The Hearing Implant Company

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MEDICAL ELECTRONICS

# Abstracts

# HEARING PRESERVATION WORKSHOP VIII

VIENNA
OCTOBER 15-18, 2009

hearingpreservation.com

## Dear friends and colleagues,

It is an honour to host the 8th Hearing Preservation Workshop in Vienna, where cochlear implantation has been tradition since 1977. The conference venue is located in the Palais Niederösterreich (built before 1513) in the historic heart of Vienna, the imperial city of music and conferences.

In 2009 we celebrate the 200th commemoration day of the famous composer Josef Haydn (teacher of Mozart and Beethoven) who passed away on May 31st 1809 in Vienna. Bringing together well known international experts and participants for scientific discussion in a vibrating and stimulating environment will provide for an unforgettable experience.

Last but not least, we offer social events focusing on the highlights of Austrian tradition and history. The Palais Daun-Kinsky and a typical Vienna "Heurigen" evening will complete an unforgettable time for all participants.

I wish you a successful and prosperous conference. Have a very nice time in Vienna.

Sincerely Yours,

Univ. Prof. Dr. Wolf-Dieter Baumgartner
Head of Otology & Implant Division

## Dear participant,

We are delighted to welcome you to Vienna to participate in the 8th Hearing Preservation Workshop. We would like to continue the scientific discussions on the topics of preservation of cochlear function during cochlear implantation. Presentation topics will focus on clinical outcomes of electric and acoustic stimulation, surgical issues, trauma during cochlear implantation and experimental findings on neural enhancement. We hope that the selection of topics and speakers will generate new ideas in this fascinating field.

The format of this workshop has been designed to encourage exchange and development of ideas. Long presentations of 20 minutes and generous time for discussion should stimulate productive new research ideas. On Friday and Saturday evening, selected social programs should enhance discussion and friendship within the community.

With kindest regards,

Wolfgang Gstoettner, M.D.
Professor Chairman

## October 16th: Hearing preservation and EAS, rehabilitation



## October 17th: Neural enhancement and inner ear pharmacology

## Other inner ear therapies



## Future

# Clinical trial with the FLEX$^{EAS}$ electrode

*Wolfgang Gstoettner – Vienna, Austria*

By using atraumatic surgical procedures cochlea implantation with preservation of the residual hearing has been used developed within the last years. Over the time hearing preservation rates have been improved continuously.
We report on a prospective Multicenter Study implanting 18 subjects with the MED-EL FLEX$^{EAS}$ electrode for electro acoustic stimulation. Pure tone audiometric thresholds were measured in pre- and postoperatively to evaluate the degree of preserved hearing. Speech discrimination tests in quiet and with background noise were performed in patients with successful hearing preservation.

## Results

All subjects had functionally preserved hearing and could be fitted for electro acoustic stimulation. No subject showed a complete loss of hearing. 16 Subjects are DUET users, 2 subjects are CI only users.
EAS is a safe and effective treatment method for individuals with partial deafness. Using an improved electrode design hearing preservation rates are superior to studies with other electrodes.

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# Partial Deafness Cochlear Implantation (PDCI) and Electric-Acoustic Stimulation (EAS)

*B. S. Wilson – Durham, NC, USA*

## Abstract

The purposes of this talk are to (1) review briefly the experience to date with combined EAS for patients with some residual, low-frequency hearing; (2) describe the further results that have been obtained with the combination for patients with higher levels of residual hearing at the low frequencies, termed "PDCI;" and (3) present new results on the relative benefits of cochlear implantation according to the level of remaining hearing. In broad terms, PDCI and combined EAS have produced large improvements in the speech reception abilities of the treated patients, compared with electrical stimulation alone or acoustic stimulation alone. Moreover, the gains in speech reception with the addition of a cochlear implant are just as great for patients with high levels of residual hearing (PDCI levels) as they are for patients with lower levels. This finding is counter to the conventional wisdom that patients with relatively good residual hearing can be harmed by cochlear implantation and supports the idea that criteria for implant candidacy should be relaxed further so that many more patients can benefit from the procedure.

## Acknowledgments

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# Microanatomy and hearing preservation with the FLEX$^{EAS}$ electrode, RW insertion

*H. Rask-Andersen – Uppsala, Sweden*

Conditions with profound SNHL with preserved low tone hearing may have several causes and pathology may vary accordingly. In patients with progressive adult-onset SNHL neurons may be conserved even after long duration of deafness. IHCs and OHCs, supporting cells, ganglion cells and dendrites may be preserved in the apical region while in the lower turn despite atrophic organ of Corti and loss of lamina fibers ganglion cells can be present even after decades of deafness. These spiral ganglion cells may be excellent targets for electric stimulation using EAS technique that combines electric and acoustic stimulation in the same ear and utilizes both low frequency acoustic hearing and electric stimulation of preserved neurons. At the moment we are trying to elucidate the mechanism responsible for this preservation in humans and to use this knowledge for future therapy. Here we present human anatomy data including our experience of the round window insertion of the EAS electrode in Uppsala, Sweden. The exposure of the RW membrane and insertion of the electrode is related to the anatomy of the membrane and niche and its radiological appearance.

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# Soft Surgery in Cochlear Implants, Past, Present and Future

*M. Hammad – Abu Dabi, UAE*

The first thoughts for residual hearing preservation during cochlear implants (CI) surgery have to be credit to Lehnhardt who was the first to describe it in 1993. Through a specific technique named "soft surgery" he could preserve the residual hearing in three patients. The idea behind residual hearing preservation was to preserve as much of the sensory hearing structures inside the cochlea for better postoperative outcome. This was followed by many publications showing the effectiveness of soft surgery in preservation of residual hearing. However, there was no evidence that soft surgery is associated with improved patient performance even in patients with some residual hearing. Thus the technique didn't gain wide acceptance until von Illberg et al., in 1999 published the concept of combined electric-acoustic stimulation (EAS) of the auditory system. They proved that in patients with residual hearing especially in low frequencies, combined stimulation using acoustic signals (via hearing aid) and electric signals (via cochlear implants) results in better performance than either mode alone. The acoustic hearing can be in the implanted ear or the contralateral ear. Many other researchers have proved the theory and reproduced the same results obtained by von Illberg i.e. improved speech discrimination with combined EAS which make hearing preservation through a soft surgery procedure a more common procedure. The future of soft surgery together with cases presentation is also discussed.

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# Improved hearing preservation with optimized electrodes for patients with high frequency deafness

*T. Lenarz – Hannover, Germany*


## Objective

In order to preserve residual hearing in cochlear implantation both electrode technology and surgical technique have to be adopted to this goal and optimized. Here we will report about several attempts to develop electrodes which will cover most of the basal turn of the cochlear and allow a reliable hearing preservation.

## Methods

Two electrode devices with a 16 mm and 22 mm in lengths have been developed and evaluated in temporal bones as well as in clinical studies.

## Results

The 16 mm electrode covers approximately 270 degrees of the basal turn with a wide range depending on the size of the cochlear. Hearing results depend mainly on the degree of residual hearing but do not reach the results of the standard electrode array if the electrical stimulation is used without the acoustic stimulation. The 22 mm electrode allows a good placement inside the cochlear covering the whole basal turn. No severe damage has been seen in temporal bone studies. Currently this device is under clinical investigation.

## Discussion

It seems to be a potential for longer electrodes covering at least the full basal turn of the cochlear with a high percentage of hearing preservation. The appropriate electrode design together with the appropriate technique using the round window insertion pathway are mandatory prerequisites to achieve the goal of full hearing preservation in those patients.


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# A new electrode for electric-acoustic stimulation – temporal bone study and first clinical results

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## Introduction

Low-frequency hearing preservation in cochlear implantation requires the use of an electrode carrier ideally reaching a 360° insertion angle, corresponding to an insertion depth of 20 mm measured from the round window (RW) membrane. Surgical procedure and properties of the electrode carrier mainly influence results after cochlear implantation. A new electrode (FLEXEAS 20) design for hearing preservation was to be evaluated histologically.

## Materials and Method

The new electrode array consists of 12 channels distributed over 16.5 mm length, while the total insertion depth is 19.5 mm. Zigzag shaped metal wires within the array increase the flexibility of the electrode. The diameter of the electrode increases from tip to base from 0.3 mm to 0.8 mm. Ten post mortem human temporal bones were implanted with the FLEXEAS 20 using the round window insertion method. Then the temporal bones with the electrode in situ were embedded, radiologically controlled, and the undecalcified bone was sectioned. Macroscopic and histological investigations in terms of basal cochlear trauma were performed.

## Results

All electrodes were positioned into the scala tympani with minimal insertion forces. There was no deviation into the scala media or scala vestibuli. In only one of the temporal bones a trauma grade 4 (fracture of the osseous spiral lamina) occurred. Another specimen showed a lifting of the basilar membrane (grade 1). In the other eight specimens the round window approach did not result in unreasonable bone trauma. A 360° insertion could be achieved exactly in 7 out of 10 cases (mean overall insertion angle: 360°).
In one patient chosen for implantation with this new prototype a 360° insertion could be achieved and hearing was preserved. Outcomes are presented at the conference.

## Conclusions

The properties of the new electrode recommend it for clinical application in such cases. Intracochlear trauma and insertion forces are kept minimal. RW insertion ensures entrance into the scala tympani and makes the introduction of all electrode contacts by 360° insertion possible.

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# Speech perception in complex noise: Combined Electric-Acoustic Stimulation (EAS) outperforms bilateral cochlear implant

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The present study applied a multi-source noise field (MSNF), consisting of a four-loudspeaker array with independent noise sources, in combination with a closed set sentence test (Oldenburger Sentence Test, OLSA). Speech simulating noise (Fastl-noise) as well as CCITT-noise and OL-noise (overlay of multiple OLSA-sentences without temporal modulation) served as noise source. Closed set speech tests were performed in groups of patients aided in either EAS (EAS speech processor "DUET", MED-EL, Innsbruck, combined with hearing aid in the ear not implanted, 7 subjects) or bilateral CI. The bilateral CI group consisted of 10 very experienced top performing subjects with average 87% monosyllable comprehension in bilateral CI condition (Freiburger Test). A group of 22 normal hearing listeners served as controls. RESULTS: Speech reception thresholds (SRT) were severely compromised by modulated (Fastl)-noise in both groups of cochlear implant listeners compared to normal hearing listeners. Average EAS subject group SRTs were lower and therefore better than average results of the bilateral CI group in all noise conditions. In reference to the OLSA-noise condition, the EAS group data showed better SRTs especially in the Fastl-noise condition. The overall better performance in modulated noise conditions in the EAS group might be explained by 1) "glimpsing", the enhanced ability of the residual acoustic hearing to listen into temporal gaps or 2) improved transmission of fundamental frequency cues in the lower frequency region of acoustic hearing, which might foster grouping of speech auditory objects. Furthermore, the results do indicate, that binaural interaction between EAS implanted ear and residual acoustic hearing in the opposite ear enhances speech perception in complex noise situations.

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# New approach to the partial deafness therapy

*H. Skarzynski – Nadarzyn, Poland*

*PDT from International Center of Hearing and Speech of the Institute of Physilogy and Pathology of Hearing, Kajetany/Warsaw*

Partial Deafness Treatment (PDT) constitutes a great challenge and a great chance for a significant number of patients. For many years the treatment was based on cochlear implants, and it was called partial deafness cochlear implantation (PDCI). In the world literature PDCI was also described as electric-acoustic stimulation (EAS) or Hybrid stimulation. Current new approach in PDT management much more precisely defines various means of aiding residual hearing by means of cochlear implant (CI), middle ear implant (MEI) and hearing aid (HA).

Before deciding on partial deafness cochlear treatment with a cochlear implant (PDT-CI) application of middle ear implant or a hearing aid in case of partial deafness may be a temporary and therapeutic solution to stimulate existing residual hearing on low frequencies (partial deafness treatment with middle ear implant, PDT-MEI; partial deafness treatment with hearing aid, PDT-HA). The final procedure in case of failure of the above mentioned methods of PDT may be use of the electric stimulation alone from the same implant, without reoperation (partial deafness treatment with electric stimulation only (PDT-ES)). 20 mm electrode is the only condition that must be fulfilled.

In case of ineffective amplification of the existing hearing loss using a hearing aid or middle ear implant, cochlear implants has proved to be the most efficient in treatment of partial deafness (PD-CI) that is confirmed by our long-term observations. Further development of this kind of therapy aims to separate homogenous groups of patients with various hearing losses defined as partial deafness. The biggest challenge is a group of patients with normal low frequency hearing, electrically complemented (EC) with cochlear implants. Based on the long-term observation of the PD-EC patients the authors demonstrated the most technically advanced combination of residual hearing of patients and electrical hearing produced by the cochlear implant (partial deafness treatment with electrical complementation – PDT-EC). The second possible treatment applied in significant number of patients with partial deafness is combination of electric and acoustic stimulation using a cochlear implant and a hearing aid that is determined by us as a partial deafness treatment with electric-acoustic stimulation (PDT-EAS).

In the summary authors will present results of minimum 3 years observation of homogenous groups of patients – PDT-HE, PDT-MEI, PDT-EC, and PDT-EAS and PDT-ES.

The proposed concept is a clear approach to the strategy of partial deafness therapy. It assumes homogenous selection of groups of patients and comparable homogenous hearing loss.

### Partial Deafness Treatment (PDT) – Electrical Complementation (EC)

Partial deafness treatment (PDT) using cochlear implants (PDT-CI), broadening the former conception of the partial deafness cochlear implantation (PDCI) brings about new possibilities of hearing improvement for much wider group of patients. New conception of the partial deafness treatment (PDT) encompasses different means of supporting in low frequencies the existing residual hearing. The greatest opportunity of the effective PDT therapy is aiding the normal in low frequencies hearing with electric stimulation in high frequencies with the cochlear implant, which should be treated as the complementary electrical stimulation – electrical complementation (EC). The authors present long-term results of rehabilitation of homogenous group of patients, whose therapy was defined as the partial deafness treatment with electrical complementation (PDT-EC). The conclusions underline the fact that irrespective of the original cause of the impairment of the high-frequency hearing – congenital or acquired – the deterioration of existing hearing in low frequencies was not observed over the period of five years.

Concluding, electric stimulation with the cochlear implant (EC) complementing the good low-frequency hearing is the lasting and effective therapeutical solution in partial deafness.

### Partial Deafness Treatment (PDT) – Electrical Stimulation (ES)

With a developed round window surgical procedure and a limited electrode insertion, hearing can be preserved in the majority of patients with partial deafness (PD). However the risk of hearing loss after implantation exists. The acoustic hearing of the patient may also decline in time after surgery. The aim of the study was to assess the speech perception benefit with and electric stimulation (ES) after partial deafness treatment (PDT) in case of loss of low frequency hearing.
The subjects that lost hearing immediately, or at some time after surgery, were able to obtain a significant advantage by using ES and relying on natural hearing in the contralateral ear.

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# Preliminary results using the MED-EL SONATA$_{TI}^{100}$ FLEX$^{EAS}$ electrode array

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This presentation will discuss our initial results of hearing preservation surgery and the associated speech perception outcomes after implantation with the MED-EL SONATA$_{TI}^{100}$ FLEX$^{EAS}$ electrode array.
Subjects were adult candidates for cochlear implantation, recruited according to local selection criteria. Devices were implanted according to a "soft" surgery protocol with the aim to preserve residual hearing in the implanted ear. Subjects who retained any residual hearing post operatively were issued with the DUET speech processor which combines both acoustic amplification and electrical stimulation. The results of aided thresholds and speech perception tests will be presented.

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# Genetic background of candidates for EAS (Electric-Acoustic Stimulation)

*S. Usami, Ph.D. – Matsumoto, Japan*

There are a certain number of patients with so-called ski-slope hearing loss, in which there is good hearing for lower frequencies in spite of little /no hearing in high frequencies. Hearing aids are sometimes not beneficial and these cases are beyond criteria for traditional cochlear implant. EAS (Electric-Acoustic Stimulation) has recently been introduced for such patients with residual hearing at lower frequencies.

Ski-slope hearing loss can have either a progressive nature or be rather stable therefore decisions regarding timing of surgery are sometimes hampered. One advantage of genetic testing is that the possible prognosis for hearing, i.e., progressive or not, can be predicted for individual patients. The present study was performed to estimate the frequency of ski-slope hearing loss and genetic background of the candidates for EAS.

A 4501 DNA database of sensorineural hearing loss established by Shinshu University in corroboration with 33 ENT (mostly university hospital) departments in Japan was used in this study. 151 (3.4%) cases fulfilled the criteria for EAS. In addition to examining inheritance mode, progressiveness, and onset, four common genes with mutations in Japanese hearing loss patients were screened to identify the responsible gene. Concerning, inheritance mode, 52% were sporadic/recessive inheritance, 30% were dominant/mitochondrial inheritance, and in 18% family history was unavailable. Progressiveness was recognized in 55% of the 151 patients, in contrast with 20% overall. Onset ages ranged from congenital to 77 years old. Genetic analysis identified mutations in 30% of the patients, including the mitochondrial 1555A>G mutation (16%), SLC26A4 (7%), GJB2 (3%), and CDH23 (3%).

As most of these patients showed a progressive nature in their hearing, genetic testing adds important additional information for the candidates for EAS.

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# Electric Acoustic Cochlear Implantation at St. Thomas Hospital

*A. F. O'Connor, D. Jiang*

The Electric Acoustic Cochlear Implantation programme at St. Thomas' commenced in 2002 as a research project and to date 14 patients have been implanted. The presentation will encompass the audiological criteria and used to select patients, the surgical techniques utilised based primarily on the Medel European EAS study. Outcome measures will be discussed including an individual case of great interest where acoustic hearing improved post implantation. Comparison will be made between bony cochleostomy and round window insertion based on our study of round window accessibility. A systematic review of EAS will be discussed along with a review of a worldwide questionnaire on otologists/implant surgeons views on EAS.

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# Application of DUET and DUET 2 in Partial Deafness Treatment (PDT)

*A. Lorens – Nadarzyn, Poland*

## Introduction

The concept of combined Electric Acoustic Stimulation in one ear, introduced by Prof Christoph A. von Ilberg in the group of so called borderline CI adult candidates required an amplification of residual hearing, which was accomplished by application of an inner ear hearing aid (HA) (von Ilberg et al, 1999). In 2002 a new method of partial deafness treatment was proposed by Skarzynski et al, (2003), which incorporates the introduction of a round window surgical technique for hearing preservation and the application of combined EAS in the new group of patients with steeply-sloping audiograms, so called patients with partial deafness. It was proved that in this group satisfactory results of EAS can be achieved without use of HA in the implanted ear, due to substantial low frequency hearing, which remained preserved after implantation (Skarzynski 2006, Skarzynski 2007). However not all patients can benefit from EAS to full extend without the amplification of hearing in the implanted ear because of their limited range of low frequencies hearing. Moreover the use of HA as a second device was found to have limitations and was often rejected by patients (Helbig et al, 2008). Therefore the DUET audio processor was developed by MED-EL, Innsbruck, Austria. It combines a CI speech processor and an acoustic stimulation unit specifically designed to achieve amplification in the low frequencies between 125 and 1,500 Hz in one single device.

## The application of DUET in Partial Deafness Treatment

Our group demonstrated that patients with partial deafness are able to use their natural low-frequency hearing without amplification together with their cochlear implant (CI) to obtain outstanding results in speech tests (Skarzynski et al, 2007). Despite this finding we decided to upgrade patients with partial deafness to the DUET audio processor, after the processor became available. We assumed that by amplification of ipsilateral hearing the low frequency acoustic hearing in both ears would be more symmetrical. Due to the selection policy to implant always worse ear or due to the partial hearing loss after surgery, the postoperative asymmetry in hearing between ears was found in some patients. The hypothesis was that the bilaterally balanced access to low frequencies would possible increase the patients' speech reception, especially in noise. The results obtained fully support this assumption, showing greater benefits for the patients with partial deafness when fitted with the DUET Hearing System than when using their cochlear implant alone (Lorens et al, 2008)

## DUET to DUET 2 upgrade study – preliminary results: Materials and Methods

The second generation of the DUET audio processor, the DUET 2, has been recently introduced by MED-EL company. The DUET 2 offers all the features of the DUET

plus additional new features. It has a new, ergonomically improved design with a reduced weight of only 14 g (including batteries) and is provided with the FineTuner, a remote control for switch-free adjustment of the settings. An optimized frequency range, stronger acoustic amplification and the improved separate signal processing for CI and acoustic amplification, equip users with the newest hearing technology. The study objective was to show sound quality and speech perception outcomes as well as subjective satisfaction with the new DUET 2 as compared to the DUET.
10 adults, age ranges at upgrade from Duet processor to Duet 2 from 29 years to 72 years who had minimum of 12 months of DUET experience were fit and tested with the DUET2. The average age at upgrade was 43 years (29 – 72 years). The patients were tested using the monosyllabic words reception test in quiet and in noise. The patients also completed visual analogue scales questioning device preference, when listening to speech and to a pop song. Tests were administered at the moment of upgrade (interval I) after 1 month (interval II) and after 3 months (Interval III).

## Results

Results for the speech reception test in quiet and in noise revealed that patients performed equally well or better in DUET 2 Results for the VAS devices comparison indicated significant preference for DUET 2 audio processor.

## Conclusions

Achieved results support applications of Combined Audio Processors for people with partial deafness. DUET2 can provide additional advantages over DUET. Patients reported a better satisfaction with the DUET2 as compared to the DUET. Speech perception outcomes with the DUET 2 was comparable to the DUET.audio processor.

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# Electrophysiologic parameters indicating imminent cochlear damage – an animal model for electric acoustic stimulation

*O. Adunka – Chapel Hill, USA*

## Introduction

The contributing factors for hearing preservation/loss during cochlear implant surgery are widely unknown. To better understand the underlying factors, we established an animal model of intracochlear electrode insertion. This model should help to identify electrophysiological parameters indicating imminent intracochlear damage through electrode advancement.

## Methods

Experiments were conducted in urethane-anesthetized, normal-hearing gerbils. After exposing the round window, a metal electrode was placed on the surface of the round window and recordings of the cochlear microphonic (CM) and compound action potential (CAP) were made in response to free-field stimulation (tone bursts ranging from 1 to 16 kHz in one octave intervals at intensities of 15-72 dB SPL in 3 dB steps). The electrode was then advanced incrementally through the round window, with CM and CAP measurements taken following each advancement step. These data were compared to data taken at the round window, and the electrode was withdrawn when a significant change in either threshold or suprathreshold amplitude was observed. Also, cochlear damage was examined histologically in a whole-mount preparation.

## Results

Results show that upon electrode insertion through the round window, an increase in thresholds and loss of amplitude in the CM and CAP occurs after damage to cochlear structures such as the basilar membrane. Loss of activity is first apparent in the CAP rather than the CM. When a significant reduction in CAP suprathreshold amplitude was first identified, withdrawal of the electrode could be associated with full or partial restoration of the CAP amplitude.

## Conclusions

These results suggest that a reduction of the CAP can be an early marker of interaction of the electrode with cochlear structures prior to irreversible damage. If comparable measurements were taken intraoperatively, the surgeon could use them to prevent loss of residual ipsilateral hearing, thus optimizing combined electric and acoustic stimulation of the auditory system.

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# Intraoperative monitoring of residual hearing in EAS surgery

*A. Radeloff, S. Brill, W. Shehata-Dieler, R. Mlynski, R. Hagen, J. Mueller – Würzburg, Germany*

Hearing preservation is of increasing interest since the indication criteria for CI implantation has shifted to patients with residual hearing. However, complete hearing preservation is not achieved in every patient. The underlying mechanisms are not clearly revealed until now, but may include direct traumatization and delayed effects of intrascalar tissue formation or immune response. Intraoperative frequency specific monitoring may be a reasonable tool to assess critical points for hearing preservation during surgery.

Presented is a stimulation and recording technique that allows a quick and frequency specific intraoperative threshold determination.

Using this technique, we were able to specify the extent and time point of intraoperative threshold deterioration. Moreover, in some patients, a reversibility of threshold deterioration could be demonstrated after a slight pull back of the electrode array.

Intraoperative frequency-specific monitoring of the residual hearing may be a valuable tool for scientific studies dealing with intraoperative deterioration of the hearing function. During surgery, it may help to define an individual critical insertion depth whenever preservation of a significant residual hearing is intended.

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# Developing testing and training materials for the high frequency

*G. Plant – Durham, USA*

Until relatively recently, the high frequency consonants have presented great problems for listeners with hearing loss. Technology such as cochlear implants, EAS, and frequency shifting hearing aids have provided reliable access to the important consonants for the first time. This paper will review the acoustic structure of the high frequency consonants produced by adult male, adult female, and child speakers, and consider the need for structured training to ensure that users of new technology have the best chance of optimizing the use of this information.

The presentation will also focus on a series of analytic and synthetic exercises developed for use with clients using EAS. The analytic exercises include present/absent lists for detection, and consonantal contrasts for identification. The synthetic exercises present materials at the sentence level to replicate everyday listening situations. The exercises are designed for clinical and home training and include a number of self training materials using PowerPoint.

Consideration will also be given to appropriate high frequency test materials including word lists made up of only high frequency consonants and vowels with higher second formants. Suggestions will be made for adapting these materials into other languages.

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# Genetic testing, outcomes, and candidacy

*M. Pfister – Tübingen, Germany*

The last 15 years of Molecular Medicine were intensively influenced by the progress of the Human Genome project. This development led to the identification of genetic and molecular risk factors of hundreds of rare hereditary disorders including hereditary hearing impairment. However, from a diagnostic point of view, the current medical evaluation of hereditary impairment still involves a myriad of clinical and laboratory tests, few of which provide diagnostic or prognostic information. These tests are costly, time-consuming, and stressful for the patient. Most recently additional molecular testing strategies could be implemented due to the identification of molecular risk factors. However, only a limited number are presently available for diagnostic tests. This is in part due to the large degree of genetic heterogeneity of hearing loss making it difficult to decide which gene to test in a given patient. Currently different approaches are taken to overcome this gap between the scientific achievements and the diagnostic approaches.

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# Progressive re-organisation of the organ of Corti with hair cell loss

*A. Forge – London, GB*

There is a general pattern of progressive pathology with many conditions that cause death of cochlear hair cells, both acquired and hereditary. Outer hair cell (OHC) death progresses from base towards the apex; inner hair cell (IHC) death succeeds death of OHCs; and neural loss follows IHC death. The loss of a hair cell is accompanied by expansion of the supporting cells that surround it to close the lesion at the surface of the sensory epithelium. Following loss of all hair cells there is an extensive re-organisation of the tissue that results in the replacement of the normal columnar epithelium with a simpler, cuboidal-like epithelium. This is the likely condition of the organ of Corti of patients who have been deaf for some time. The majority of OHC death appears to result from the triggering of apoptosis, with free radical attack being one likely proximal cause. Inner hair cell death however, is delayed, often by several months, and the characteristics of IHC death in several different conditions are different from those of outer hair cells. This suggests that IHC death is triggered by factors different from those that kill OHCs and that the mode of cell death differs. This may have implications for proposed therapeutic interventions to protect hair cells from damage, and for preservation of innervation; death of spiral ganglia is a sequelae of IHC loss. The re-organisation of the epithelium that accompanies hair cell loss creates the cellular environment upon which any therapy intended to ameliorate deafness is expected to work. During this re-organisation, supporting cells retain many of their differentiated characteristics for some time, indicating that they do not de-differentiate towards a less specialised cell form. Cellular migration occurs during the re-structuring. The extent and speed of the changes are influenced by the genetic background and they do not occur uniformly along the cochlea. These features make it difficult to predict the likely cellular nature of the organ of Corti in a profoundly deaf person. Knowledge of the cellular environment upon which a regenerative therapy is expected to work is necessary to for any such a therapy to succeed. It should also be noted that hair cell loss may not be the only defect in a deaf cochlea. There maybe strial atrophy and/or loss of fibrocytes in the spiral ligament and changes in the tectorial membrane as well. These and other considerations represent challenges to strategies for regeneration of hair cells as therapies for deafness.

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# Integrating an understanding of trauma mechanisms into clinical practice

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Hearing preservation techniques are being applied to a progressively wider population of implant candidates including pediatric patients. Recent experience with this technique has shown that there are several different patterns of hearing loss that may be seen when performing this type of surgery. Acute losses are most likely due to intra-operative trauma and involve severe tissue damage and necrosis. Delayed losses may be related to induction of inflammatory pathways and result in induction of apoptosis (programmed cell death). A third category of loss are the patients that loose hearing in their implanted ear months to years after initial implantation. It is assumed that this loss is related to the presence of the implant since the contralateral hearing ear is not affected. Currently rodent models can help us understand the acute and subacute injury process. If no overwhelming injury during the implantation process occurs, subacute injury and induction of apoptosis may be controlled with anti inflammatory agents or a variety of anti apoptotic agents. Evidence from mouse models clearly implicated TNF alpha signaling as a key component in this process. Currently we are capable of achieving deep insertion into the cochlea without significant loss of function. To reliably expand this patient population we have to expand the number of medications that can be used to prevent trauma.

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# Digital Volume Tomographie (DVT), a new tool of evaluating the cochlea before and after electrode insertion

*J. Kiefer – Regensburg, Germany*


## Background

Hearing preservation in cochlear implant surgery is related to the exact definition of insertion depth and atraumatic insertion, avoiding for example penetration of the basilar membrane. Human cochleae may vary considerable in size and curvature from one individual to the other. Precise three-dimensional imaging techniques could help us determining the required insertion depth, entry point and direction preoperatively. Postoperatively, imaging of the electrode inside the cochlea serves as quality control and may enable us to analyze reason for success or failure of hearing preservation.

## Method

Digital volume tomography (Morita 3D-Accuitomo) of the temporal bone was acquired in patients in preparation of cochlear implantation or other ear surgery. Three-dimensional image analysis was performed to specifiy length and individual form of the cochlea. Postoperatively, electrode position and insertion depth was determined using the same technique.

## Results

DVT allows for precise imaging of the human cochlea as well as electrode position inside the cochlea. High precision with reduced dose of radiation can be obtained. It can be used as a new tool to plan cochlear implant surgery in regard to hearing preservation and to evaluate postoperative results of insertion.


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# Hearing preservation in animal models of cochlear implantation

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Up to now, few animal models have been designed for preservation of hearing during cochlear implantation (Eshraghi and Van De Water, 2005, 2007; James et al., 2008; Nguyen et al., 2009). The reasons why hearing declines after a cochlear implantation in small animals remain unclear, although many assumptions have been formulated on the putative so-called otoprotective effect of drugs applied locally into or around the cochlea (Leary Swan et al., 2008).

We have developed an animal model for cochlear implantation using silicone array as in human beings. Two sets of experiments were performed in guinea pigs using either a 254 µm external diameter tip with a inside silver wire, or a 300 µm tip with a 110 µm drug delivery channel and a platinum wire (MEDEL co). In both experiments, a controlled cochleostomy was performed, and the 3 mm insertion depth in basal turn was controlled by CT-scan. Hearing level was evaluated by evoked auditory brainstem potential recordings. Drugs were administered systemically (methylprednisolone, 2mg/kg intraperitoneally), and locally (N-acetylcystein, 10-3 M, osmotic pump connected to the intracochlear drug channel, 7 days).

The main findings were: i) after a cochleostomy without or with a transient (less than ~5 min) array insertion, hearing remained unaltered; ii) after implantation, a hearing loss of ~30dB was observed, which was stable during the 4-week post implantation period; iii) the post implantation induced hearing loss was reduced by ~40% after systemic administration of methylprednisolone; iv) no change in hearing level was noticed after local perfusion of N-acetylcystein.

In conclusion, refinements in cochlear implant array and quality of insertion would reduce the post implantation induced hearing loss in animal models. The "otoprotective" effects of locally applied drugs should be compared with those obtained after systemic administration of corticoids.

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# Smart drilling system for cochleostomy

*P. Brett, D. Proops, A. Reid and C. Coulson – Birmingham, UK*

In this presentation a surgical robotic device is described that is able to discriminate tissue interfaces and other controlling parameters ahead of the drill tip. The advantage in surgery is that tissues at interfaces can be preserved. The smart tool is able to control interaction with respect to the flexing tissue to avoid penetration or to control the extent of protrusion with respect to the position of the tissue. For surgical procedures where precision is required the tool offers significant benefit. The device is easy to set-up and operate, and uses standard drill bits.

The micro-drill has been used to prepare cochleostomies in theatre and was used to remove bone tissue leaving the endosteal membrane intact. This enabled preservation of sterility and the drilling debris to be removed prior to insertion of the electrode. It is expected that this technique will promote preservation of hearing and reduce the possibility of complications. The presentation will describe the device showing the stages leading up to the first clinical investigation.

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# Histological effects of dexamethasone eluting silicone implant in guinea pig cochlea

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## Introduction

There has been a resurgence of interest in directed therapy to inner ear, because indirect, systemic therapy has shown limited success and significant morbidity. Cochlear implants like any other prostheses meant to enter a body organ, induce an inflammatory response. An anti-inflammatory (Dexamethasone) loaded cochlear electrode with the ability of elution, is investigated in guinea pig as an animal model. Material & Methods: Thirty male, white guinea pigs weighed 350-450 g were divided to 3 groups. In the case group, eluted electrode was implanted in cochlea. In the first control group, simple electrode was implanted and in the second control group, only cochleostomy was performed. The inflammatory indices in histological cochlear specimens were analyzed in day 3 and 13. Results: In day three, the specimens of the case group (eluting electrode) showed reduction in macrophages, eosinophils and plasma cells infiltration and fibrosis and increase in capillary formation. These differences were statically significant for capillary and plasma cell ($p<0.1$). The differences in cell infiltration were more prominent in day 13 in all inflammatory indices and capillary formation was significantly reduced in the case group. Conclusion: Histological effects of dexamethasone-eluting cochlear electrode on down regulation of inflammation were shown in vivo which is in favor of the ability of electrode to sustain release of the drug.



## Keywords

Drug delivery, cochlear implant, silicone elastomer, Dexamethasone, inflammatory indices



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# Hearing preservation by means of dexamethasone and correlation with intracochlear tissue growth: one-shot application versus eluting rod

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An increasing number of deaf patients with residual low frequency hearing benefit from the combined electric acoustic stimulation (EAS) via cochlear implant and hearing aid. Especially speech understanding and music appreciation are improved. However, in some cases the residual hearing deteriorates some time after the implantation supposedly due to inflammatory and apoptotic processes. Glucocorticosteroids are known to suppress these processes. On the other hand, they also suppress tissue growth and might therefore delay the healing of the cocheostomy and allow bacteria to enter the cochlea.

Two independent guinea pig studies with two different local glucocoticosteroid application methods are compared regarding the correlation between hearing preservation and tissue growth: a) One shot intracochlear infusion of dexamethasone (24 g) prior to implantation and b) implantation with a drug eluting silicone rods loaded with 2% dexamethasone. Frequency specific CAP- (study a) and ABR- (study b) were performed. Control ears were treated with artificial perilymph (study a) or implanted with non-eluting rods (study b). Cochleae were processed for histology after 3 months (study a) and 1 month (study b) and growth of connective tissue was measured in per cent of total area of Scala tympani.

Results of study a: A one shot infusion significantly reduces hearing loss in the middle and high frequencies during the first month but not after the third month. Study b: Implantation with eluting rods leads to a significant reduction of hearing loss in the middle and high frequencies 1 month post implantation. This effect is still persistent after 6 months. Both studies revealed no correlation between hearing loss and tissue growth.

Despite the differences in design the two studies clearly demonstate the beneficial effect of dexamethasone for hearing preservation. At least with the doses applied here dexamethasone does not suppress tissue growth even after continuous application and is therefore not supposed to suppress healing of cochleostomy.

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# Safety of dexamethasone elution (tissue seal and evaluation at 10%)

*A. Martini – Ferrara, Italy*

Dexamethasone is a common antiinflammatory agent added in cochlear implants to reduce hearing loss due to insertion trauma. We evaluated the safety of eluting silicone rods containing 10% dexamethasone in a guinea pig model. Six animals were unilaterally implanted with dexamethasone eluting silicone rods, six others were implanted with non-eluting rods as controls. Prior to implantation and during the next two weeks hearing audiogram data were acquired by recording compound action potentials with electrodes near the round window. In animals implanted with dexamethasone eluting rods the mean threshold shifts, two weeks after implantation, were 2dB +/- 2dB, vs. 7dB +/-2dB in controls. After two weeks the bullae of each animal were extracted to verify cochleostomy sealing, by paraffin embedding and hematoxilin-eosin staining. Sections were examined for macrophages, percent tissue growth in scala tympani and complete tissue sealing around cochleostomy. Silicon rod samples were also explanted and tested for bacterial contamination. No bacterial contamination nor enhanced number of macrophages were observed in any sample. A slight tissue growth, not significantly different between experimental and control group, was found in scala tympani. According to our results, in the guinea pig model the use of eluting silicone rods containing 10% dexamethasone appears safe as anti-inflammatory slow-release additive in cochlear implants.

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# Conservation of hearing by elution of dexamethasone from a cochlear implant: efficacy & mechanisms

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## Introduction

Inner ear trauma involves an inflammatory response that may be mediated by inflammatory cytokines, e.g. TNFalpha. In vitro studies have demonstrated that TNFalpha kills auditory hair cells via apoptosis. Both dexamethasone (DXM) and dexamethasone base (DXMb) protect auditory hair cells from TNFalpha-induced death. Biorelease DXMb studies have demonstrated the eluted DXMb is an effective otoprotectant agent against TNFalpha ototoxicity. Materials & Methods: Guinea pig model of electrode insertion trauma (EIT)-induced hearing loss; CI electrode blanks with- 1) uncoated; 2) SIBS; and 3) SIBS with DXMb; organ of Corti explants, TNFalpha; DXMb; LY-294002; SH-6; NFkBI peptide; Real time RT-PCR, FITC-phalloidin staining; hair cell counts. Results: In Vivo-Guinea pigs receiving uncoated and SIBS coated CI electrodes experienced 40 to 60 dB SPL hearing loss at 16kHz that translated into a permanent hearing loss while in sharp contrast the animals receiving the CI electrodes coated with SIBS + DXMb had only a minor 5 dB SPL deficit at 1 month post EIT. The otoprotective action of the eluted DXMb also included the lower frequencies, i.e. 1-4 kHz pure tone stimuli. Preliminary observations show a localized inflammatory response present in the scala tympani of both the uncoated and SIBS coated CI electrode animals whereas the SIBS + DXMb CI electrode animals did not have inflammatory cells in their scala tympani. In Vitro- organ of Corti studies have shown that activation of PI3K/Akt & NFkB by DXMb is crucial for DXMb's ability to protect hair cells against TNFalpha ototoxicity. Inhibition of NFkB in TNFalpha/DXMb treated explants prevents DXMb initiated up and down regulation of apoptosis-related genes that are necessary for the otoprotective action of DXMb.

## Conclusions

DXMb eluted from a CI electrode protects the cochlear against EIT-induced hearing loss in our animal model of cochlear implantation. DXMb acts via the cell signaling pathways of PI3K/Akt & NFkB and the activation of NFkB is required for the activation of genes that protect the auditory hair cells against the ototoxicity of TNFalpha. Dexamethasone is an excellent candidate drug for elution from a CI electrode array for the protection of auditory hair cells and conservation of hearing during and after the process of cochlear implantation.

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# Disposable drug delivery catheter for use in cochlear implantation: radiological study in cadaver temporal bones

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## Introduction

Acute drug delivery to the inner ear during cochlear implantation would be best achieved using a disposable catheter designed to enter up to 20 mm of scala tympani. A catheter approach to deliver drugs to the inner ear is even more compelling since in vitro experiments in a cochlear model demonstrate that an unknown quantity of drug delivered at the cochleostomy does not enter the scala during electrode insertion.

## Materials

A conical inner ear catheter was developed and tested in vitro and in situ. The catheter has the same outside dimensions and profile as one electrode used by a CI manufacturer. Regular marking indicate the insertion depth of the catheter. The catheter loaded with a marker solution was inserted in a scala tympani model at several insertion depth and fluid injected. Temporal bones were inserted with the catheter, prior to electrode insertion, through the round window and through a cochleostomy. 10 µL of an iodine solution was injected in the scala tympani at depth of 15 to 20 mm. Four multi slice CT sequences were performed, after catheter insertion, after injection of the small bolus, after removal of the catheter and after electrode insertion.

## Result

In vitro the fluid injected does not travel past the tip of the catheter. Electrode insertion flushes the fluid out and does not carry the marker solution forward. Insertion of the catheter in human temporal bones was a unproblematic. No resistance was met. Insertions depths of 15 to 20 mm were easily achieved. Radiologically, the iodine injected stays in the scala tympani and there were no perforation of basilar membrane.

## Conclusion

Drug delivery during cochlear implantation requires the use of an intra cochlea catheter. A catheter if soft enough can be inserted without trauma to a distance of up to 20 mm.

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# The effect of intracochlear steroids on electrode impedance and hearing preservation in patients submitted to cochlear implant surgery

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## Introduction

Novel indications for cochlear implants, such as Hybrid or partial deafness cochlear implantation, have made the preservation of hearing during surgery a major concern. Various factors such as the survival of bipolar ganglion cells, stable interface between the electrodes and the nerve fibers as well as the prevention of local degeneration may influence cochlear implant results. Electrode insertion trauma can cause injury to the inner ear, alter the mechanical properties and may cause further degeneration of hearing or total hearing loss. Impedance measurements are associated to fluid and tissue resistance interacting with the electrode chain. These measurements verify adequate function of the unit as well as confirm an open or a short circuit of the electrodes. The use of intracochlear corticosteroids may decrease the inflammatory reaction and fibrosis and as a result reduce the impedance of the electrodes due to the approximation of the electrode array to the modiolus and consequently the nerve fibers. Steroids may also reduce the stress caused by trauma due to the introduction of the electrodes and consequently reduce apoptosis. Cochlear protection via an atraumatic surgery, prevention of the inflammatory process, oxidative stress reaction and apoptosis prevention may possibly meliorate clinical results. The challenge is identifying drugs that are effective at protecting the cochlea as well as finding safe ways to introduce these substances into the cochlea, without augmenting the risk of infection and obtaining better the clinical results.

## Objectives

To evaluate the influence of intra cochlear steroids on electrode impedance measurements as well as the preservation of hearing in patients undergoing cochlear implant surgery.

## Methods

Prospective study of one hundred and twenty eight patients submitted to cochlear implant surgery divided into 4 groups. Group I, the control group, consisted of 76 patients submitted to CI surgery using traditional surgical technique; Group II had 12 patients submitted to CI surgery using "soft surgery" technique; Group III had 20 patients submitted to CI surgery using "soft surgery" technique and 3 µl injection of intra-cochlear triancinolone; Group IV had 20 patients submitted to CI surgery using "soft surgery" technique and 3 µl injection of intra-cochlear methyl-prednisone. Perioperative impedance telemetry was performed, as well as on the day of activation, three, and six months following implantation.

## Results/Discussion

Before the first activation, impedance of the electrodes increased slightly and decreased with time in all four groups. Contrary to what was originally anticipated, the two steroid groups (III and IV) had higher global impedance measurements than the two non-steroid groups (I and II). The two groups using intra-cochlear steroids had less uniform impedance measurements throughout the cochlea, presenting statistically significant lower impedance measurements of the basal electrodes. This became more apparent at 6 months after surgery.

## Conclusion

Contrary to what was postulated, patients utilizing intra-cochlear steroids presented higher impedance measurements in general than those that did not, however did influence positively the impedance levels in the basal region of the cochlea.

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# Inner ear sustained release of dexamethasone

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The thermo-reversible triblock copolymer poloxamer 407 was investigated as a drug delivery vehicle for micronized dexamethasone into the middle and inner ears of guinea pigs. Following intratympanic injection, significant drug levels within the perilymph were observed for at least 10 days, while systemic exposure was minimal. The sustained release kinetics profile could be significantly modulated by varying the concentrations of poloxamer and dexamethasone. Assessment of auditory function revealed a small transient shift in hearing threshold, of conductive nature, that resolved itself within a week. No significant histological changes of the round window membrane or cochlea could be noted. Poloxamer 407 thus represents an effective and safe delivery system to achieve sustained release of dexamethasone to the inner ear.

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# Otoprotection with the JNK ligand AM-111

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Permanent sensorineural hearing loss may be prevented by pharmacological interventions prior to acute cochlear insults or during a short therapeutic time window thereafter. While corticosteroids or vasodilators have frequently been used to provide acute otoprotection, scientific evidence for their efficacy remains mixed. Based on the increasing understanding of the pathological mechanisms of sensorineural hearing loss, newer approaches are seeking to intervene with novel therapeutics more specifically therein.

AM-111 is a cell-permeable peptide that selectively blocks JNK MAPK mediated apoptosis of stress injured hair cells and neurons in the cochlea. The compound further has anti-inflammatory properties and attenuates viral replication. AM-111 showed significant otoprotective effects in animal models of noise trauma, ototoxic medication, CI electrode insertion trauma, cochlear ischemia, acute labyrinthitis and semicircular canal transection in the presence of P. aeruginosa. AM-111 is being developed as a treatment for acute sensorineural hearing loss by way of intratympanic injection. A phase I/II study in Germany with victims of acute acoustic trauma showed that AM-111 was well tolerated in humans. A large phase IIb clinical trial was initiated in 2009 in Germany and Poland to evaluate AM-111's efficacy in the treatment of sudden deafness and acute acoustic trauma.

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# Intratympanic steroid therapy using the Silverstein Microwick™ for refractory sudden sensorineural hearing loss increases speech intelligibility

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## Objective

Determine if delivery of methylprednisolone to the round window can improve hearing and in particular speech intelligibility after failure of conventional treatment for sudden sensorineural hearing loss administered for 10 days after the onset of the hearing loss.

## Intervention

A Silverstein microwick™ was placed under local anesthesia and endoscopic control in the round window niche allowing self-administration of methylprednisolone twice a day for 4 weeks. Treated patients were compared to a control group composed of similar patients, treated with the same systemic regimen but who did not receive local therapy.

## Results

Of the 26 patients enrolled in this non randomized retrospective study, 14 patients (54%) showed an improvement of the PTA and 12 remained unchanged. The 14 patients that responded to treatment demonstrated a significant (mean 25.86 ± 9.73 dB) improvement in the PTA. The articulation function, which was calculated from speech audiogram curve and is defined as the mean speech discrimination score obtained at 40dB, 55dB and 70dB, improved of 35.28 ± 27.44 % for 18 patients, demonstrating a significant increase of speech intelligibility. For the 12 patients with an unchanged PTA, 9 showed an increased speech intelligibility. Patients of the control group did not show any improvement of the PTA nor in speech intelligibility.

## Conclusion

Local administration of steroids to the inner ear through the round window route improves hearing and speech intelligibility in patients after failure of conventional therapy.

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# siRNA delivery to the mouse cochlea: a comparison of three techniques

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Delivery of short interfering RNA (siRNA) to the cochlea could provide an important therapeutic and investigative tool, not only for hearing preservation, but also potentially hearing restoration as new molecular therapies emerge. A major limitation to this technology has been obtaining efficient delivery to cells within the cochlea. Currently, it is unknown whether delivery of siRNA can effectively transfect cochlear cells in mice, much less suppress gene expression. To address this, we tested three delivery methods to the mouse cochlea and compared their effectiveness by histology and quantitative PCR (qPCR), using fluorescently tagged and targeting siRNA against an organ of Corti expressed gene. We found that perfusion through the round window membrane (RWM) caused sufficient auditory disruption to limit functional application and was not effective by histology. Application to the RWM and cochleostomy to both the basal and 2nd turns better preserved hearing, however the RWM application was ineffective by histology and qPCR. Cochleostomy to the basal turn was found to be the superior method of siRNA delivery to the spiral limbus, spiral ligament, Reissner's membrane, basilar membrane, stria vascularis, and cochlear walls but was ineffective at reducing an organ of Corti expressed gene. This study advances upon the technique to target specific cells within the mouse cochlea and details specific limitations that must be overcome to adopt these techniques for widespread use.

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# The use of nanotechnology for cochlear regeneration

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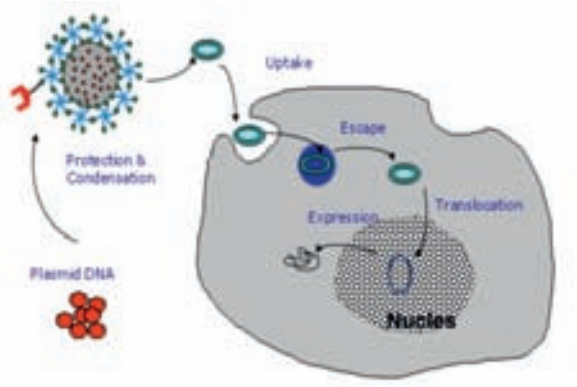
Following the loss of sensory cells of the inner ear, the de-afferented peripheral processes of the auditory nerve will degenerate. In time the spiral ganglion cells (SGCs) of the nerve and central projections also die. The death appears to be due to apoptosis from loss of survival factors (largely neurotrophins) provided by the normal inner ear. The primary obstacles of inner ear drug/gene therapy is the lack of vectors that are safe, efficacious, cell/tissue-selective and able to enter the nucleus to activate the repair mechanisms. Data from animal and human studies now unanimously support the view that neurotrophin treatment extends the survival and excitability of the remaining auditory nerve following deafness.

It has been recently documented that Math-1 gene also in mammalian inner ear can transform the supporting cells to outer hair cells. The normal development of an organism is the result of an integrated network of differentiation programs and signaling pathways that control cell cycle exit. The timely ordered expression of tissue-specific genes is executed by transcription factors of the basic helix-loop-helix (bHLH) family. Following binding to Id (Inhibitors of DNA binding and differentiation) proteins, bHLH cannot contact DNA, and the result is loss of transcriptional activity and inhibition of differentiation. Thus, Id proteins are natural inhibitors of bHLH-mediated transcription. One alernative way to abate the inhibition is to use shRNA.

The cell entry and membrane trafficking is one limiting factor in drug/gene incorporation process. At present it seems that the nano-carriers are capable of using caveolin and integrin mediated clathrin pathways in addition to non-specific macro-pinocytosis to pass round window membrane and in cell entry. These processes can be facilitated by using viral TAT-protein for enhancing the incorporation process. The critical size for cellular trafficking seems to be 80 nm of particle size but for nuclear entry it must be smaller and causes challenges for gene delivery.



In the Nanoear project we have incorporated the Math-1 plasmid, and Id-shRNA plasmid into lipid core nanocapsules, silca, polylycin, lipoplexes and chitosan nanoparticles and in hydrogel. The preliminary results indicate that the transfected cells are expressing the reporter gene (GFP) and math -1 gene. Further we have demonstrated that in the cochlear nerve precursor cells can be stimulated to differentiate with BDNF and they form new SGCs. We have studied the passage of nano-carriers through the rat and human round window membrane. For cellular targeting and in inoculation process, the transfection rate is in vivo experiments still relatively low, and more efforts have to be made to improve the transfection with synthetic vectors by enhancing the inefficient migration of DNA through cellular membrane and translocation across nuclear pore complexes. The application of the nano-carriers on the round window membrane indicates that depending on type of nanoparticle different migration pathways are employed and optimal carriers can be designed depending on cargo. The use of nanoparticle as drug/gene carrier is especially attractive in conjunction with cochlear implantation or even included in the implant as a drug/gene reservoir.

www.nanoear.org. NANOEAR; 3g-Nanotechnology based targeted drug delivery using the inner ear as a model target organ. EU-Contract number:026556-2

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# Inner ear stem cells from postmortem tissues of rats and humans

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## Background

Stem cells, as recently described in the inner ears of mice, would be primary candidates for hair cell regeneration. However, in humans, those stem cells have not yet been identified.

## Objective

To prove the existence of stem / progenitor cells in the human inner ear.

## Methods

The protocol has been approved by the local ethical board. Autopsy-derived human temporal bones are dissected to isolate progenitor or stem cells. The progenitor/stem cells are propagated and differentiated into inner ear cell types such as hair cells, supporting cells and spiral ganglion neurons using previously established methods.

## Intermediate results

Sphere-forming progenitor cells have been successfully isolated from (n = 15) postmortem utricles of adult humans, but not yet from the cochlea. Propagation was found to be challenging with the spheres of human origin and was successful only until the fourth generation. Sphere-derived cells of human origin were successfully differentiated into hair cell marker (Myosin VIIa, rhodamin-conjugated phalloidin) positive cells and neuronal marker (TUJ) positive cells.

## Intermediate conclusion

Postmortem human vestibular tissues are a source for isolating viable and functional inner ear progenitor/stem cells for up to three days postmortem. Longer postmortem intervals lead to an increased risk for infections. Propagation of spheres was successful only until the fourth generation. Sphere-derived progenitor/stem cells were successfully differentiated into hair-cell marker positive cells and neuronal marker positive cells, although in small numbers only and too low for a meaningful quantification.


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# Enhanced survival of spiral ganglion cells after cessation of treatment with brain-derived neurotrophic factor in deafened guinea pigs

*M. J.H. Agterberg, H. Versnel, W. Grolman, J. C. M. J. de Groot, S. F.L. Klis – Utrecht, Netherlands*

Exogenous delivery of neurotrophic factors into the cochlea of deafened animals rescues spiral ganglion cells (SGCs) from degeneration. To be clinically relevant for human cochlear implant candidates, the protective effect of neurotrophins should persist after cessation of treatment and the treated SGCs should remain functional. In this study the survival and functionality of SGCs were investigated after temporary treatment with brain-derived neurotrophic factor (BDNF). Guinea pigs in the experimental group were deafened and two weeks later the right cochleae were implanted with an electrode array and drug-delivery cannula. BDNF was administered to the implanted cochleae during a four week period via a mini-osmotic pump. After completion of the treatment the osmotic pumps were removed. Two weeks later the animals were sacrificed and the survival of SGCs was analyzed. To assess the functionality of the auditory nerve, electrically evoked auditory brainstem responses (eABRs) were recorded in awake animals throughout the experiment. BDNF treatment resulted in enhanced survival of SGCs two weeks after cessation of the treatment and prevented the decreases in size and circularity that are seen in the untreated contralateral cochleae. The amplitude of the suprathreshold eABR response in BDNF-treated animals was significantly larger than in deafened control animals and comparable to that in normal-hearing control animals. The amplitude in the BDNF-treated group did not decrease significantly after cessation of treatment. The early eABR latency in BDNF-treated animals was longer than normal and comparable to that in deafened control animals. These morphological and functional findings demonstrate that neurotrophic intervention had a lasting effect, which is promising for future clinical application of neurotrophic factors in implanted human cochleae.

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# Ephrin/Eph mediated spiral ganglion axon guidance: potential implications for cochlear implants

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Studies with perimodiolar electrodes in both animals and humans have demonstrated lower evoked auditory brainstem response thresholds. Nevertheless, these apparent physiological benefits have not definitively translated to improved speech perception performance. However creating a contact mediated stimulation paradigm may better approximate the normal physiology and discrete stimulation of spiral ganglion neurons to enable improved speech recognition and sound quality for implant users. The molecular cues that guide spiral ganglion neurons to appropriate targets to establish tonotopic innervation are poorly understood. An understanding of these mechanisms would be essential in developing strategies to guide spiral ganglion axons to appropriate electrodes on an cochlear implant array for contact mediated stimulation in a manner that maintains precise innate frequency mapping.

Ephrins are membrane bound axon guidance molecules that bind to Eph receptors to guide growing axons to appropriate synaptic targets. Previously, we and others have shown that these proteins are expressed in the peripheral and central auditory system of chicks and rodents. To determine functional consequences of ephrin/Eph signaling in the mammalian cochlea, we have used lipophilic dyes to label the spiral ganglion nerve fibers innervating the organ of Corti in early post natal EphB1, B2, B3, and B6 quadruple knockout mice. Analysis demonstrated that deletions of EphB receptors resulted in aberrant innervation of the organ of Corti. In addition, we have performed in vitro experiments that demonstrate that EphB2 inhibits the outgrowth of spiral ganglion neurites in culture. These results imply a role for EphB receptors in establishing and fine tuning cochlear innervation patterns during development and suggest the potential use of ephrin/Eph signaling in strategically directing outgrowth of spiral ganglion neurites toward specific electrodes of a cochlear implant array.

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# Notes

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