LA-ICPMS Imaging Of Cisplatin Accumulation

Study of Human and Murine Cochlea

Introduction

Cisplatin chemotherapy is approved by most global agents, including the FDA, as a treatment of cancer. Following cisplatin chemotherapy, 40-80% of patients experience permanent hearing loss. Cochlear hair loss has been associated with ototoxicity. Directly visualizing the cochlea with LA-ICPMS makes it possible to evaluate whether the hair loss is caused by the hair accumulating cisplatin or by alternative processes (cisplatin pharmacokinetics).

Platinum is rare in normal biological tissues, therefore, platinum detected can be interpreted as an indication of cisplatin – a platinum-based drug – accumulation.

Breglio et. al. 2017[1] demonstrated Pt imaging of available human cochlea (Figure 1) using 25 µm x 25 µm square laser spots.

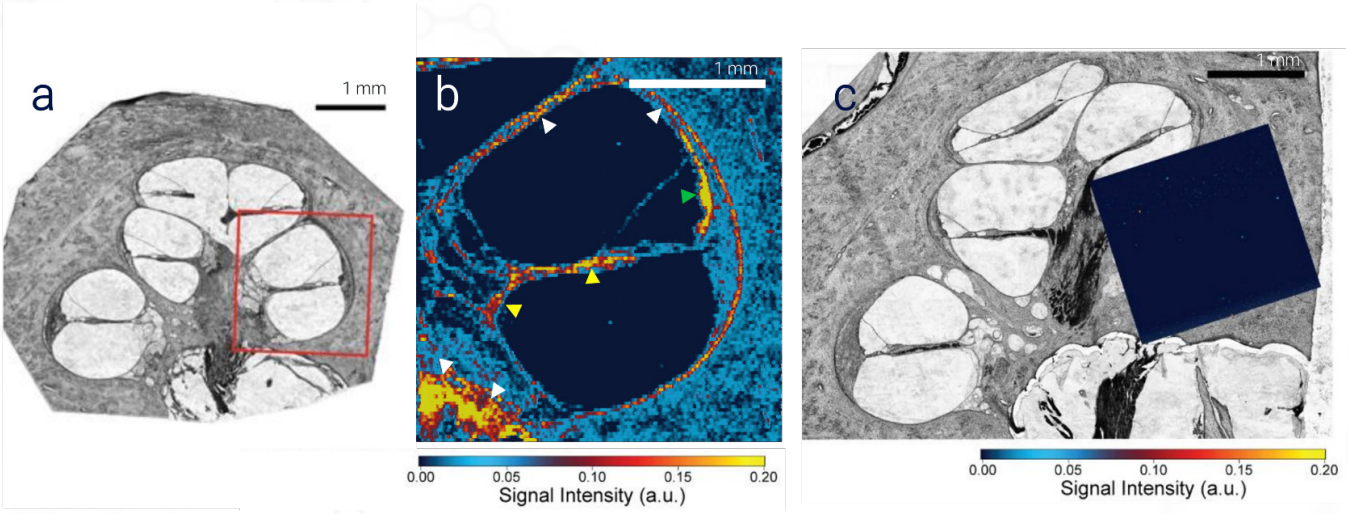

Figure 1. Comparison work on human cochlea from Breglio et. al. 2017. (a) White light image of human cochlea treated with cisplatin; (b) LA-ICPMS elemental map of the boxed area in panel (a) where green arrows (▶) mark the stria vascularis, yellow arrows (▶) mark cochlear nerve fibers, and white arrows (▷) mark the nerve-bone boundary; (c) Merged white light and LA-ICPMS image of human cochlea control showing no Pt. Human LA-ICPMS images were created with a NWR213 (now ESL213) using a 25 µm x 25 µm spot.

Unlike humans, mice can be studied in controlled laboratory conditions, but imaging the Pt distribution in murine cochlea requires different parameters and technology due to the smaller feature size. The work presented in this note uses a 2 µm x 2 µm square laser spot to create high-resolution Pt images of a cisplatin-treated mouse cochlea.

Method

A NWR193 (now ESL193) laser ablation system equipped with a TwoVol2 sample chamber (Figure 2a) and Dual Concentric Injector (DCI) torch modification (Figure 2b) of a quadrupole ICPMS was used to image cisplatin in a cochlear section of a cisplatin-treated mouse. Square spot shapes were created using the X-Y Rotational shutter (XYR) device to give a flat leading edge of ablation lines for uniform sampling.

The high sensitivity from the DCI provided measurable signal at 2 µm x 2 µm spots – without the greatly improved transport efficiency, signal would not have been detectable above background. The DCI also reduced the washout time of each pulse by approximately 10x, allowing faster scanning and decreasing experiment duration. Fluence was selected to consume the entire sample. While this led to some sampling of the glass slide substrate at 193 nm, the absence of platinum in the slide prevented impact on the image.

The laser parameters were optimized to minimize experiment duration while maintaining sensitivity of ^{195}Pt above background (Table 1). Images were generated using Iolite v.3.6 and log files generated by the laser software.

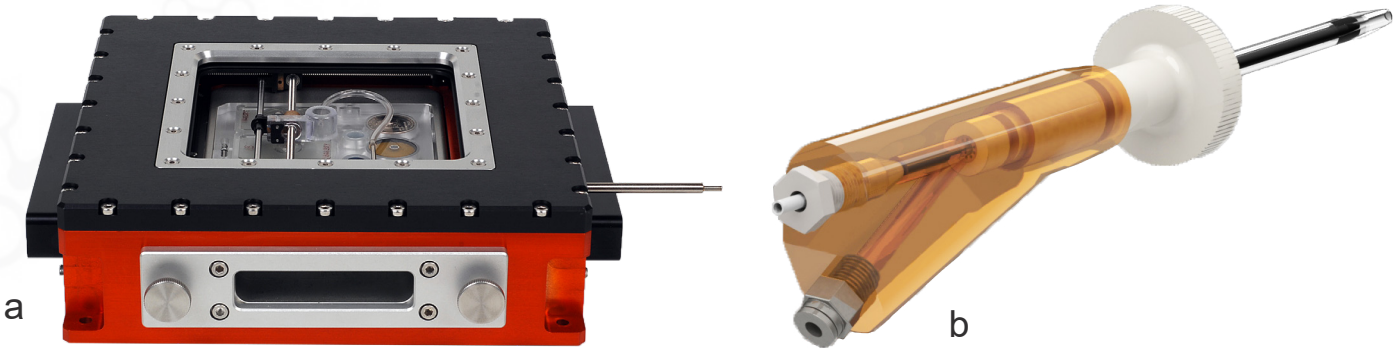

Figure 2. (a) The TwoVol2 sample chamber; (b) The Dual Concentric Injector (DCI).

Table 1. Parameters used for mouse cochlea map.

Parameter	Setting
Laser Ablation System	NWR193
Sample Chamber	TwoVol2 with DCI
Laser Repetition Rate	250 Hz
Laser Scan Speed	250 µm/s
Laser Spot Size	2 µm X 2 µm (square)
Fluence	6 J/cm^2
Elements	^{195}Pt
Experiment Duration	5 Hours

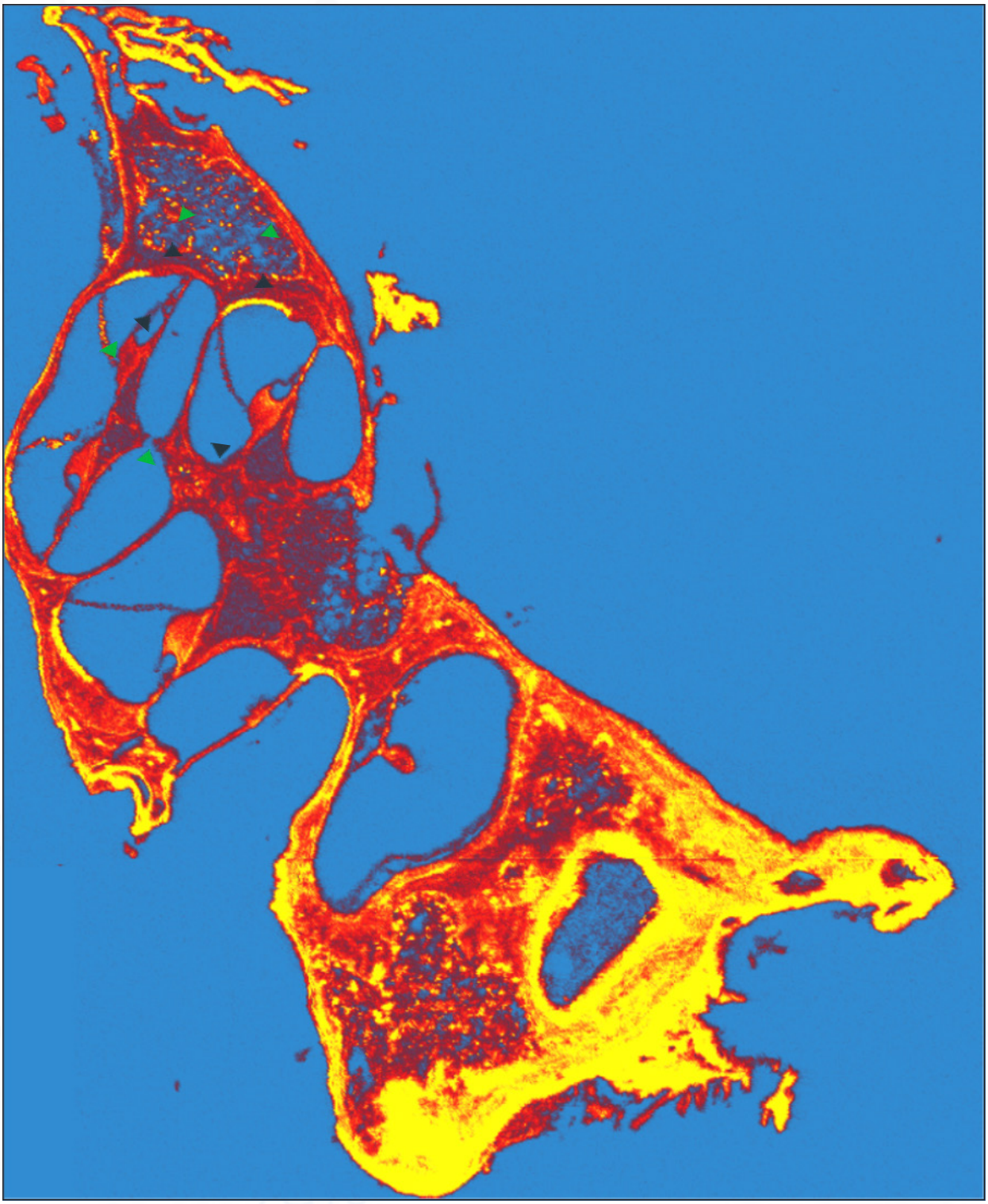

Figure 3. LA-ICPMS image of cisplatin in a mouse cochlea section, where green arrows (▶) mark the stria vascularis and black arrows (▶) mark the spiral limbus.

Results

The image generated from the experiment is shown in Figure 3. Across the cochlea, we observed platinum distribution similar to that seen in human tissue – high signal consistently occurring in the stria vascularis and spiral limbus, and intensities decreasing from base to apex with each cochlear turn. The occurrence of cisplatin in these regions is consistent with observed cisplatin-induced hearing damage, and indicates high cisplatin retention in the cochlear base.

Conclusions

The high resolution mouse cochlea image demonstrated similarities in cisplatin accumulation between human and mice subjects. It shows that cisplatin is not preferentially accumulated in hair cells compared to the rest of the cochlea.

High resolution elemental mapping, achieved by using small sampling spots, is required for analysis of fine biological features. With poor particle transport efficiency, signal from samples cannot be detected above background at small spot diameters. High efficiency imaging of analytes at high resolution was possible because of the ultra-fast washout technology of the DCI.

References

1 Breglio, Andrew M. et al. “Cisplatin Is Retained in the Cochlea Indefinitely Following Chemotherapy.” Nature Communications 8.1 (2017): n. pag. Nature Communications.