.
- 1970: Potts and Inoue demonstrate electrical stimulation of retinal neurons via a contact lens.

Brindley 1968; Potts 1968; Potts 1970; Ryan 2013.
History of the Argus II

- 1996: Mark Humayun produces phosphenes in blind patients by direct retina stimulation
- 2002: Clinical trial for the Argus I – 16 channel wired stimulator.
  - 6 RP patients at one center
- 2009: Clinical trial for the Argus II – 60 channel wireless stimulator
  - 30 patients at 10 centers
- 2011: Argus II approved for use in Europe
- 2013: Argus II receives FDA approval

Humayun 1996.
How does the Argus II work?

- Anatomy of the visual system
- Approaches to artificial vision
- Anatomy of the Argus II
- The Argus-Eye interface
- Results of clinical trials
Anatomy of the Eye

http://healthcare.utah.edu/moran/patient_care/refractive_surgery_lasik/how_the_eye_works.php
The Normal Retina

Yannuzzi 2010
The Normal Macula

Yannuzzi 2010
The Normal Macula

Yannuzzi 2010
The Normal Macula

Spaide 2011
Approaches to Artificial Vision

EPIRETINAL

SUBRETINAL

Spaide 2011
Approaches to Artificial Vision

Optic Nerve

Cortex

http://www.mattsms.com/2013/04/optic-nueritis-blurry-vision-or-loss-of.html
Why a Retinal Prosthesis?

- Best for spatial discrimination
  - Optic nerve is too small (2 mm in diameter)
  - Visual Cortex is too specialized
- Vitreous acts as a heat sink – safer
  - Optic nerve requires closely packed electrodes – increasing risk of thermal damage
- Safer Surgery
  - Optic nerve and cortical approaches both enter the central nervous system – increased risk of infection or brain trauma.
- Cortical and optic nerve prosthetics are also in development but have not been as successful as the Argus retinal implant.
## Epiretinal v. Subretinal

### Epiretinal (Argus II)
- Vitreous acts as heat sink
- Further from bipolar cells – requires more current
- Requires tack fixation
- Space for implantation
- Entire procedure visualized
- Safer surgery?

### Subretinal
- Heat may damage retina
- Closer to bipolar cells – less current
- No mechanical fixation
- Limited subretinal space
- Procedure done blind
- Risk of subretinal hemorrhage
Anatomy of the Argus II

Anatomy of the Argus II

How the Argus II Works

- Video camera captures the visual field
- Video Processing Unit (VPU) digitizes the image into a gray-scale 60 pixel grid (10x6)
- Signal is wirelessly transmitted to the receiver on the implant
- Receiver sends an electrical pulse to the electrode array corresponding to the digitized signal from the VPU.
- Electrical current activates retinal neurons.
The Argus-Eye Interface

http://officialandreascy.blogspot.com/2013/02/fda-approves-argus-ii-first-bionic-eye.html
Argus II Clinical Trial

- 10 center, single-arm, prospective, feasibility study
- International sites: US, Mexico, UK, France, Switzerland
- 30 patients with RP, LCA, or choroideremia
- Outcomes: Safety and utility of the implant

Humayun 2012.
Argus II Clinical Trial

- Inclusion Criteria:
  - Retinitis Pigmentosa (or outer retinal degeneration in EU)
  - Bare LP or NLP vision with confirmed inner retina function
    - Full-field flash or Electrical evoked responses
  - Confirmed history of useful form vision
  - Age 25 or older. (18 or older in EU)
  - Willing and able to receive follow-up and training
  - Lives within two hours of the clinical center

Humayun 2012.
Argus II Clinical Trials

- **Exclusion Criteria**
  - Ocular diseases damaging the inner retina
    - CRAO, Advanced DM, Optic nerve disease, etc.
  - Conditions affecting visualization of the retina
  - Conditions that predispose to eye rubbing
  - Axial length <21.5 mm or >26.0 mm
  - Inability to understand the experiment or consent
  - Cannot undergo general anesthesia; or tolerate peri-op meds.
  - Pregnancy
  - Another implantable device (cochlear implant)

Humayun 2012.
Argus II Clinical Trials

- Mean age: 57 years old (27-77)
- 70% Male
- 28 Retinitis pigmentosa, 1 Leber congenital amaurosis, 1 choroideremia
- Follow-up 6 months – 2.7 years

- Visual acuity testing:
  - Square localization – white square on black background
  - Direction of motion – follow path of a white bar moving across a screen
  - Grating Visual Acuity - differentiate the orientation of white and black bars on a black screen
  - Door test – locate a door in a large room
  - Line test – follow a white line across the unpainted floor.

Humayun 2012.
Argus Clinical Trials

- 20 patients had no serious adverse events.

<table>
<thead>
<tr>
<th>Serious Adverse Events</th>
<th>All Subjects (n = 30)</th>
<th>Last 15 subjects enrolled in study (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td># Subjects with Event</td>
<td>95% Confidence Interval</td>
</tr>
<tr>
<td>Conjunctival dehiscence</td>
<td>3</td>
<td>2.1 – 26.5%</td>
</tr>
<tr>
<td>Conjunctival erosion</td>
<td>2</td>
<td>0.8 – 22.1%</td>
</tr>
<tr>
<td>Presumed Endophthalmitis</td>
<td>3</td>
<td>2.1 – 26.5%</td>
</tr>
<tr>
<td>Hypotony</td>
<td>3</td>
<td>2.1 – 26.5%</td>
</tr>
<tr>
<td>Re-tack</td>
<td>2</td>
<td>0.8 – 22.1%</td>
</tr>
<tr>
<td>Retinal detachment - rhegmatogenous</td>
<td>1</td>
<td>0.1 – 17.2%</td>
</tr>
<tr>
<td>Retinal Detachment - tractional</td>
<td>1</td>
<td>0.1 – 17.2%</td>
</tr>
<tr>
<td>Retinal Tear</td>
<td>1</td>
<td>0.1 – 17.2%</td>
</tr>
<tr>
<td>Uveitis – inflammatory</td>
<td>1</td>
<td>0.1 – 17.2%</td>
</tr>
</tbody>
</table>

Humayun 2012.
Square Localization Test

Humayun 2012.
Direction of Motion

Humayun 2012.
Find the Door Test

Humayun 2012.
Follow the Line Test

Humayun 2012.
Argus II Clinical Trial

- Adverse reactions were similar to other ocular surgeries – compared directly to glaucoma implants
- Adverse reactions improved over the course of the study – no cases of endophthalmitis in the second 15 patients.
- Visual acuity improved in all patients.
- Obtained European Commission (CE) marking based on these results in 2011.

Humayun 2012.
Argus II Long-Term Outcomes

- 2013 study with mean duration 19.9 (8.6-34.2) months after implantation
- 21 enrolled in the study
  - of the original 30, 2 excluded due to Corneal ulcer, retinal detachment
- Patients were trained to read letters and short words.
- White letters on dark background in a dark room.
- Letters were progressively decreased in size and were smaller in longer words.

da Cruz 2013.
Training and Tests

- **Training**: Subjects shown each letter once and told what it is.
- **Test 1**: subjects asked to identify each letter of the alphabet in random order
  - Group A: Horizontal and vertical lines only (H, I)
  - Group B: Oblique lines the full height of the letter or variations on a circle (A, W, C, D)
  - Group C: Oblique lines for part of the letter (K, R)

da Cruz 2013.
Training and Tests

- **Test 2: Letter size reduction**
  - Only subjects that got 50% of each group in Test 1
  - 5 random letters of the same size, 60 s time limit.
  - Test ended when all 5 were wrong

- **Test 3: Word recognition**
  - 4 subjects that got 10 letters in Test 2
  - 2, 3, and 4 letter words shown to subjects based on frequency tables
  - Time limit 60 s per number of letters.

- **Two controls:** system off and letters scrambled

 da Cruz 2013.
Results: Test 1

da Cruz 2013.
Results: Test 2

- 6 subjects; each sat 30 cm from the screen.
- Minimal Letter Size: 4.8 (0.9 – 18) cm
  - Smallest letter read
- Optimal Letter Size: 10.5 (2.3-22.6) cm
  - Letter size of the smallest line

da Cruz 2013.
### Table 2: Word reading outcome table

<table>
<thead>
<tr>
<th>Subject</th>
<th>System off Unpatched</th>
<th>System on scrambled mode Unpatched</th>
<th>System on standard mode Unpatched</th>
</tr>
</thead>
<tbody>
<tr>
<td>51-009</td>
<td>2</td>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>52-001</td>
<td>1</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>61-003</td>
<td>0</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>61-005</td>
<td>0</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>51-009</td>
<td>1</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>52-001</td>
<td>1</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>61-003</td>
<td>0</td>
<td>0</td>
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<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>61-005</td>
<td>0</td>
<td>0</td>
<td>10</td>
</tr>
</tbody>
</table>

Table summarising the number (out of 10) of two-, three- and four-letter words read correctly by the four subjects in five conditions. The test conditions are indicated by the column labels.

da Cruz 2013.
Long-Term Studies

- Demonstrate functioning device over long term
- Some subjects clearly performed better than others
  - Learning and adaptation
  - Rate of degeneration
  - Programming of the device
  - Level of degeneration at time of implantation
- Factors in perception threshold
  - Electrode-retina distance
  - Placement of the electrode over the macula.
FDA Approval

- Approved by the FDA on February 14, 2013.
- “Humanitarian Use Device”
  - Used to treat or diagnose < 4,000 people annually
  - Must demonstrate the benefit outweighs risk
  - No comparable device on the market for the disease or condition
- Indication: Advanced Retinitis Pigmentosa
- Government Support: > $100 million
  - Department of Energy, NEI, NSF
Indications for Use (FDA)

- Adults age 25 or older
- Bare Light Perception or No Light Perception Vision in both eyes
  - For NLP Eyes, evidence of intact inner retinal function must be demonstrated.
- Previous history of useful form vision
- Aphakic or Pseudophakic
  - If phakic, lens will be removed during implantation
- Patients willing and able to receive post-implant follow-up, device fitting and vision rehabilitation.

Second Sight Argus II Surgeon’s Manual; 2013
Contraindications (FDA)

- Ocular diseases that prevent it from working
  - Optic nerve disease, central retinal artery occlusion, retinal detachment, trauma

- Conditions that prevent implantation
  - Thin conjunctiva, axial length <20.5 or >26 mm, corneal ulcers

- Ocular diseases that prevent visualization of the inner structures of the eye

- Inability to tolerate general anesthesia or antibiotic and steroid medications

- Metallic or active implanted devices in the head

- Cognitive deficits preventing understanding of informed consent

- Predisposition to eye rubbing
Warnings (FDA)

- The device should be turned off on planes
- MR Conditional
  - The implant is safe for MRI (Rating 1.5 or 3 Tesla)
  - The VPU and glasses are not interchangeable
- The wireless transmission may interfere with medical monitoring or life support equipment
- May interfere with electrical devices including cell phones, routers, metal detectors.
- The VPU and glasses are not interchangeable
- Some medical procedures may damage the device. It should be evaluated before and after any medical procedure
Retinitis Pigmentosa

- Currently the only indication for the Argus II
- A group of hereditary retinal degeneration
  - Progressive vision loss from retinal atrophy
  - Decreased night vision → tunnel vision → total blindness
- Prevalence: 1:5000 worldwide
- Inheritance: Recessive, Dominant, X-linked
  - More than 100 genetic mutations linked to RP
- Age of onset: Usually 1st three decades
  - Late onset forms also exist

Ryan; 2013
RP - Fundus

Yannuzzi 2010.
RP - OCT

Evaluation and Follow-up

- Confirm age, diagnosis, and history of form vision
- Vision assessment. Retina must respond to electrical stimulation
  - Full-field stimulus threshold ERG response
  - Dark-adapted detection of a photo flash
  - Electrical evoked response
- Full eye exam
- Review past medical history +/- Psych eval
- Diagnostic testing: Axial length, Ultrasound, Fundus Photography
Evaluation and Follow-up

- Post-op Eye Exams:
  - Day 1
  - Weeks 1, 2, 4
  - Months 3, 6, 12, and then annually

- Testing of device begins at post-op week 1
  - Video processing, orientation, and stimulation
  - Checking and troubleshooting implant function

- Fundus Photos and OCT at week 4 on
Evaluation and Follow-up

- **Patient Training** – this is not plug and play!
  - Location in space of phosphenes affected by:
    - Location of the array on the retina
    - Patient’s eye position – must keep eyes straight despite no visual feedback on eye position
  - Location of the RF coil relative to the implant coil
    - Optimal location is determined during training
  - Head scanning – tactile targets for training
  - Inverse Mode and Filter selection
    - Inverse mode: reverses dark and light areas; useful on sunny days – stimulation will only coincide to dark objects
    - High Contrast Enhancement – low light
    - Edge Enhancement – improves ability to see lines
  - Maintenance training
Centers offering Argus II

- Ann Arbor, MI
- Atlanta, GA
- Baltimore, MD
- Chicago, IL
- Cleveland, OH
- Dallas, TX
- Durham, NC
- Los Angeles, CA
- Miami, FL
- Nashville, TN
- Philadelphia, PA
- San Francisco, CA

Qualifying as a center requires training with the pre-op evaluation, ability to train patients on independent use of the device, and surgical training with at least one surgery performed with a surgeon experienced at implanting the device.
Conclusions

- The Argus II is capable of restoring useful vision in patients blind from retinitis pigmentosa.
- It is likely to be useful for patients with other diffuse outer retinal degenerations.
- It requires intact retinal neurons, optic nerve and visual cortex.
- Argus II is the only FDA approved visual prosthesis
- Continued work will improve the resolution of the device and expand its clinical applications.
Thank You

- https://www.youtube.com/watch?v=tbv2hebWdlM
References

Choroideremia

Yannuzzi 2010.
Leber’s Congenital Amaurosis

Yannuzzi 2010.
Age-Related Macular Degeneration

Yannuzzi 2010.