

Strategies to Improve the Anti-Cancer Properties of Gold(III) Complexes

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cis-Diamminedichloroplatinum(II) (*cis*-platin or *cis*-[Pt^{II}(NH₃)₂(Cl)₂]) with biological properties discovered serendipitously by Rosenberg in 1965 and with approval given by the Food and Drug Administration in 1978 went on to become an important clinically-used agent for the treatment of cancers [1]. This platinum drug together with its derivatives carboplatin and oxaliplatin are highly effective towards various kinds of cancers such as testicular cancer. Nevertheless, the toxic side effects of these platinum(II) complexes, including nephrotoxicity, emetogenesis and neurotoxicity, along with the wide range of cisplatin-resistant cancer cells, make them far from ideal drugs [2]. The tandem success and limitations of these platinum(II)-based drugs opened up a wealth of research into other classes of metal-based chemotherapeutic agents [3].

In view of the structural similarity, square-planar gold(III) complexes were thought to interact with DNA and other biomolecules in a way similar to that of the platinum(II)-based drugs. The gold(III) ion could covalently bind to methionine, ribonuclease A, and disulfides, and induce DNA strand breaks under physiologically-relevant conditions [4]. Some cyclometalated gold(III) complexes with tridentate terpy ligands (wherein terpy = 2,2':6,2''-terpyridine) were found to interact with DNA via intercalation [5]. Several reports have revealed that gold(III) ion is capable to interact with small peptides or proteins such as human serum albumin, thioredoxin reductase and glutathione *in vitro* [4,6].

A dimethyl gold(III) complex was reported in early 1980s to display modest *in vivo* anti-cancer activities on mice bearing P388 leukemia [7]. This report subsequently triggered the anti-cancer studies of various gold(III) complexes containing monodentate or bidentate ligand(s). Many of these complexes were found to exhibit favorable *in vitro* anti-cancer properties with comparable cytotoxic activities to that of cisplatin [8]. Yet, the development of these gold(III) complexes as clinically-useful anti-cancer therapeutics had been severely hampered by their relatively poor stability under physiological conditions. The instability of gold(III) may also lead to the gold(I)-associated toxicity *in vivo* [9].

In 1996, a relatively stable gold(III) complex with tridentate damp ligand (wherein damp=2-[(dimethylamino)methyl]phenyl) has been found to display a moderate *in vivo* anti-tumor activity against human carcinoma xenografts [10]. Prompted by the result of this study, various highly anti-cancer active gold(III) complexes with tridentate bipyridyl ligands and dinuclear gold(III)-oxo complexes having a common Au₂O₂ motif which are stable in aqueous solutions have been identified [6]. Some gold(III) dithiocarbamate complexes have recently been found to significantly inhibit the tumor growth of MDA-MB-231 breast tumor-bearing mice associated with proteasome inhibition and massive apoptosis induction [11].

Apart from the stability issue, several factors including the high toxicity, induced drug resistance, poor cancer-cell specificity and limited bioavailability have also hampered the development of gold(III) complexes to be used clinically. Over the past decade, researchers have made enormous efforts to improve the anti-cancer efficacy of gold(III) complexes. The strategic approaches included the (1) use of multidentate ligands containing strong σ -donor atoms to stabilize gold(III) ion; (2) preparation of gold(III) complex possessing a net

cationic charge to enhance cellular uptake efficacy; (3) introduction of cancer targeting group(s)/ hydrophilic substitution(s) to the ligand system; (4) encapsulation by polymeric substances to reduce the complex concentration under physiological conditions; (5) formation of dinuclear/ multinuclear gold(III) complexes to enhance their cytotoxic potencies; and (6) co-addition of cytotoxic agents to achieve synergism.

By using the robust porphyrinato ligand scaffold, a highly stable gold(III)-porphyrin complex system [Au^{III}(porphyrin)]⁺ possessing a net cationic charge was designed. The promising *in vitro* anti-cancer activities of a series gold(III) porphyrin complexes have been reported in 2003 [12]. In the subsequent studies, a drug lead [Au^{III}(TPP)]Cl (denoted as gold-1a, wherein H₂TPP = *meso*-tetraphenyl porphyrin, (Figure 1) has been identified to display promising anti-tumor activities in various nude mice and rat models against hepatocellular carcinoma [13], colon cancer [14], neuroblastoma [15], melanoma [16], nasopharyngeal carcinoma (NPC) [17] and NPC-associated metastasis [18]. In a more recent study, the gold-1a was reported to block the self-renewal ability of cancer stem-like cells by regulating micro RNAs including miR-106a and miR-106b [19].

The acute toxicity of gold-1a on nude mice has been examined. Its LD₅₀ value (median lethal dose) was determined to be 6.8 mg/kg (c.f. effective anti-cancer dosage ~ 3.0 mg/kg) [19]. One approach to reduce its toxicity is to prepare microcapsules of gold-1a; the sustained release gold-1a from the microcapsules could reduce the initial high complex concentration in biological system. Enhanced *in vivo* anti-cancer property of gold-1a has been demonstrated by using polymeric encapsulating materials such as PEG [20] and mixture of gelatin and acacia [21]. More recently, the sustained-release property of gold-1a has also been demonstrated in an organo gold(III) supramolecular polymer

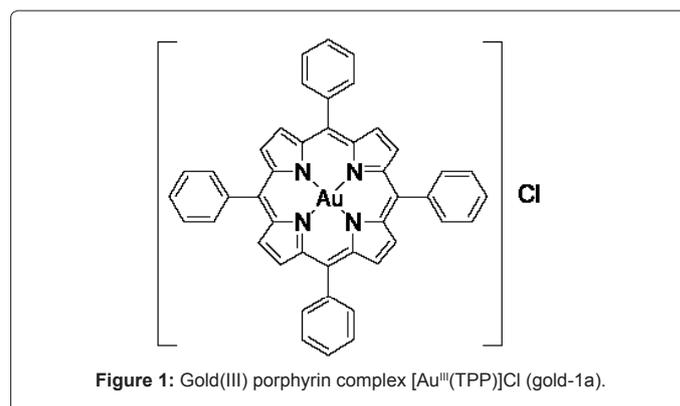


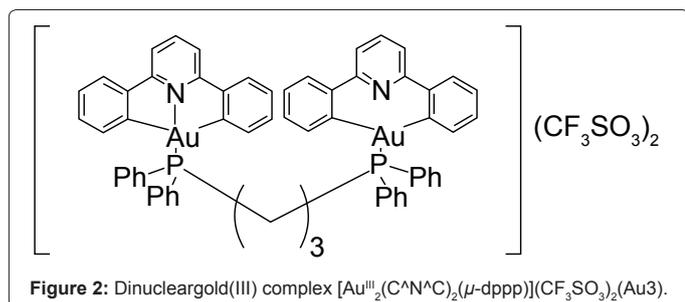
Figure 1: Gold(III) porphyrin complex [Au^{III}(TPP)]Cl (gold-1a).

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containing $[\text{Au}^{\text{III}}(\text{C}^{\wedge}\text{N}^{\wedge}\text{C})(4\text{-dpt})]^+$ moieties (wherein $\text{HC}^{\wedge}\text{N}^{\wedge}\text{CH} = 2,6\text{-diphenylpyridine}$; $4\text{-dpt} = 2,4\text{-diamino-6-(4-pyridyl)-1,3,5-triazine}$) [22].

One additional advantage for the medical development of the $[\text{Au}^{\text{III}}(\text{porphyrin})]^+$ system is the ease in structural modification of the gold(III) complexes. Over 25 gold(III) porphyrin complexes containing different substituents such as saccharide conjugation, lipophilic/hydrophilic moieties have been prepared [23]. The biological properties including cytotoxicity, affinity to anti-apoptotic bcl-2 protein, inhibition on thioredoxin reductase and topoisomerase were found to be significantly altered upon structural modification. In 2010, an asymmetrical gold(III) porphyrin analogue [5-(4-hydroxyphenyl)-10,15,20-triphenylporphyrinato gold(III) chloride (gold-2a) was found to display promising *in vivo* anti-tumor activity towards breast carcinoma in nude mice xenografts [24].

Apart from the $[\text{Au}^{\text{III}}(\text{porphyrin})]^+$, another system of gold(III) complexes $[\text{Au}^{\text{III}}(\text{C}^{\wedge}\text{N}^{\wedge}\text{C})(\text{NHC})]^+$ (wherein $\text{NHC} = \text{N-heterocyclic carbene}$) was also identified to have potent anti-cancer activities. A representative complex $[\text{Au}^{\text{III}}(\text{C}^{\wedge}\text{N}^{\wedge}\text{C})(\text{IME})]\text{CF}_3\text{SO}_3$ ($\text{IME} = 1,3\text{-dimethylimidazol-2-ylidene}$) was found to be stable under physiological conditions, to significantly poison topoisomerase I *in vitro*, and to suppress tumor growth in nude mice model [25]. Another series of cyclometalated gold(III) complexes $[\text{Au}^{\text{III}}_m(\text{C}^{\wedge}\text{N}^{\wedge}\text{C})_m\text{L}]^{n+}$ ($m=1-3$; $n=0-3$) was prepared by ligand substitution reaction of L with N-donor or phosphine ligands [26]. A dinuclear gold(III) complex $[\text{Au}^{\text{III}}_2(\text{C}^{\wedge}\text{N}^{\wedge}\text{C})_2(\mu\text{-dppp})](\text{CF}_3\text{SO}_3)_2(\text{Au}_3)$ (Figure 2) shows at least 100-fold higher cytotoxicity towards cancer cells *in vitro* than its monomeric gold(III) analogue [27]. Complex Au3 shows potent inhibition on hepatocellular tumor growth in nude mice and rat models with low acute and sub-chronic toxicities. Results from transcriptomics and connectivity map analyses have suggested that Au3 is a prominent inhibitor of thioredoxin reductase with an IC_{50} value as low as 2 nM, and also an inducer of endoplasmic reticulum (ER) stress. Meanwhile, treatment of Au3 on hepatocellular carcinoma cell line PLC was found to significantly enhance the expression of death receptor 5 (DR5). Understand the action mechanism of Au3 thus leads to the identification of cytotoxic TRAIL, a biological ligand for DR5, as a synergistic agent of the anti-cancer property of Au3 (Figure 2).

A number of gold(III) complexes have been reported to display promising *in vitro* anti-cancer activities and *in vivo* anti-tumor activities on various nude mice/ rat models over the past two decades. All these appealing activities, together with the feasibility in structurally modifying the gold(III) complexes to tune the biological activities, have highlighted the prospect in developing gold(III) complexes as promising anti-tumor therapy.

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