Cochlear implant: mini swine or sheep? Such a tricky choice

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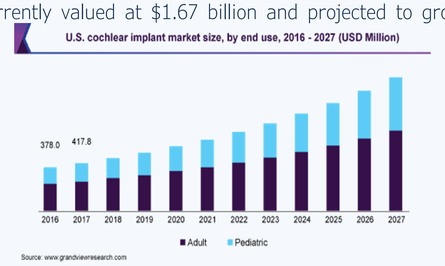
Abstract

Cochlear implants (CI) have a growing market currently valued at $1.67 billion and projected to grow 10.6%/year from 2020 to 2027.
Since the first implantation in 1961, CI have undergone continuous technical improvements in sound processing, requiring associated safety testing in animals. While small animals provide a cost effective preclinical model for assessing hearing, their anatomical dimensions are not representative of the human, creating a need for large animal models.



We therefore investigated miniature swine and sheep as models for cochlear implantation using histology, endoscopy and functional readouts. Histology revealed round window membrane thickness to be species dependent, with the ovine anatomy more closely mimicking the human compared to mini swine. As these differences are irrelevant for CI studies, we developed species specific endoscopic guided surgical procedures for accessing swine and ovine round windows.

Cochlear implantation was performed on 3 mini swine (5-10 kg) through a posterior mandibular approach using the paracondylar process as anatomical point of reference. The middle ear/round window was accessed by drilling at the edge of the auditory canal with a 45° angle. Implantation was verified perioperatively using CT scan.

ABR recordings were performed at 5 frequencies (2, 4, 8, 12 and 16 kHz) pre-implantation (baseline), and 30, 60 and 90 days post-implantation using an in-house custom-made ABR system that, unlike standard ABR systems, is sufficiently sensitive to acquire readouts from a standalone subcutaneous electrode. Evaluation of the un-implanted ear showed no sign of hearing deficiency at D90 compared to baseline, whereas the implanted ear showed a threshold shift of 40 to 50 dB at all frequencies.

Following necropsy, the implanted ear was processed for histopathology using a hard-tissue approach involving whole specimen resin embedding and serial micro-grinding and staining with eosin y-toluidine followed by pathologist assessment. No clearly visible inflammatory changes or fibrosis were associated to the examined sections in all implanted cochlea. The un-implanted cochlea were processed for cochleogram. Max projection images obtained from confocal scanning were fed to a customized image processing program for efficient hair cell count of the unusually large samples. No hair cell loss was reported at the 5 frequencies tested during ABR (Figure 3) confirming the absence of processing artifacts.

Taken together, these studies provide the methodology for cochlear implant study in mini swine, from image-guided surgery, through functional readouts and down to immunohistochemical endpoint readouts such inflammation and cell death. This methodology can be adapted to sheep, with some preliminary results already in place.

Results

Histology of the Round Window Membrane

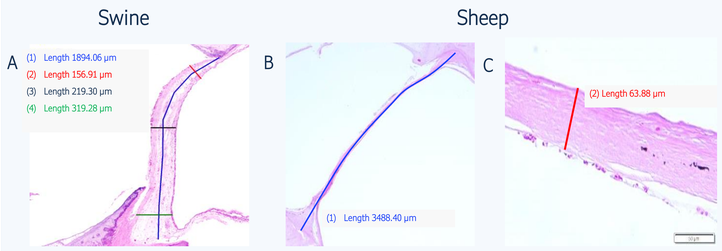


Figure 1: Cross section of round window membrane: (A) from Swine (Yorkshire, 60 Kg). (B and C) from sheep (PolyA+, 50 kG). Round membrane from swine appears to be smaller (~2 mm in diameter, A) than the one from Sheep (~4 mm in diameter, B). Round window membrane thickness from sheep is closer to human with a ~60 µm (C) compared to pig ~160 to 320 µm (A).

Computer Tomography Scan

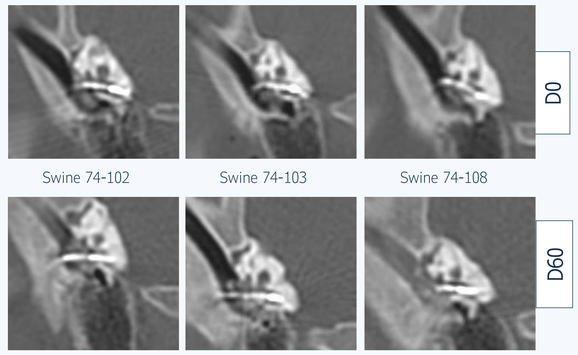


Figure 2: CT-Scan of cochlear implant day of implantation (upper panel) and 60 days post Implantation. CT-Scan was used as a meaning to confirm good implantation following surgery and absence of rejection 60 and 90 days following implantation.

Auditory Brainstem Response

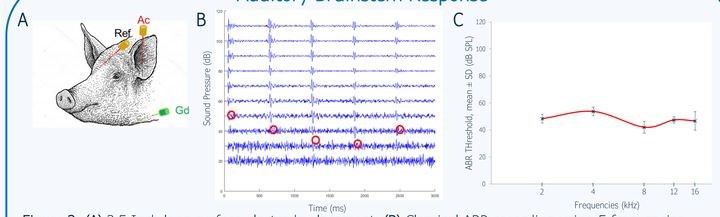


Figure 3: (A) 2.5 Inch long surface electrode placement. (B) Classical ABR recording using 5 frequencies delivered at once with 5 ms intervals. (C) ABR threshold of the 3 swines used in this study (mean +/- SD) showing repeatability of measure between animals.

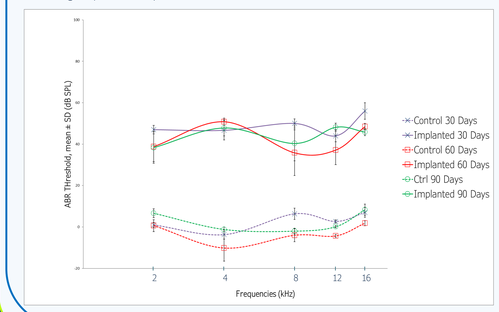


Figure 4: ABR threshold shift compared to baseline level. Control ear show around 5 dB in variability across frequencies and time points. Implanted ear shows a threshold shift of around 40-50 dB at D30 but shows some sign of recovery for frequencies above 8 kHz at D60 and D90.

Histopathology and Cochleogram

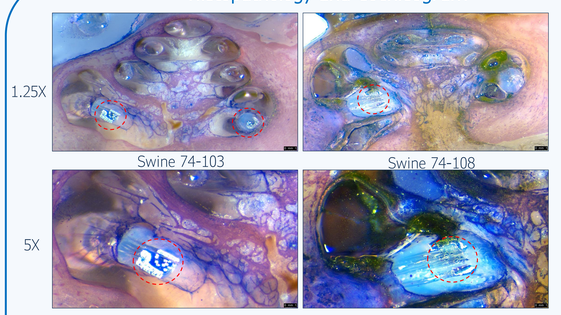


Figure 5: Microgrinding of Resin embedding cochlea. Device cross sections were present in each photographed section of two animals (74-103 and 74-108). There was no evidence of fibrosis/sheath associated with implants, no cochlear exudate or significant inflammation.

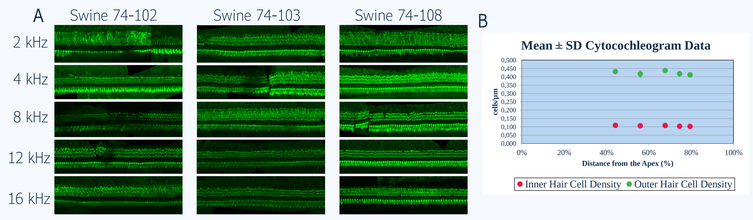


Figure 6: (A) Immunohistochemistry of Myo7a on dissected cochlea fragments.
(B) Hair cells count reveal no hair cells loss across the frequencies tested in all animals.

Conclusion

CILcare/CBSET have already implemented, using large animals, the necessary surgical procedure (round window approach) and readouts (Histology, CT-Scan, ABR, Cochleogram and histopathology) to perform auditory studies. The data presented today were performed using Yucatan swine (10 kg at days of implantation) but we have developed in parallel everything needed to perform studies using sheep.