New Approaches to Preserve Residual Hearing and Improve Performance for Cochlear Implant Recipients

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Cochlear Limited

www.hearingcrc.org
‘seamless transition between the hard world of electronics and the soft world of biology’

Nanowerk, July 17 2007
“cochlear implants, which use multiple electrodes that are implanted into the cochlea to stimulate auditory nerves, are one of the most successful medical bionic prosthetics”
Modern Cochlear Implant Systems

Advanced Bionics

Med-EL

Cochlear

Neurelec
Development of Nucleus® Technology

1986
CI22M

1997
CI24M

2000
CI24R
(Contour™)

2005
CI24RE
(Freedom™)

2009
CI512

1983
WSP

1989
MSP

1994
Spectra

1997
SPrint™

1998
ESPrit™

2002
ESPrit 3G

2005
Freedom™

2009
CP810

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Technology: Perimodiolar Positioning

Contour

Advance

Half-banded
Improving the Electro-neural Interface - Positioning

Shepherd et al., 1993

- EABR recordings at differing positions in the cochlea
Pre-Curled Electrode Studies

Psychophysics

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Applying Polymer Technology to Improve the Electro-neural Interface

1994
Perimodiolar Curling Array using hydrogels concept studies initiated with IPRI

1995
First bioengineering & insertion studies Curling and pre-curled arrays

1997
Histology on first perimodiolar designs Curly with Stylet studies

1998
Prototype pre-curled electrode implanted 3 adult patients

1999
First Contour implants

2001
Contour Array Phase II Trials

2003
Advance & AOS Insertion
Technology: Perimodiolar Positioning

Standard Nucleus 24® electrode

Nucleus 24® Contour electrode

Courtesy of J. Xu
Technology: Perimodiolar Positioning

- AOS surgical technique critical to atraumatic insertion
AOS™ insertion technique

- Flexible, pre-curved electrode
- Softip™
- Minimal lateral wall forces with AOS™

Applying Polymer Technology to Improve the Electro-neural Interface

Contour Advance

- no insertion trauma cochlear structures
CI Patients: Pre-Operative Hearing Levels

CNC word: Left 18%, Right 3%, Binaural 19%

CNC word: Left 12%, Right 12%, Binaural 14%

CNC word: Left 17%, Right 12%, Binaural 21%

CNC word: Left 11%, Right 15%, Binaural 21%
Nucleus® Electrode Portfolio

N24 Straight

Contour Advance

Hybrid S8 Research

Hybrid L RW Insertion
Nucleus® electrodes

Straight Banded array
24mm overall
Base : 0.6mm
17mm lateral wall
Tip : 0.4 mm

Contour advance
Base : 0.8mm
17-19mm perimodiolar
Tip : 0.5 mm

Hybrid-L™ Electrode
16mm lateral wall
Base : 0.55 x 0.4mm
Tip : 0.35 x 0.25mm
Nucleus® Hybrid-L CI System

Shorter electrode to avoid potential for trauma to apical end of cochlea

Hybrid L RW Insertion

Frequency (Hertz)

Hearing Threshold Levels (dBHL)

HA stimulates low frequencies

CI stimulates high frequencies
1-month post-operative data selected to indicate hearing preservation with Hybrid-L
Unaided Thresholds – Pre & I month Post Op

**SYD-5**
- Pre-operative
- Post-operative

**SYD-7**
- Pre-operative
- Post-operative

**MELB-6**
- Pre-operative
- Post-operative

**MELB-8**
- Pre-operative
- Post-operative
Clinical Trial – Benefits of Hybrid-L

Electroacoustic + Acoustic
CI + HA
HA

COMBINED MODE

Localisation
RMS Error Total (1 speaker = 25 degrees)

Subject
S11 S6 S1 S7 S5 S4 S8 S9 S2 S3 S13 S12

Speech & Noise Front
Percent Correct

Bimodal Combined

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Two subjects showed unstable hearing post-operatively; one at 3-months (coincided with labyrinthitis) and one at 6-months (no clinical signs)
What is the benefit of adding acoustic to electric stimulation?

**Preoperative versus Postoperative Benefit?**

Word scores are better postoperatively (electric alone) compared to preoperatively (HAs).

Electric alone

Benefit from 20%–34%

Electric + Acoustic

Benefit greater when acoustic stimulation combined with electric stimulation compared to electric alone

Benefit from 37%–49%
How does Post-op Combined (EA+A) use compare with Bilateral Acoustic Inputs (A+A)?
Horizontal Localisation

- N = 14, aged 45 – 81 years
- Nucleus CI system
  - Hybrid L24 (6)
  - CI422 (SRA) (6)
  - MRA (1)
  - Freedom CA (1)
- MAP parameters
  - ACE sound coding
  - MP1+2 stim mode
  - 25 μsec pulse width
  - 7200 Hz total stim rate
- Test condition: EA+A vs A+A
Localisation

Effect of device: $p=0.48$

$\text{EA} + \text{A} \approx \approx \text{A} + \text{A}$

Fig. 2. Freiburger monosyllable scores (free field condition, 65 dB SPL) for electric-acoustic stimulation and bilateral cochlear implant users. Horizontal bars represent average score. EAS, electric-acoustic stimulation; HA, hearing aid.

EEA + A > A + A
How does Post-op Combined (EA+A) use compare with Bimodal (E +A)?

Or:

Is hearing preservation in the implanted ear useful?

Kerrie Plant
Clinical Trial – Benefits of Hearing Preservation

- n = 13, aged 55 – 83 years
- Nucleus CI system
  - Hybrid L24 (5)
  - CI422 (SRA) (7)
  - MRA (1)
- Two test conditions:
  - EA+A vs E+A

Measures:
- Subjective ratings (SSQ)
- Musical sound quality ratings
- Speech perception in noise
- Localisation ability
Subjective Rating

EA+A vs E+A

**QUESTIONNAIRE COMPARATIVE RATING**

- **SPEECH:** 1.5***
- **SPATIAL:** 1.1***
- **QUALITY:** 1.4***

**MUSIC PLEASANTNESS**

- **E+A:** 2.6
- **EA+A:** 3.0*

*creating sound value™*
Speech Perception and Localization

**Speech Perception**

- **SRT (dB)**
  - E+A: 2.7
  - EA+A: 0.8

**Localisation**

- **RMS Error (Degrees)**
  - E+A: 51.3
  - EA+A: 7.4

Better Performance

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![Graph showing mean word recognition scores in quiet and noise conditions.](image)

Fig. 3. Mean word recognition scores for the usual best-aided condition and simulated “bimodal” condition; in quiet and in noise. Error bars denote standard deviations. Differences: NS indicates not significant, *p < 0.05.

- EA vs. E + A
  - p = 0.34
  - p < 0.05

n = 30
What about if all acoustic hearing is lost in the implanted ear?
Speech Perception

Best Aided; Pre-Operative HAs, Post-Operative Bimodal (n=19)

CVC words at 65dBSPL
Spatial Release from Masking

Best Aided; Pre-Operative HAs, Post-Operative Bimodal

SRM: SRT S0N90 – S0N0
Positive Value = advantage provided by spatial separation
Localisation

Best Aided; Pre-Operative HAs, Post-Operative Bimodal (n=14)

Consistent trend all subjects

50% subjects had poorer post-operative localisation ability
Subjective Ratings of Benefit:

Best Aided: Pre-Operative HAs. Post-Operative Bimodal

SSQ Questionnaire

Rating

Speech  Spatial  Quality

Pre  Post

***  ***  ***
Nucleus® Electrode Portfolio

N24 Straight

Contour Advance

Slim Straight (422)

Hybrid L RW Insertion
Nucleus® electrodes

Straight Banded array
24mm overall
Base : 0.6mm
17mm lateral wall
Tip : 0.4 mm

Contour advance
Base : 0.8mm
17-19mm perimodiolar
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Hybrid-L™ Electrode
16mm lateral wall
Base : 0.55 x 0.4mm
Tip : 0.35 x 0.25mm

CI422 (Slim Straight)
20mm lateral wall
25mm overall
Base : 0.6mm
Tip : 0.3mm
Unaided Thresholds (Pre- vs Post-Operative)
Unaided Thresholds (Pre- vs Post-Op): Straight Slim

Subject 5

Subject 6

Subject 7

Subject 8
Nucleus CI422 Slim Straight electrode

Prospective study of outcomes for 90 adult CI422 implant recipients at RVEEH

<table>
<thead>
<tr>
<th>CI422 Recipients</th>
<th>Mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at implant (years)</td>
<td>61.2 (16.2)</td>
</tr>
<tr>
<td>Duration of loss - CI ear (years)</td>
<td>15.4 (11.8)</td>
</tr>
<tr>
<td>Duration of loss - contralateral ear (years)</td>
<td>16.9 (12.9)</td>
</tr>
</tbody>
</table>
Pre-op vs Post-op Hearing

Pre-operative hearing - CI422 recipients

Post-operative hearing - CI422 recipients

Post-operative hearing - CI422 recipients

(n=55)

Pre-Op thresholds:
- 250 = 52.8
- 500 = 65.4
- 1K = 87.4
- 2K = 102.5
- 4K = 107.2

Post-Op (3mth) thresholds:
- 250 = 76.6
- 500 = 88.0
- 1K = 103.4
- 2K = 110.7
- 4K = 115.5

Post Op (12mth) thresholds:
- 250 = 88.5
- 500 = 99.0
- 1K = 112.3
- 2K = 117.4
- 4K = 118.9
30% had drop of greater than 30dB in acoustic hearing
Preservation of Residual Hearing

- Mean change in hearing thresholds at 500 Hz by 3M post-op is \(-23.3\) dB

- Examining the degree of change to 500 Hz threshold from pre-op to 3M post-op:

<table>
<thead>
<tr>
<th>Degree of Change</th>
<th>% of CI422 recipients (n=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 10 dB loss at 500 Hz</td>
<td>36.4 %</td>
</tr>
<tr>
<td>15 – 25 dB loss at 500 Hz</td>
<td>23.6 %</td>
</tr>
<tr>
<td>≥ 30 dB loss at 500 Hz</td>
<td>40.0 %</td>
</tr>
</tbody>
</table>

- **Is the hearing useful?**
  - 67.2 % (37) of CI422 recipients had hearing thresholds of **80 dB or better** pre-operatively
  - At 3 months post-op, **40.5 % (15)** of these 37 had hearing thresholds of 80 dB or better
For insertion >360 degrees no apparent increase in hearing loss with deeper insertion as might be predicted from increase in lateral wall force.
## Comparing Speech Perception

<table>
<thead>
<tr>
<th></th>
<th>PRE-OP Monaural Sentence in Noise (%)</th>
<th>PRE-OP Binaural Sentence in Noise (%)</th>
<th>3M Monaural Sentence in Noise (%)</th>
<th>3M Binaural Sentence in Noise (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hybrid-L24</td>
<td>45.91</td>
<td>56.54</td>
<td>64.94</td>
<td>77.66</td>
</tr>
<tr>
<td>CI422</td>
<td>21.40</td>
<td>43.91</td>
<td>58.94</td>
<td>75.53</td>
</tr>
</tbody>
</table>

Pre-op, Hybrid-L24 patients had better pre-op speech perception in the implanted ear (p=0.003)

No difference post-op between the groups on monaural or binaural
Future Directions for Electrodes?

Where are we headed?, and how to get there?
Nucleus® Electrode Portfolio

- N24 Straight
- Slim Straight (422)
- Contour Advance
- Modiolar Research Array
- Hybrid L RW Insertion

Note: MRA research device not approved for clinical use.
Perimodiolar Positioning

MRA - Concept

SOFT TUBE
0.64mm
SHEATH
LUMEN/STYLET
0.8mm
CA

Ø0.5 Ø0.8 Ø0.3
Volume = 1.769mm³

Volume = 8.266mm³
MRA Electrode - Concept

Sheath opens when pulled back against electrode handle

- Design goal: thinner electrode for atraumatic insertion
- Insertion concept: precurved electrode held straight for insertion by soft polymer sheath

Note: Research device, not approved for clinical use.
Current spread is through an ‘electrolytic’ medium
- Fibrous tissue sheath may significantly dissipate electric current
- Mechanisms to control tissue reaction could be beneficial
Electro-neural Interface & Tissue Reaction

st: scala tympani  sv: scala vestibuli

1 = New bone  2 = Fibrous tissue

Low impedance

High impedance
Dex-eluting array reduced hearing loss from implantation in the guinea pig model
Cochlear Implant-based Steroid Delivery

Passive Drug Delivery from Surface

DEX can be incorporated into the silicone by physical hand-mixing or by solvent casting.
Evaluating Drug-eluting Processing

Faster Dex release from solvent casting films

S = solvent casting
M = physically mixed
Electrode Design for Passive Delivery

An augmented Cochlear™ Nucleus® Freedom® implant with Contour Advance® electrode

40% w/w dexamethasone (DXB, Sanofi) in the tip & spine regions of the intra-cochlear array
Shelf Life Validation

No significant difference in purity (demonstrated by amount of substance recovered), left, and in vitro pharmacokinetics, right, was evident after normal and accelerated aging.

Recovered dexamethasone after 30 days incubation in PBS at 37°C, n=3

Pharmacokinetic profile for each shelf life conditioning timepoint, 3 replicates
8 Dunkin-Hartley guinea pigs implanted with electrode arrays loaded with 50% w/w DXB were compared to a control group implanted with a drug-free variant.

Mean SGN densities in each turn of implanted cochleae:

Proportion of new Loose Fibrous Tissue, LFT, or Dense Fibrous Tissue, DFT and bone, NB, evident in the scala tympani.
30 male Hooded-Wistar rats were inoculated with $10^3$, $10^4$, $10^5$ CFU of *Streptococcus pneumoniae* to determine the level of inoculum required to induce meningitis (left).

10 rats were then implanted with a device composed of 50% w/w DXB and inoculated with $10^4$ CFU *Streptococcus pneumoniae* 5 days later (right). A control group of n =10 was also included, implanted with the same device without DXB.
First Time in Human Study

Objectives:
1. Ease of use and effectiveness
2. Safety in controlled adult population

Subjects:

<table>
<thead>
<tr>
<th>Centre</th>
<th>RVEEH</th>
<th>RPAH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contour Advance with 40%w/w DXB</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Contour Advance (no DXB)</td>
<td>30</td>
<td>6</td>
</tr>
</tbody>
</table>

Evaluation Schedule:

<table>
<thead>
<tr>
<th></th>
<th>Pre-op</th>
<th>Surgery</th>
<th>+1wk</th>
<th>+2wk</th>
<th>+1, 3, 6, 12, 24M</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-point (local) impedance</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Speech perception</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>3 &amp; 12M</td>
</tr>
</tbody>
</table>
Interim Findings

Passive delivery of DXB is safe for humans, as demonstrated by in vitro and pre-clinical investigations.

A modified commercial device has been used in a FTIH study and has demonstrated initial benefits in impedance.
Controlled Drug Delivery with Hollow Fibre Systems

- Controlled membrane porosity by redox induced conformational change
- Solvated ion flux activated by doping / dedoping process

Cochlear implant based steroid delivery

Polymer doping / dedoping induced release of drug
1. Electrosynthesis of polypyrrole incorporating Dexamethasone 21-phosphate disodium salt under different conditions and their relation with Dex release.

<table>
<thead>
<tr>
<th>Current Density</th>
<th>0.5mA/cm²</th>
<th>1.0mA/cm²</th>
<th>1.5mA/cm²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roughness</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A. ~81nm</td>
<td>B. ~124nm</td>
<td>C. ~198nm</td>
<td>5mM</td>
</tr>
<tr>
<td>(RMS)</td>
<td>D. ~69.8nm</td>
<td>E. ~121nm</td>
<td>10mM</td>
</tr>
<tr>
<td></td>
<td>F. ~68nm</td>
<td></td>
<td>20mM</td>
</tr>
</tbody>
</table>

Tab 1. Film growth condition vs. film roughness ([Py]=0.2M, Q=1C/cm²)

- With higher current density and lower Dex concentration, higher roughness obtained
- 80% of Dex released out of the film with highest roughness

Fig 1. Dex release efficiency vs. different film growth conditions

(Potential: -500mV, Drug loading: 380ug/cm²)
Focus in Electrode Design

Focus of electrode design on:
• preservation of internal cochlear structures
• positioning to reduce spread of current
• designs for electro-acoustic stimuli
Summary

• preservation of acoustic residual hearing can be accomplished with good electrode design and attention to surgical procedure ~ but outcomes remain unpredictable

• a drug eluting electrode is a feasible vehicle for delivery of therapeutic agents into the cochlea, (but must not compromise insertion characteristics)

• elution rates in passive designs are dependent on drug loading and processes of formulation

• active systems may enable similar drug load delivery through a smaller cross-sectional area electrode array
This research was financially supported by the HEARing CRC established and supported under the Australian Government’s Cooperative Research Centres Program