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trans-Platinum Reporting for Duty

HIV infects millions of people worldwide; however, no cures for this AIDS-causing retrovirus exist. A new approach using *trans*-platinum-nucleobase complexes to inhibit viral replication by disrupting the nucleocapsid protein-RNA interaction is presented in this issue of *Chemistry & Biology* [1].

Every student of bioinorganic chemistry is familiar with the discovery and chemistry of platinum anticancer drugs. The success of cisplatin in treating cancer established an important paradigm for the potential of drug discovery at the interface of inorganic chemistry and biology [2]. Over 40 years ago, Barnett Rosenburg and coworkers discovered that platinum complexes had the unique ability to inhibit the mitosis of bacteria [3], and shortly afterwards they reported the antitumor activity of cisplatin (*cis*-diaminedichloroplatinum(II) or *cis*-DDP) [4]. Since the FDA approved cisplatin in 1978, cases of testicular cancer that were once fatal have been cured with a >90% success rate. This clinical success has pushed cisplatin to the forefront of metal-based chemotherapies used today. A number of cisplatin analogs have been reported, but only a select few like carboplatin have found utility in cancer treatment [5]. One seminal observation from the early studies was that the geometrical isomer *trans*-DDP is ineffective in treating tumors (Figure 1). As thalidomide established the importance of enantiomeric purity for the activity of organic drugs, cisplatin demonstrated importance of structure-function relationships in inorganic pharmaceuticals.

The oft-repeated pronouncement of *trans*-isomer inactivity has proven to be only partially accurate as platinum research has matured over the last 15 years. The nature of the DNA crosslinks formed [6] and the recognition of these adducts by proteins [7] are major factors that prevent *trans*-DDP from exhibiting anticancer properties; however, after studying some simple structural modifications, active *trans*-platinum complexes have been discovered. Inclusion of alkyl amine [8], pyridine [9], iminoether [10], or photoactive ligands [11], as well as using linked platinum complexes [12], provides potential anticancer agents, including several that exhibit activity against cisplatin-resistant tumors. These and other investigations have focused on approaches to enhance the cytotoxicity of *trans*-complexes by using the *trans*-geometry to take advantage of unique interactions between the platinum, DNA, and proteins inaccessible to the *cis*-isomer.

Because of the success of cisplatin, most research on *trans*-platinum complexes has concentrated on developing new cancer treatments; however, Farrell and coworkers have developed a strategy to utilize these complexes to target and treat HIV [1]. These *trans*-configured compounds target the zinc fingers found on retroviral nucleocapsid proteins by taking advantage of noncovalent interactions and the *trans*- geometry of the complex to orient the platinum for an attack on a zinc finger "knuckle" sequence. Binding of the *trans*-platinum complex initiates a cascade of reactions that ultimately results in removal of a Zn^{2+} ion from the finger motif, leading to loss of the protein's tertiary structure (see Figure 7B in [1]).

Farrell and coworkers first hypothesized that platinum-nucleobases might be attractive targets for antiviral agents based on their discovery that a quinoline derivative had some ability to remove Zn^{2+} from nucleocapsid proteins [13]. Subsequent efforts attempted to promote and enhance noncovalent recognition between proteins and nucleobases by platination [14] and to elucidate the mechanism of Zn^{2+} removal using model complexes [15]. The most recent work brings all these concepts together in a comprehensive study to develop an antiviral platinum drug candidate. With $[PtCl(9\text{-}EtGH)(pyr)_2]$ (EtGH = 9-ethylguanine), a noncovalent π-stacking interaction between the platinated guanine and a tryptophan residue in a peptide derived from the C-terminal zinc knuckle of the HIV nucleocapsid protein, NCp7, provides the first step in a proposed antiviral mechanism. This interaction positions the complex for electrophilic attack on a Zn bound cysteine, which is part of a structural zinc finger. After the cysteine thiol displaces the labile chloride ligand, a second cysteine thiol from the zinc finger motif displaces the nucleobase, ejecting the Zn^{2+} in the process, to give a platinum complex with *trans*-pyridine and *trans*-cysteine ligands. This series of changes in the tertiary structure renders the nucleocapsid protein incapable of binding with RNA, which could thereby prevent viral replication.

Despite the difference in disease targets for cisplatin and Farrell's *trans*-nucleobase complexes, some parallels in the two systems are immediately apparent and illustrate important fundamental principles of the relationship between biological and inorganic chemistry. Binding of proteins like high mobility group 1 (HMG1) to cisplatin-modified DNA has been identified as an important feature in the antitumor activity of the metal complex [16]. The crystal structure of the *cis*-$[Pt(NH_3)_2]$ d(GpG) intrastrand crosslink revealed that bending and unwinding of the DNA duplex created a hydrophobic notch into which a phenylalanine residue of HMG1 is intercalated [17]. Platinum binding predisposes the aromatic ring of the guanosine base to π-stack with the phenylalanine group [18] in a manner similar to the

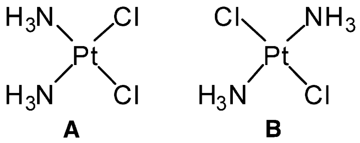

Figure 1. The Structures of *cis*- and *trans*-DDP

(A) *cis*-DDP; (B) *trans*-DDP. Only the *cis*-isomer is effective in treating cancer.

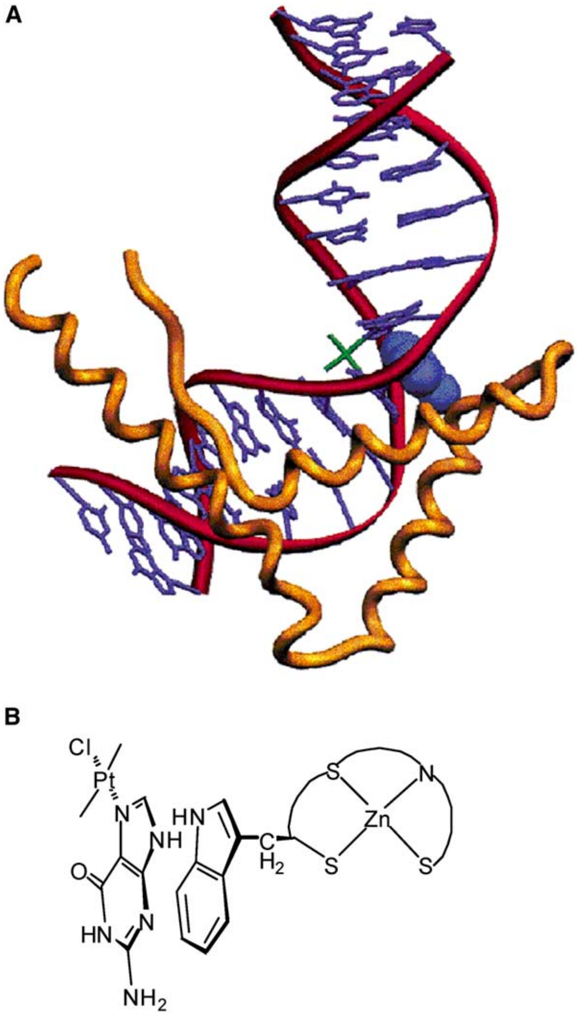

Figure 2. Similar π-Stacking Interactions Are Key Features in the Efficacy of Cisplatin as an Anticancer Drug and for the *trans*-Platinum-Nucleobase Complex in Ejecting Zn^{2+} from Zinc Fingers of Nucleocapsid Proteins

(A) For cisplatin (green), a phenylalanine (blue) of HMG1 stacks with a platinum bound guanosine mediating the protein-DNA binding.

(B) For the *trans*-complex, the platinum bound guanine π-stacks with a tryptophan residue.

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interaction observed between the tryptophan residue and the guanine *trans*-platinum complexes in Farrell's work [1, 14] (Figure 2).

The comparison of cisplatin and the *trans*-nucleobase compounds also extends to the ligand-exchange reactions that play an intricate role in the interaction of platinum with biomolecules. Once cisplatin enters the cell, it loses a chloride ligand(s) to generate active aqua-platinum complexes; the soft nitrogen donors of nucleotide bases subsequently displace the water ligands to form various platinum-DNA adducts. The newly reported antiviral *trans*-platinum complexes also are proposed to undergo a series of ligand-exchange reactions before the final platinum-modified protein is produced. One essential feature is the labile chloride ligand that is displaced by a Zn bound cysteine after the initial noncovalent recognition event in a manner analogous to the nucleobase-water ligand exchange for cisplatin. In the final complex, both the chloride and the nucleobase ligand have been replaced by the softer cysteine donors to give a new *trans*-platinum complex.

Some of the observed side effects of cisplatin treatment stem from nonspecific interactions with proteins and nucleic acids. These new *trans*-platinum complexes also have the potential to participate in adventitious binding events. However, the NCp7 target appears to possess features that predispose the therapeutic approach for success. Although zinc finger motifs are among the most widespread metal binding sites in biology, the specific CCHC sequences found in the nucleocapsid proteins are quite rare [19]. In addition, both of the capsid's zinc finger domains must be intact to mediate the protein's interaction with RNA, so loss of a single Zn^{2+} ion should be sufficient to inhibit viral replication. The combination of these two factors suggests that even if the *trans*-platinum-nucleobase complex exhibits only moderately selective recognition of the dual zinc finger domain, the complexes have great potential to be effective therapeutic agents.

Several decades of research were required to transform cisplatin from a simple coordination complex to a universally accepted cancer therapy. With the exception of a few examples of inorganic pharmaceuticals, transition metal complexes are less frequently screened as drug candidates compared to organic molecules; however, the cisplatin and now *trans*-platinum stories illustrate the potential of metal-based therapeutics. HIV/AIDS afflicts millions of people, particularly those in the developing world where prevention proves difficult, so the need for a cure is critical. Perhaps this is the beginning of a new chapter in the success story of medicinal platinum chemistry: one that illustrates how basic chemical research can yield unpredicted applications. None of the early cisplatin researchers who dismissed *trans*-DDP as an ineffective cancer drug could have predicted that, one day, related compounds might provide a treatment for another fatal disease.

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Selected Reading

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