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<th>Strategies to Improve the Anti-Cancer Properties of Gold(III) Complexes</th>
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<td><strong>Author(s)</strong></td>
<td>Sun, RWY</td>
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cis-Diaminedichloroplatinum(II) (cisplatin or cis-[Pt(NH3)2Cl2]) 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 bio-
molecules 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 dmp ligand (wherein dmp = 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) dihydroxycarbamates complexes have recently been found to significantly inhibit the tumor growth of MDA-MB-231 breast

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 [AuIII(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 [AuIII(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 [AuIII(TPP)]Cl (gold-1a).
One additional advantage for the medical development of the \([\text{Au}^{III}(\text{porphyrin})]_n\) 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 thioreredox reductase and topoisomerase were found to be significantly altered upon structural modification. In 2010, an asymmetrical gold(III) porphyrin analogue (5-[4-(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 \([\text{Au}^{III}(\text{porphyrin})])^+\), another system of gold(III) complexes \([\text{Au}^{III}(\text{C}^N\text{C})(\text{NHC})]^{+}\) (wherein \(\text{NHC}=\text{N}-\text{heterocyclic carbene}\) was also identified to have potent anti-cancer activities. A representative complex \([\text{Au}^{III}(\text{C}^N\text{C})(\text{NMe})]\text{CF}_3\text{SO}_3\) (\(\text{NMe}=1,3\)-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 \([\text{Au}^{III}(\text{C}^N\text{C})(\text{NMe})]^{+}\) (\(m=1-3; n=0-3\)) was prepared by ligand substitution reaction of 1 with N-donor or phosphine ligands [26]. A dinucleargold(III) complex \([\text{Au}^{III}(\text{C}^N\text{C})(\mu-\text{dppp})]\text{CF}_3\text{SO}_3\) ([Au3]) (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 thioreredox 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 cytoxic TRAIL, a biological ligand for DR5, as a synergistic agent of apoptosis in human cervix epithelial cancer cells. Chem Commun (Camb) 1718-1719.

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