Atomic telemetry: in situ determination of anti-cancer drug mechanism of action

Metals have long been used in chemotherapy medications, and platinum compounds have proven the most successful. The search for effective anticancer metallocomplexes, both platinum-based and otherwise, is ongoing, but identifying successful compounds is a challenge because of the lack of molecular mechanistic understanding. For example, DNA is the main biomolecular target after metallocomplexes are activated by hydrolysis, but for most compounds, the specific interactions with DNA are not well understood.
In this lecture, I present a physical chemistry methodology developed in our research group, termed 'atomic telemetry' (1), for the in vivo monitoring of metal complexes and their hydrolysis and interaction with biomolecules in cancer cell lines, including DNA. Using resonant X-ray emission spectroscopy and multiscale molecular dynamics simulations, we unveiled the mechanism of action for two promising platinum-based drugs that have shown anticancer activity both in vivo and in vitro against cisplatin-resistant cellular and animal models (fig. 1).
The atomic telemetry spectroscopic method is label-free and can be employed for in vivo measurements, allowing the direct study of the interaction between the complex and biomolecules within shorter times than those of current practices. Another advantage of atomic telemetry is that low drug dosages commonly used in the treatment of cancer can be detected and analyzed, making it a valuable method for elucidating the relationship between structure and mechanism of action, which is crucial for determining the biological activity of any external compound introduced into the human body.

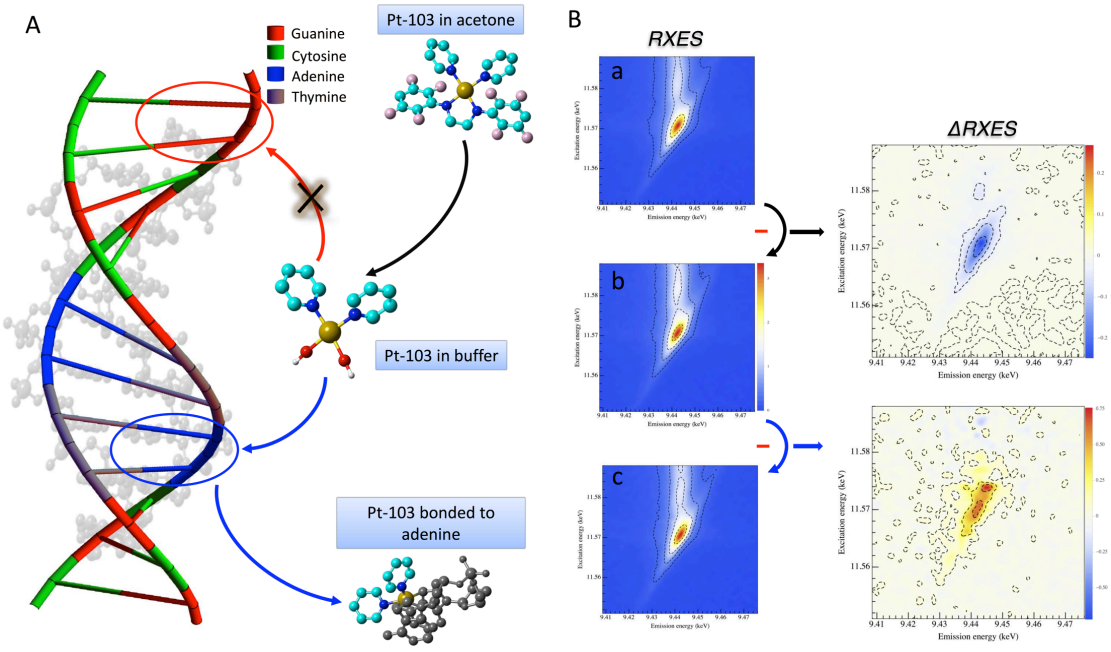

Figure 1: Example of anti-cancer drug mechanism of action discovered by atomic telemetry.

[1] a) J. Czapla-Masztafiak, J. Sá, et al. J. Phys. Chem. Lett. 8 (2017) 805; b) J. Sá, et al. Dalton Trans. 43 (2014) 13839; c) J. Czapla-Masztafiak, J. Sá, et al. Biophys. 110 (2016) 1304; d) J. Sá, et al., Drug Discov. Today Technol. 16 (2015).