Binding manners

Claudia Turro from The Ohio State University talks *Nature Chemistry* through the different binding modes small metal complexes can adopt when interacting with DNA — and why elucidating them in detail matters.

Why are we interested in tinkering with DNA through small metal complexes?
Metal complexes that interact with biomolecules have a number of potential applications, such as in therapeutics and diagnostics. DNA contains genomic information, base mismatches and specific sequences known to be associated with diseases. Targeting these promises effective drugs, and fast, sensitive diagnostics — but for that we need to understand how a given type of interaction gives rise to a specific effect. Take cisplatin, for example. It was used for decades without knowledge of its therapeutic mechanism, then structural data revealed that it bends the double helix on covalently binding to it. This provided invaluable insight into the cellular responses, and ultimately the cell death it elicits.

Why is it important to determine binding modes so precisely?
Different interactions with DNA can lead to specific cellular responses or signals. For example, long-range charge transport can be altered with some small-molecule binders, whereas gene regulation requires a binder with sequence specificity.

Metallo-insertion — in which a molecule replaces a mismatched base pair — and full intercalation of a compound between two base pairs do not bend the double helix or break its π-stacking. In contrast, a molecule that intercalates only partially bends the DNA — in a similar way to cisplatin. It is reasonable to hypothesize that, if such 'semi-intercalation' could be stabilized in solution, it may induce cellular responses similar to those observed with cisplatin. Long-range charge transport through DNA is thought to play a role in signalling associated with protection of the genome from oxidative damage. Cisplatin and semi-intercalators are thus expected to interfere with this signalling.

Similar arguments can be made for major- versus minor-groove binding. The exact location and geometry of each interaction can have very different consequences.

You mostly work with ruthenium and dirhodium complexes — how do they compare with the well-known cisplatin?
Structural work has shown that the deformation of the double helix stemming from the coordination of a dirhodium complex to DNA can be nearly superimposed with that of cisplatin, and ruthenium complexes that bind covalently to DNA are expected to exhibit similar specificity. We are interested in activating these complexes with low-energy visible and near-infrared light, such that they only bind to DNA on irradiation.

Photodynamic therapy (PDT) is now recognized as an alternative — in some cases a better one — to traditional cancer treatments because of its low level of invasiveness, controlled dose and localized action. The PDT systems currently in use or undergoing clinical trials are organic molecules that rely on the sensitized production of singlet oxygen to achieve cell death through oxidative damage. In our group, we investigate agents that do not depend on the presence of oxygen, which may be important in the treatment of solid tumours with low oxygen content. Transition metals with reactive excited states — which may act as cisplatin does, but only when irradiated — might offer one solution to this challenge.

What is the main difference between these metal complexes and other DNA binders?
Typically, larger species have much slower binding kinetics; threading intercalators also involve DNA melting — the two strands coming apart in the binding region. They are desirable when a binder is required to remain bound for long periods of time, such as for blocking transcription-factor binding events, rather than for applications that rely on faster on/off binding, for example hybridization sensing.

Oligonucleotides and peptide nucleic acids that form triple helices can recognize certain sequences and also regulate gene expression.

What are the main experimental difficulties to overcome in studying interactions between small molecules and DNA?
Many characterization methods provide limited information, and must be combined to build a picture of the binding mode, both in solution and the solid state.

Single-crystal X-ray diffraction helps identify possible binding motifs, and validate those proposed from indirect techniques — but growing suitable crystals is not easy. Also, many complexes can bind with DNA through different areas, making interactions harder to elucidate. Furthermore, the adducts that crystallize may not be representative of all, or the predominant, binding modes in solution — the medium operative *in vivo*. NMR spectroscopy can provide structural information in solution, and a better quantitative picture of the predominant interactions. These two techniques are the most valuable, but also the most challenging.

From a broader perspective, it is also difficult to determine the effect of a compound *in vivo*. Although we can monitor certain biological processes, it is difficult to pinpoint where the complex cellular 'machinery' is being affected at the molecular level.

Further work is still needed to understand better which properties of the complexes result in certain types of binding, and the predominant cellular responses associated with those. Another major challenge is to take successful complexes from the lab to the clinic. Despite the success of platinum drugs, a negative perception towards metal-containing therapeutics has dramatically hindered their screening compared with organic molecules.

INTERVIEW BY ANNE PICHON