Corroborating micro-CT and histological data to understand the biological response to cochlear implantation at the electrode-tissue interface and the implications for hearing performance

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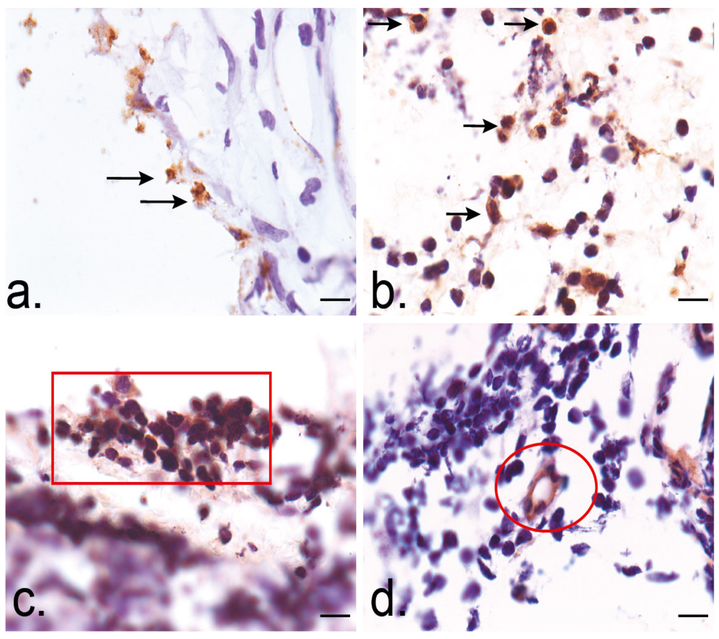
Introduction

Cochlear implants are prostheses which restore hearing by replacing the function of damaged sensory cells in the cochlea. Electrodes directly stimulate neurons of the auditory nerve which relay sound information to the brain, where it is perceived. Despite the success of cochlear implants, some people experience poor hearing outcomes with their implants. These are not due to the implant but are likely due to the biological response at the electrode-tissue interface. As availability of human tissue to investigate the tissue response to cochlear implantation is limited, there is need for an effective relevant *in vivo* model to study the interface. We are establishing a mouse model for cochlear implantation. We are using μCT and 3D X-ray histology to investigate the response at the electrode-tissue interface with the aim of understanding how the tissue response to the array may alter stimulation of the auditory system and consequently alter hearing performance.

The clinical challenge



Evidence of an ongoing fibrotic response in tissue isolated from an implant after surgical removal. Tissue labelled immunohistochemically. a. CD68 (macrophages), b. Ki67 (proliferating cells), c. CD3 (T cells), d. VEGFR2 (proliferating blood vessels).
Scale bar = 10 μm

Insertion of an electrode array into the cochlea elicits an immune response. This is part of the wound healing process - consisting of inflammation, proliferation and remodeling. In some cases exuberant unresolved wound healing appears to be associated with poor hearing performance. The timing of this deterioration can vary. We have investigated the biological response at the electrode-tissue interface of a device that was surgically removed because of poor hearing performance.

Over 10 months there was a reported decline in hearing, a gradual increase in impedance and partial migration of the array out of the cochlea. On removal the device was found to be coated in a fibrotic sheath. Tissue analysis revealed evidence of active inflammation (macrophages, T cells, eosinophils, neutrophils), proliferation (myofibroblasts) and active angiogenesis (VEGFR2) in this fibrotic sheath. We hypothesise that this environment was toxic to the cochlea and surrounding structures causing damage to the neurons and therefore affecting auditory stimulation.

Project goal:

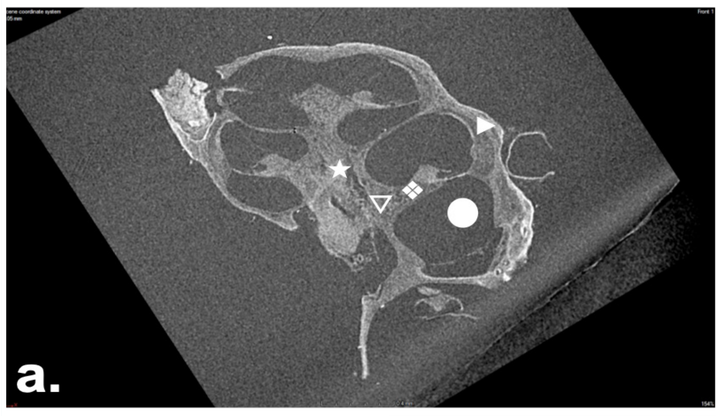
To establish an optimised mouse model of cochlear implantation for the investigation of the biological response and implications for device function at the electrode-tissue interface and consequences on central auditory processing.

μCT: Determine 3D structural detail of the mouse cochlea to inform device design. Validate surgical technique post-implantation. Identify the location of gross tissue damage caused by the electrode.

3D X-ray histology: To corroborate the 3D structural information with detailed 2D cellular information from post-mortem histological analysis to gain further understanding in the biological response at the electrode-tissue interface.

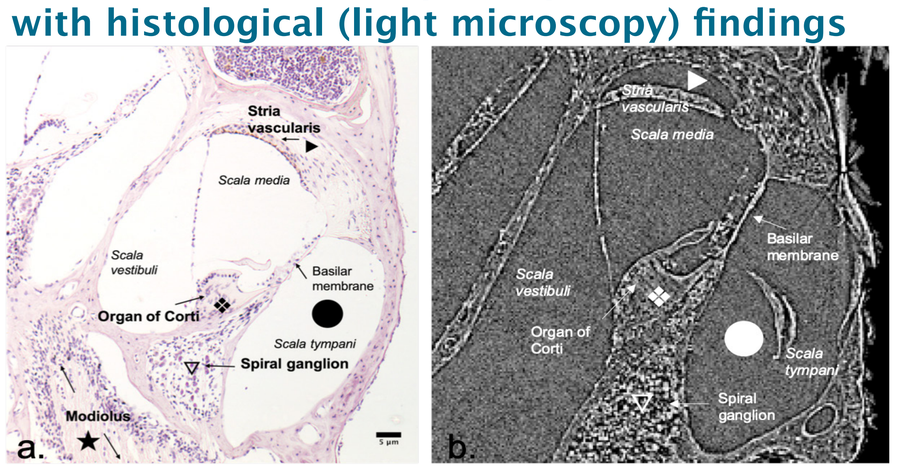
Results

Pilot study to determine imaging capabilities and limits of resolution on decalcified cochleae



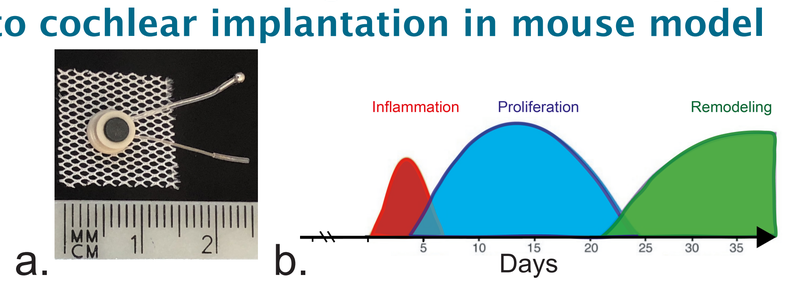
Pilot μCT data of a cochlea
a. A single digital mid-modiolar section of the cochlea.
b,c. Overall 3D render of the cochlea at high resolution.

Corroboration of 3D (μCT) spatial information with histological (light microscopy) findings



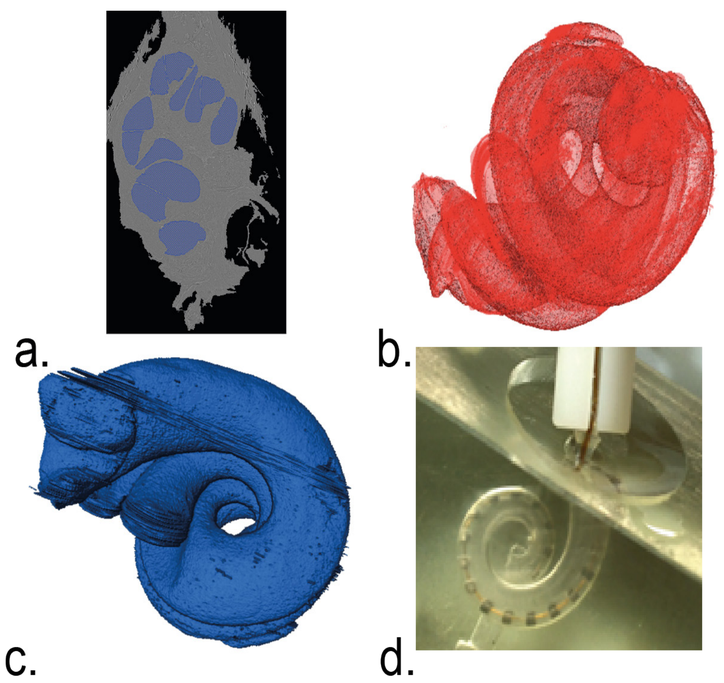
Cochlea anatomy highlighting keys regions of interest
Comparison between a mid-modiolar cochlea section imaged by light microscopy with conventional histology (a.) and μCT (b.)

Validation of surgical technique post-implantation and investigation of fibrotic response to cochlear implantation in mouse model



Investigating the fibrotic response to cochlear implantation using a mouse model
a. The electrode array assembly - designed and produced by Oticon medical.
b. Schematic describing the stages of the wound healing process responsible for the formation of fibrotic sheath around the electrode array. This will be investigated in this model.

3D structural analysis of the cochlea for device design of a small animal cochlear implant



3D structural data
a. Manual segmentation of the mouse cochlea in Avizo. b. Surface reconstruction of the material in Avizo. c. 3D modelling of the segmented cochlea in Avizo. d. Human 3D printed cochlea with electrode-array, produced by Oticon medical - used to optimise implant design and stimulation.

Future work

- Optimise μCT scan parameters for mineralised and de-mineralised paraffin embedded mouse cochleae to establish the best contrast and resolution. Translate this data for use in post-operative *in-vivo* scanning after implantation for monitoring of fibrotic response.
- Optimise conditions to obtain μCT scan of implanted mouse head to validate surgical technique and identify position of electrode-array.
- Carry out detailed immunohistochemical analysis of immune cells to determine the kinetics of the biological response at electrode-tissue interface and study the central response (alterations to auditory processing) to the presence of fibrosis as a proxy of poor hearing outcomes.

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