Quantification of Pt-based chemotherapeutics using HAADF STEM

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High-angle annular dark field (HAADF) scanning transmission electron microscopy (STEM) is a powerful method for imaging heavy elements. The very high spatial resolution, combined with an image contrast mechanism dependent on atomic number [1], provides readily interpretable data suitable for use with quantification procedures. Such techniques have become routine in materials science [2,3], but have so far enjoyed relatively little popularity in the realm of life sciences.

Platinum-based chemotherapeutics are instrumental in the fight against cancer. The chance 1960s discovery of cisplatin revolutionised the treatment of testicular cancer, and has been instrumental in increasing the cure rate from just 10% to in excess of 85% today [4]. Cisplatin's sibling compound oxaliplatin, discovered a decade later, is widely used to treat colorectal cancer. However, despite the highly effective nature of platinum-based chemotherapy, the side-effects associated with such treatment can be significant. In particular, chemotherapy-induced peripheral neuropathy (CIPN) can cause sometimes irreversible pain and numbness in the extremities, which cannot be alleviated with analgesics.

Due to their platinum-based structure, cisplatin and oxaliplatin therefore represent excellent candidates for investigation with HAADF STEM. We present atomic-resolution images of clinical formulation oxaliplatin (Figure 1) and cisplatin (Figure 2), revealing a pronounced difference in platinum distribution within the drugs [5]. In cisplatin, the majority of the Pt atoms are arranged in 1-2nm nanoparticles; in oxaliplatin Pt displays no evidence of crystallinity, with many single atoms and loose clusterings of atoms. We will present evidence showing that difference in structure is unlikely to be due to radiation damage during imaging or vehicle solution residue. We also present images of neuronal rat tissue following systemic administration of clinically-formulated oxaliplatin, demonstrating the first evidence of single-atom detection of platinum drugs in cells (Figure 3), alongside a cross-section based quantification procedure for element identification.

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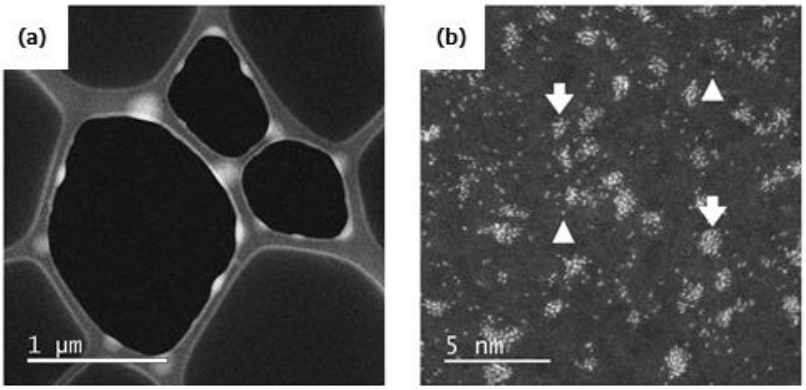

Figure 1: Oxaliplatin is one such drug, which is often used to treat colorectal cancer. (a) shows clinically formulated oxaliplatin dispersed on a lacey carbon Cu TEM grid, while arrows and arrowheads in (b) show clusters and individual atoms of platinum as detected by HAADF STEM. The quantitative nature of HAADF imaging allows us to conclude these clusters are quasi-2D, having flattened along the carbon support during the drying process. [4]

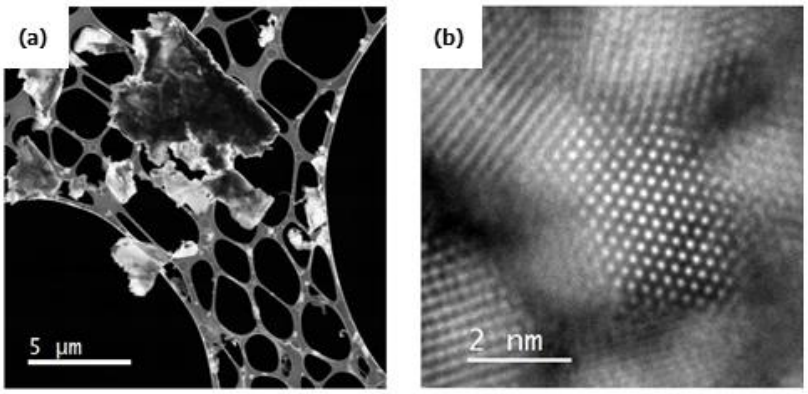

Figure 2: Another Pt-based drug of interest is cisplatin, commonly used to combat testicular cancer. (a) shows dried clinically formulated cisplatin, while (b) shows Pt nanoparticles of around 2nm diameter. [4]

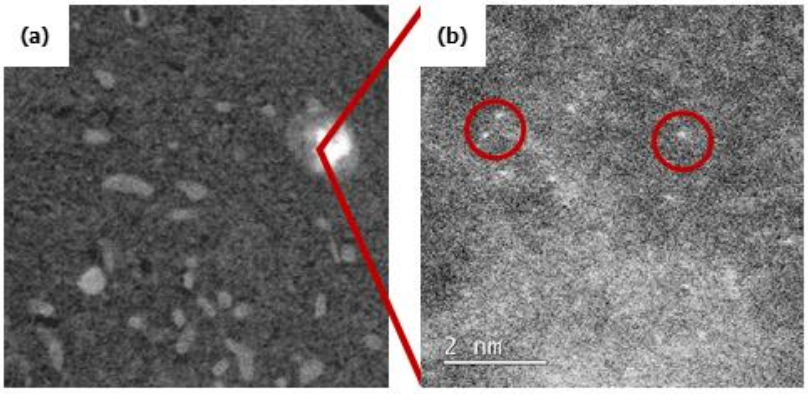

Figure 3: (a) HAADF STEM image of a platinum cluster within a cell body. (b) Sufficiently high magnification reveals single atoms of Pt (circled) within the cluster.