S26-1 Basic research for development of next-generation platinum-based anticancer drugs

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The FDA approval of the anticancer platinum complex, cisplatin, in 1978 enhanced opportunities for utilizing metal-containing compounds as clinical drugs. Twenty-five years later, the annual global market of the platinum anticancer drugs came to 2.8 billion USD and is still increasing by more than 20% every year. This fact indicates that their high therapeutic efficacy boosts demand, although its chemotherapy is known to accompany some serious side effects. Our and Farrell's groups focused on the antitumor efficacy of the platinum complexes and have found that the series of polyamine- or azolato-bridged cationic polynuclear Pt(II) complexes are promising candidates for next-generation anticancer drugs, which could reduce potential side effects without spoiling therapeutic efficacy. The polynuclear Pt(II) complexes originally possess high positive charges, whereas cisplatin is a neutral molecule. The formations of covalent cisplatin-DNA adducts are thought to be critical parameters in the mechanism of cisplatin antitumor activity. The cationic polynuclear Pt(II) complexes would, on the other hand, experience electrostatic (non-covalent) pre-associations before the covalent interactions, since DNA is negatively charged. Therefore, using X-ray crystal analysis, we have investigated the non-covalent interaction modes with DNA to elucidate the mechanism of action of the series of cationic polynuclear Pt(II) complexes.