Co-funded by
the European Union

nanotechnology
based cochlear
implants

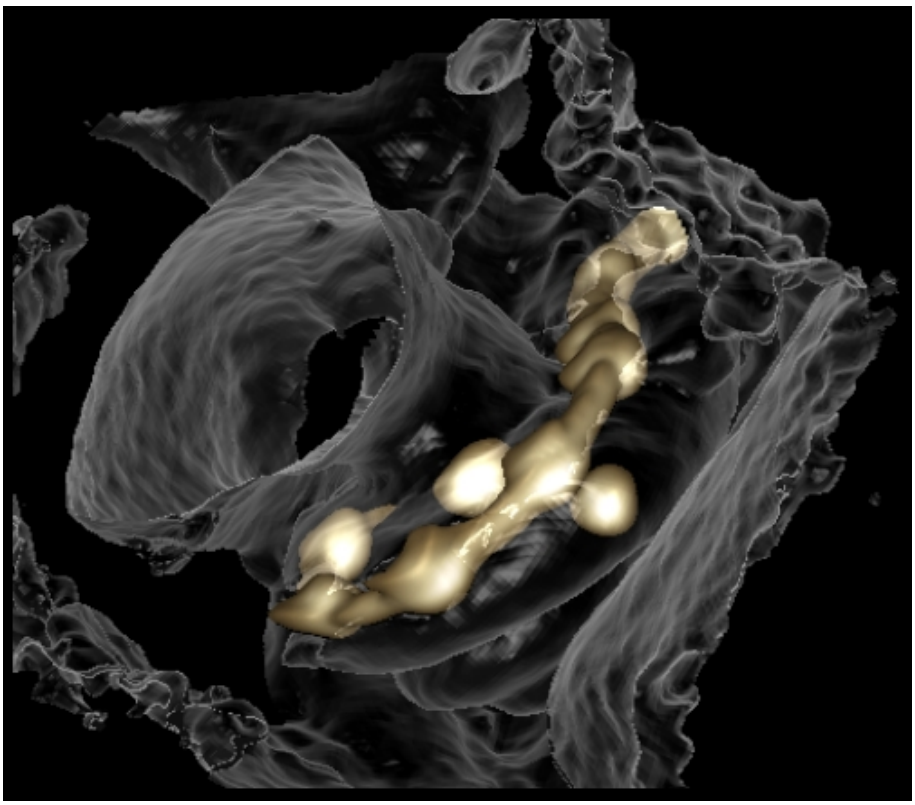
NANOCI

Nanotechnology based cochlear implant with gapless interface to auditory neurons

Grant Agreement No.: 281056

First Periodic Report
1 September 2012 - 28 February 2014

Publishable Summary



Functional hearing can be restored in the majority of deaf patients using a neuroprosthesis called cochlear implant (CI). However, some limitations remain, which are mainly caused by the anatomical gap between auditory neurons and the electrode array in the cochlea. NANOCI aims at improving CI performance by creating a gapless human-machine interface in the inner ear. Methods of biomedical engineering, regenerative medicine and nanotechnology are used in concert to achieve this ambitious goal.

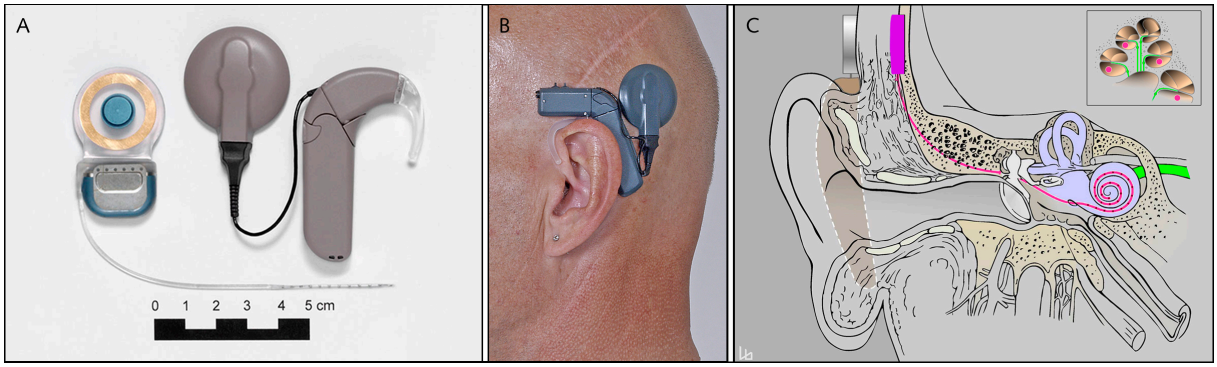


Figure 1. MEDEL cochlear implant system with implantable stimulator/receiver unit and externally worn speech processor (A). Clinical CI system with behind-the-ear speech processor (B). Schematic view with CI electrode array (pink) inserted into the cochlea of the inner ear for direct stimulation of the auditory neurons (green).

The concept

Over 60 million individuals in the EU suffer from hearing loss with its restrictions in quality of life and consequences for professional and private development. About 44 million individuals are significantly handicapped and require some sort of treatment. For mild to moderate forms, conventional hearing aids alleviate the communication problems. In severe forms of hearing loss and deafness, the auditory function can only be restored by a neuroprosthesis, called cochlear implant (CI, Fig. 1), which functionally replaces lost inner ear sensory cells by directly stimulating the auditory nerve. By using a CI, formerly deaf subjects or deaf-born children can achieve functional hearing and learn to communicate with speech. Over 200'000 devices are already in use worldwide.

Despite the success, there is a substantial variability of performance across users of cochlear implants. It is generally acknowledged, that the major bottleneck for optimal stimulation is the **anatomical gap** between the electrode array and the peripheral processes of the auditory nerve in the cochlea (Fig. 2D). As a consequence, current devices **consume high amounts of electrical energy** while having a **low specificity of neuronal stimulation**, resulting in suboptimal sound quality and variability of speech understanding. The high energy consumption is one of the main factors slowing down the development of fully implantable systems, which would have several advantages such as usability for small children, invisibility, general ease of use, reliability or hearing while swimming or sleeping. Additionally,

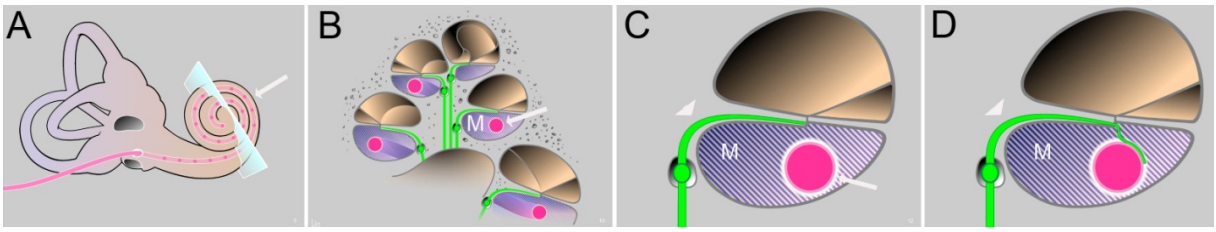


Figure 2. The main goal of the NANOCI project is to eliminate the anatomical gap between the intracochlear electrode array (arrow in Figs. A-D) and the peripheral processes of the auditory neurons (arrowheads in Figs. C, D). The nerves will be attracted through surface release of growth factors from the array (arrow in Fig. C), supported and guided through the scala tympani using a neurotrophic nanomatrix (M) and permanently locked on the array through nanostructuration of the surface (D).

the **energy consumption generates costs** of several hundred Euros per implant per year for disposable or rechargeable batteries.

It is generally acknowledged that eliminating the gap between neurons and electrode array would greatly improve efficiency of auditory nerve stimulation. Physically moving the device closer to the neurons remains impractical and potentially traumatic to cochlear tissues. There remains the other option, to **attract the peripheral processes of the auditory nerve towards the electrode array**.

We intend to **design a novel neuroprosthesis**, which **permanently eliminates the gap** between the electrode array and the auditory neurons in the cochlea (Figure 2).

The end point of the NANOCI project is an animal-grade, multichannel, bidirectional cochlear implant with a gapless interface to auditory nerve endings which is ready for a more specific, energy-saving and cost-effective neural stimulation based on new coding strategies.

Achievements in the first period

Nanomaterials, compounds and nanostructurization methods

In order to attract/guide towards and permanently lock peripheral nerve processes of auditory neurons on the CI electrode array, several materials have to be selected, modified or newly developed. The materials are tested and selected in appropriate structural/chemical assays and ultimately, bioassays.

The initial attraction of nerve fibres shall be induced by the soluble brain derived neurotrophic growth factor (BDNF) or a biomimetic analogue. Because BDNF is difficult to handle, expensive and of short biological half-life, analogues with better properties are of key importance for the project. From a pool of 17 literature-derived or de novo developed analogue candidates, 3 promising candidates have been selected and are now further developed in the second period. In parallel, a model to simulate diffusion of active compounds from reservoirs on the array surface has been created taking into account size of compounds, size of reservoir pores and properties of target liquids.

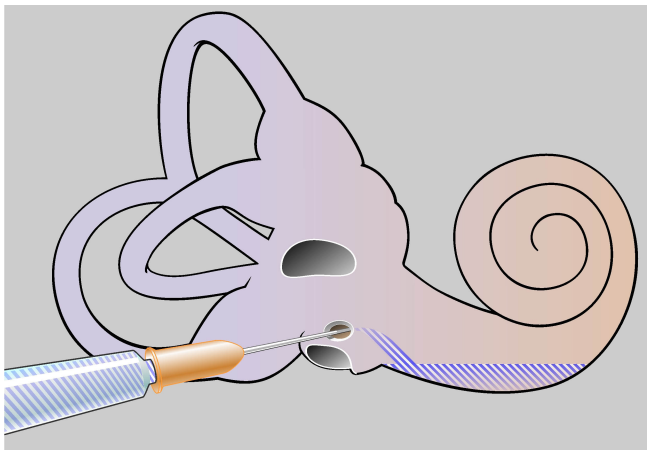


Figure 3. The physico-chemical properties of the nanomatrix need to be compatible with fluid injection and a subsequent gelation and stiffening process within the inner ear.

To overcome the fluid-filled space between the original position of the nerve fibres and the CI array, a matrix has to be provided to the nerves, which is permeable for neurotrophins and gives adequate structural support for the growth cones to crawl along (Fig. 3). From a pool of 9 commercially available gel-like matrix candidates, one promising matrix candidate with adequate physico-chemical and biological properties has been selected. In a second step, the selected, commercially available gel matrix has been resynthesized to enable further biofunctionalization.

To stably lock nerve endings on the surface of the electrode array, to maximize electrical conductance and to minimize the risk for bacterial colonization, the electrode pads and the remaining surface have to be modified at the micro- and nanoscale (Fig. 4). Innovative carbon-nanotube-based filled polymer-composites have been developed and tested for coating of the electrode pads, the actual interface between the nerve endings and the array. First tests revealed promising effects on electrical properties. In parallel, ion beam lithography and sonochemistry

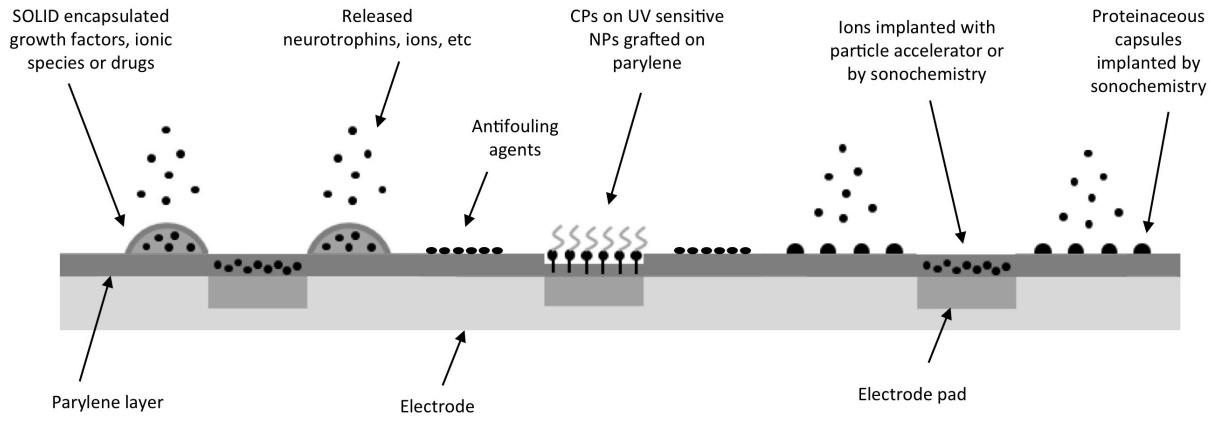


Figure 4. Overview of nanostructurization technologies applied to the CI electrode surface 1) to release neurotrophic factors from the surface, 2) to lock neurons on and to improve electrical conductance of electrode pads and 3) to create antifouling sites. SOLID = patented solid on liquid technology for encapsulation of liquids under a parylene membrane. NPs = Nanoparticles.

have been adapted to create sites for nerve docking and antimicrobial activity on planar and curved surfaces. Whereas ion implantation did not yet lead to preferred neural docking sites, implantation of antibacterial nanoparticles by sonochemistry proved successful to create antimicrobial sites, which was verified for different compositions and for different strains of bacteria relevant in the context of cochlear implantation.

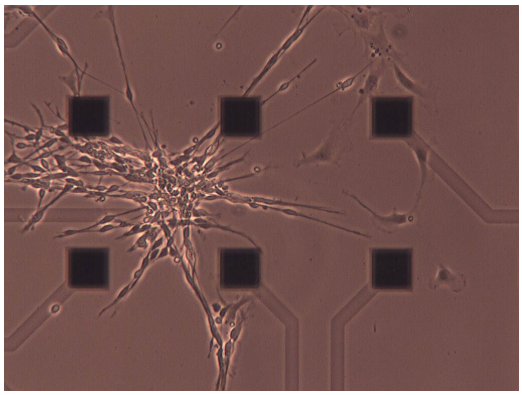


Figure 5. Human auditory neurons cultivated on a Multi-Electrode Array (MEA), which allows for physiological stimulation and recording of neuronal activity in vitro. Each of our MEAs features 64 channels, where activity can be recorded separately and simultaneously.

Modelling, coding & information transfer

If all technical and biological challenges can be overcome and the NANOCI-concept proves to be feasible in vivo, stimulation strategies to fully exploit the theoretical advantages of the gapless, bi-directional interface need to be at hand. To this end, a model of the NANOCI project has been created in vitro, which allows to study response profiles of auditory neurons in dependence of the distance between auditory neurons and stimulating electrode and in dependence from various stimulation parameters. We have been successful, to cultivate and record from auditory neurons on Multi Electrode Arrays (MEAs), which have been redesigned to answer questions with relevance for the NANOCI project. In parallel, a theoretical model of the auditory nerve is being created, which allows for anticipating the stimulation from a gapless, NANOCI-device (Fig. 5). The model takes into account the read out of the MEA experiments, which are done on real neurons. Finally, we work on improving the bi-directionality of the implant through implementing new and updating existing sensing capabilities taking into account the gapless interface.

Bioassays and biocompatibility of nanomaterials

For testing and selecting compound and material candidates, bioassays play a crucial role in the NANOCI project. The main assay to identify compounds and nanomaterials with neurotrophic activity is the neurite outgrowth assay based on mouse auditory neurons (Fig. 6). To reduce and replace animal experiments as much as possible and for early stage testing in the human context, bioassays based on human auditory neurons derived from donated surgical and post-mortem inner ear specimens have been successfully established after full approval by local ethical authorities and are currently further developed. The human bioassays are reserved for validating the most promising candidates selected in the murine bioassays. In addition, special emphasis has been placed to minimize and exclude toxic effects of nanomaterials produced for the project. For this, appropriate toxicity assays based on cell lines are used, which are fully in line with the latest and highest published standards. Similarly, antimicrobial bioassays with the most common bacteria strains

with relevance for the NANOCI project have been established and validated in the first period.

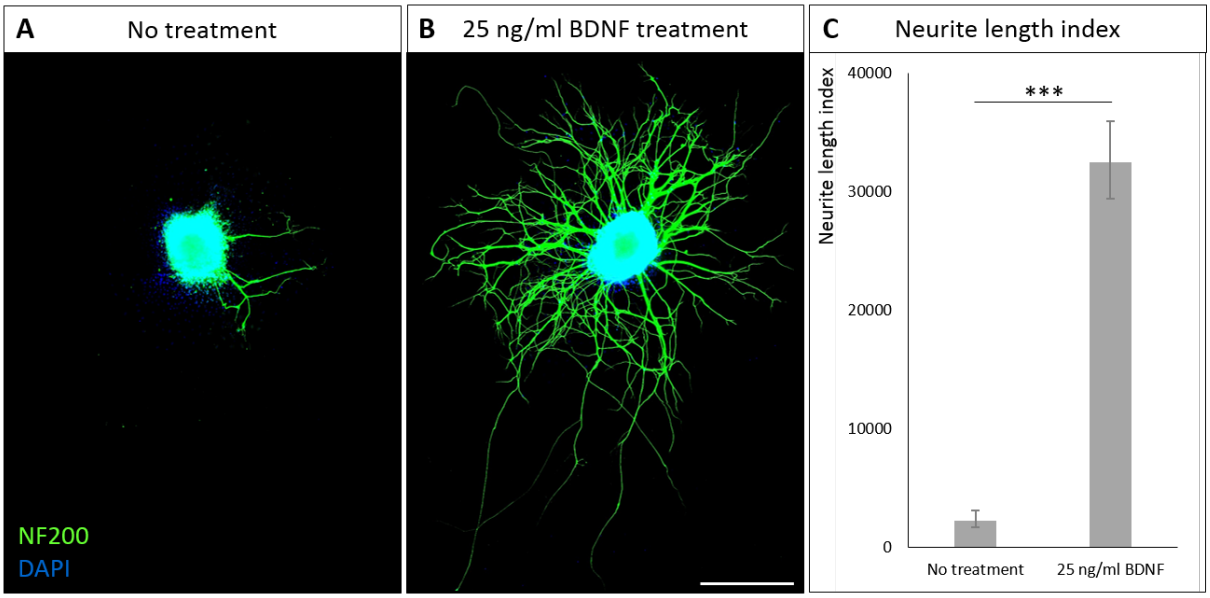


Figure 6. To visualize neurite outgrowth from mouse spiral ganglion explants, neurites were labeled using an antibody against neurofilament 200 (NF200, green). Nuclei were stained using DAPI (blue). (A) Untreated control explants with few and short, outgrowing neurites. (B) Spiral ganglion explants with numerous and long, outgrowing neuritis after treatment with 25 ng/ml brain-derived neurotrophic factor (BDNF). (C) A modified Sholl analysis was used to determine a neurite length index representing a quantitative measure of neurite outgrowth. BDNF-treated explants had a much higher neurite length index compared to untreated controls; the difference was statistically significant (***; p-value < 0.001). Scale bar: 500 µm

Imaging

Whereas magnetic resonance imaging (MRI) is used to understand the release dynamics of compounds and nanomaterials introduced into the cochlea, cone beam computerized tomography (CBCT) is crucial to visualize and understand the anatomical position of the nanoCI-electrode array and the biomorphological changes inflicted by it's presence in the 3D context of the inner ear (see figure on the cover page). But clinically available scanners do not provide a sufficiently high resolution for the needs of the NANOCI project. This issue has been addressed with manufacturers and significant progress has been achieved.

Pilot animal grade NANOCI

The ultimate multicomponent validation of the concept and the assembled product will be obtained in a series of animal experiments, where a pilot, animal-grade nanoCI-device will be surgically implanted into deafened guinea pigs. Thorough preparations have begun on the production and testing side in order to successfully conclude the ultimate multicomponent validation at the end of NANOCI.

Conclusion

The NANOCI project has been progressing according to plan in the first period and many important issues have been solved. However, more challenges need to be overcome in the second period before a judgment on the feasibility of the concept can be delivered. Independent of the final outcome, the scientific and personal interactions have been highly interesting and satisfying for the consortium partners. We aim for conserving and further developing this positive spirit until the hopefully successful completion of NANOCI.

Public website:
http://www.nanoci.org

Coordinator contact:

PD Dr. med. Pascal Senn
Inselspital
Universität Bern

Phone: +41 (0) 22 372 82 47
E-mail: pascal.senn@insel.ch