



T. Lenarz



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Thomas Lenarz

- 1987** Samuel Moos Award of the Scientific Academy at the University of Heidelberg for the best thesis submitted to the Medical Faculty
- 1987** Habilitation at the University of Tübingen
- 1988 – 1989** Postdoctoral Research Fellowship at the University of California San Francisco
- since 1993** Professor and Chairman of the Department of Otolaryngology at the Medical University of Hannover
- since 2002** Speaker of the *Sonderforschungsbereich 599* (collaborative research initiative) on biomaterials at MHH

Timo Stöver

- 1995** MD thesis at the Institute for Biophysical Chemistry of the MH Hannover (Chair: Prof. Dr. G. Maass), on the topic of restriction enzymes
- 1998** Research scholarship of the Alexander von Humboldt-Foundation (Feodor-Lynen-Research Scholarship)
- 1998 – 2000** Postdoctoral Research Fellowship at the University of Kresge Hearing Research Institute Ann Arbor/Michigan (USA) on the topic of gene transfer / gene therapy, gene expression and regulation of neurotrophic factors in the inner ear
- since 2000** Group leader
- 2001** Habilitation in Otolaryngology

Objects of Research

The development of the cochlear implant extends back over a period of almost thirty years. These devices are at present the most well-established neurobionic prostheses, and their clinical application is now a standard procedure in the treatment of deafness. In particular, surgical implantation of congenitally deaf children now constitutes the gold standard in the treatment of this patient group, and the implant enables some 80 % of the implanted children to attend mainstream schools. Nevertheless, interindividual variability in the success of cochlear implantation is very high, so that, despite the procedure being well established and having a high general acceptance rate, there is considerable scope for improvement in its effectiveness. Based on current knowledge, the cause of the considerable variability in the success of cochlear implantation lies in the variable number of preserved neurones in the auditory nerve (spiral ganglion cells), which must therefore be seen as the limiting factor determining the effectiveness of electrical stimulation by the implant. To develop new technical and therapeutical strategies to increase the effectiveness of cochlear implant is the driving force of our research.

1. Pharmacological therapy of the inner ear

In the recent past a number of pharmacological substances have been identified which act on spiral ganglion cell populations as so-called "survival factors". These substances, also termed neurotrophins, offer considerable potential in terms of local release within the inner ear and the resulting increase in spiral ganglion cell density, as well as the fact that they can be made use of electrophysiologically by cochlear implants. Among the neurotrophic factors most thoroughly tested to date is GDNF ("glial cell line-derived neurotrophic factor"), which was originally isolated from the dopaminergic cells of the brainstem. This factor exhibits strongly protective properties in relation to spiral ganglion cells, protecting them from degeneration as a result of deafness through loss of hair cells. This factor also exerts a protective effect on hair cells, countering not only the ototoxic effects of aminoglycosides but also exposure to noise. Establishing the molecular basis to the mode of action of this neurotrophic factor and using animal experiments to determine the effectiveness of a combined strategy – both electrical stimulation of the spiral ganglion cells and concurrent administration of GDNF – are the main emphases of the EU-funded experimental work being carried out within the MHH's Department of Otolaryngology.

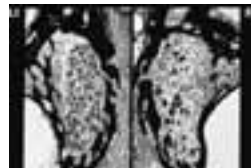


Figure 1: Effect of neurotrophine (GDNF) on spiral ganglion cells in vivo; untreated control shown on the right. Loss of spiral ganglion cells (SGC) six weeks after onset of deafness. Left: clear preservation of SGC following local administration of nerve growth factors.

2. Development of a Drug-Delivery Inner Ear Electrode (Neural Prosthesis)

The onset of deafness and the associated destruction of the hair cells inevitably leads to secondary degeneration of the spiral ganglion cells. This degeneration is the critical element affecting the capacity of the auditory

nerve to be electrically stimulated by the cochlear implant. In terms of improving the effectiveness of cochlear implants, the aim of international research is, therefore, to preserve the population of spiral ganglion cells. By increasing the population of spiral ganglion cells with the application of neurotrophic factors and improving the electrode-nerve interface, the selectivity of electrical stimulation can be enhanced, electrical impedance reduced and, ultimately, an increase in speech understanding is achieved. The project's overriding objective consists in the design and application of a new generation of cochlear implants in which the effectiveness of previous devices is considerably enhanced by combining electrical stimulation and concurrently releasing neurotrophic factors. For this purpose a human implant is currently being developed. An integral part of the new implant system will be an electrode pump mechanism which makes possible the controlled release of neurotrophic factors, even over extended periods, without influencing the electrical stimulation properties of the implant.



Fig 2: Example of a modified cochlea implant system: experimental device with a blue dye being pumped through a channel inside the electrode.

3. Neurite targeting with cochlear implant technology

Research has also demonstrated that the benefits of the cochlear implant directly depend, in part, on the extent to which excitable auditory nerve fibres have survived. Following deafness the peripheral processes of the auditory nerve degenerate. This is followed by a slow degeneration of the cell bodies (spiral ganglion cells, SGC) of the auditory nerve and their projection into the auditory brainstem nuclei. In humans it is suggested that the presence of peripheral processes and a greater population of auditory nerve neurons can lead to: lower thresholds, greater dynamic range of response, greater selectivity in activation of the auditory brainstem structures, and greater speech perception abilities among recipients of a cochlear prosthesis. Thus, a cochlear implant prosthesis would benefit from an optimized electrode as there would be closer contact between the nerve and the electrode, with lower energy consumption and better spatial resolution of the excitation. The outgrowing, projecting dendrites are an excellent instrument for contacting (potentially in a targeted fashion) the electrode carrier surface, so that an almost perfect nerve-electrode interface can be generated here. At present we determine the most effective concentration and combination of NTF to promote neural outgrowth, to finally direct the dendrites onto the electrode array.

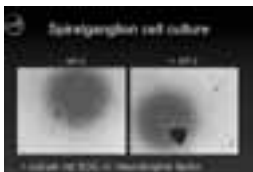


Fig 3: Effects of neurotrophic factors in vitro. Outgrowth of spiral ganglion cells from culture rat spiral ganglion cells.

4. Characterization of gene expression in the inner ear

The molecular biological investigations initially focused on characterizing the changes in gene expression induced in the rat as a result of experimental deafening. The effects on the previously described neurotrophic factors and their receptors are of great interest, since this body of work is useful in terms of indicating further potential candidates for local inner-ear therapy, or possible combinations of several factors for this purpose. Experimentally this work is based on studies using gene arrays, RT-PCR and immunohistochemical experiments. The results obtained to date reveal a multitude of genes that were previously unknown for the inner ear and how they are regulated following the onset of deafness. The relevant results have been published internationally (Cho et al., 2002) and presented at international conventions.

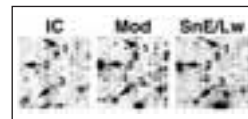


Fig 4: Gene array studies on the inferior colliculus (IC), modiolus (Mod) and sensorineural epithelium / lateral wall of the cochlea (SnE/Lw) in rats. Arrow 1: Glutamyl aminopeptidase (regulates the renin-angiotensin system in the CNS and possibly also in the stria vascularis. Arrow 2: Myelin P0 / Arrow 3:

Peripheral myelin protein 22; known expression in the peripheral nervous system (not detected in IC), clinical significance established for the Charcot-Marie-Tooth syndrome (motor degeneration and hearing loss).

Selected Publications

- [1] Kawamoto K, Yagi M, Stöver T, Kanzaki S, Raphael Y. Hearing and hair cells are protected by adenoviral gene therapy with TGF-beta1 and GDNF. **Mol Ther.** 2003;484-92.
- [2] Paasche G, Gibson P, Averbek T, Becker H, Lenarz T, Stöver T. Technical report: modification of a cochlear implant electrode for drug delivery to the inner ear. **Otol Neurotol.** 2003;24:222-7.
- [3] Stöver T, Nam Y, Gong TL, Lomax MI, Altschuler RA. Glial cell line-derived neurotrophic factor (GDNF) and its receptor complex are expressed in the auditory nerve of the mature rat cochlea. **Hear Res.** 2001;155:143-51.
- [4] Stöver T, Gong TL, Cho Y, Altschuler RA, Lomax MI. Expression of the GDNF family members and their receptors in the mature rat cochlea. **Brain Res Mol Brain Res.** 2000; 76:25-35.
- [5] Stöver T, Yagi M, Raphael Y. Transduction of the contralateral ear after adenovirus-mediated cochlear gene transfer. **Gene Ther.** 2000;7:377-83.

Group Structure

Department chair: Thomas Lenarz
 Group leader: Timo Stöver
 Senior scientists: Günter Reuter
 Doctoral fellows: Kirsten Wissel, Uta Reich, Heike Rieger
 Graduate students: Patrick Wefstaedt
 Technicians: Peter Erfurt

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