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Bioinorganic applications of gold and platinum coordination compounds: a brief historical overview and recent advances in 2017

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ABSTRACT

Gold-based metallodrugs have been studied for a wide variety of medical–related applications, although the antiarthritic auranofin is the only representative within this class that has reached the clinic. Platinum compounds, on the other hand, are the leading class of metallodrugs used against cancer, with very successful representatives worldwide, such as cisplatin, carboplatin and oxaliplatin. In this mini review, we will briefly present the development of gold- and platinum -based metallodrugs throughout the year of 2017.

1. Introduction

Medicinal applications of gold date to antiquity. The oldest records, dated to around 2500 BC, indicate that the Chinese and Arabians were the first to use gold for therapeutic purposes.[1,2] In the 8th century it was considered as an elixir of youth.[2] In the 19th century, sodium tetrachloridoaurate(I), $Na[AuCl_4]$, was prescribed to treat syphilis and chronic alcoholism. In the end of the 19th century, Robert Koch first described the activities of potassium dicyanidoaurate(I), $K[Au(CN)_2]$ for the treatment of tuberculosis.[2] With the development of modern Medicine and the emergence of new technologies, the empirical use of gold was replaced by a more rational design of gold-based medicine, to circumvent the toxic effects of $K[Au(CN)_2]$. This approach was responsible for the development of aurothioglucose (Solganol), myocrisin and later of auranofin, compounds used in the treatment rheumatoid arthritis. Curiously enough, the first uses of gold(I) compounds in treatment of rheumatoid arthritis were based on the idea that such illness was caused by a bacterial infection, which was shown to be incorrect. [1] Mirroring the historical application of gold and gold-containing compounds for the treatment of such a wide variety of diseases, the 2016-2017 period has introduced gold-based metallodrugs for applications including the molecular understanding of the mechanisms of interaction with protein targets[3–8] and development of new therapeutic agents for HIV, cancer, [9,10] bacterial infections[11] as well as parasitic infections.[12]

Platinum compounds, on the other hand, were intensively studied since the middle 1960's after the serendipitous discovery of the antitumor activity of cisplatin by Rosenberg.[13,14] Cisplatin revolutionized the treatment of testicular cancer, leading to cure rates higher than 95%. The mechanism of action of cisplatin is generalized as dependent of 4 steps: cellular uptake, aquation (replacement of the leaving ligands by water molecules, DNA binding (leading to a bending along the helical axis) and finally cellular processing, including recognition of the damage, which ultimately leads to cell death.[15] A well-stablished structure-activity relationship for cisplatin has been rationalized, and it relies on a square planar Pt(II) center surrounded by monodentate or chelating N-donors (non-leaving groups) and negatively charged monodentate or bidentate ligands (leaving ligands). Oxaliplatin and carboplatin were rationally developed expanding on the general structure of cisplatin. Both compounds feature bidentate ligands that are replaced by water molecules more slowly than the monodentate chlorides found in the structure of cisplatin.[16,17] Platinum drugs have been listed on the 2013's edition of the *Model List of Essential Medicines of the World Health Organization*, which highlights the relevance of this class of compounds and justifies the extensive research in the field. Some hand-picked examples published in the previous year will be discussed here. Within this period, we also highlight the breakthrough discovery regarding the mechanism of action of oxaliplatin, which was demonstrated to be significantly different from that of cisplatin and carboplatin.[18]

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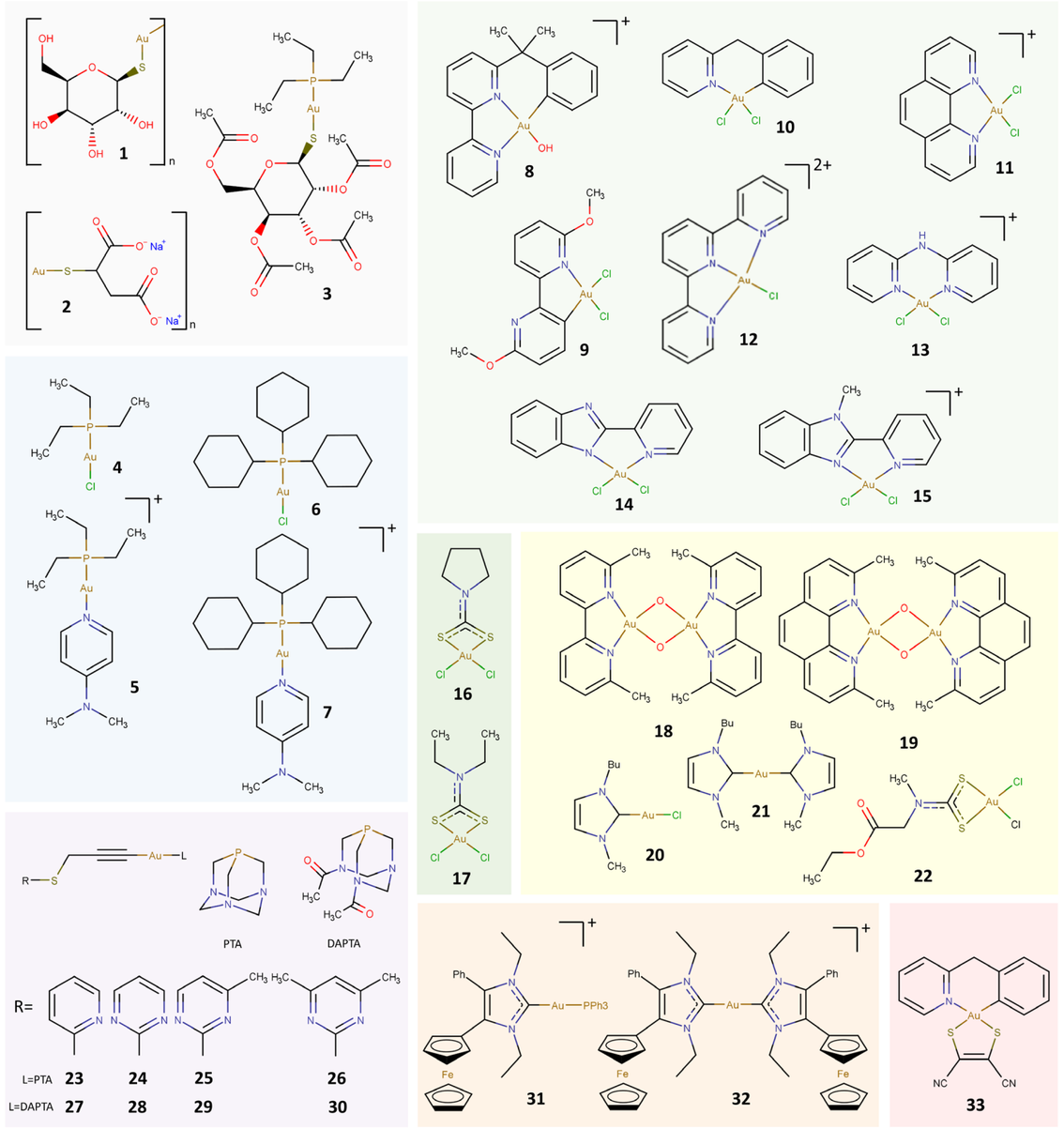

Figure 1 - Grey board: classical Au complexes used in crysotherapy, including aurothioglucose (solganol), aurothiomalate (**2**) and auranofin (**3**). Blue board: Au(I) compounds (**4-7**) designed by de Paiva et al.[3] as probes of the topography of the HIV-1 nucleocapsid zinc finger protein. Light green board: Au(I,III) compounds (**8-15**) studied by Meier et al.[5] and de Almeida et al.[6] for understanding the molecular basis of the interactions with selected biomolecules. Dark green board: gold(III) dithiocarbamate complexes (**16** and **17**) investigated by Wang et al.[7] as inhibitors of amyloid fibril formation. Yellow board: gold(I,III) complexes (**18-22**) evaluated by Massai et al.[8] as Cys-protease inhibitors and as antiparasitic agents. Purple board: Alkyne gold(I) compounds (**23-30**) studied as anticancer agents by García-Moreno and co-authors.[9] Orange board: Au(I) carbene compounds coupled to ferrocene moieties (**31** and **32**) investigated by Muenzner et al.[10] as anticancer agents. Red board: gold(III) organometallic compound (**33**) evaluated against Gram-positive and Gram-negative bacterial strains.[11]

2. Recent advances on Au(I,III) chemistry in the context of Bioinorganic Chemistry

Figure 1 shows gold-based metallodrugs published in the literature from 2016 to 2017.

Protein targeting and inhibition

A series of thiophilic Au(I)-phosphine compounds (**3-7**) was evaluated by Paiva et al.[3] for chemoselective auration of the C-terminal HIV nucleocapsid protein NCp7 zinc finger 2 (F2) and the full-length HIV NCp7 (NC), as probes of nucleocapsid topography. The nature of the phosphine and the co-ligand affect the reactivity with the C-terminal NCp7 F2 and the full-length NC. ^{31}P NMR spectroscopy showed the formation of long-lived {Au(PR_3)}−ZnF species in all cases, but a selective interaction was observed for the dmap-containing compound **5** with NCp7 F2. Auranofin (**3**) led to an unusual Au−His (rather than Au−Cys) coordination to NCp7. Modification of the fully functional NC zinc finger by Cy_3P-containing species (**6** and **7**) inhibited the NC−SL2 DNA interaction, as evaluated by fluorescence polarization.

Traveling Wave Ion Mobility-Mass Spectrometry (TWIM-MS) was used by Du, Paiva and Farrell[4] to investigate the possible coordination isomerism of Au(I) metallopeptide ions obtained by the interaction of compound **4** with the zinc fingers NCp7 F2 and Sp1 F3 (where Sp1 is the human transcription factor). Two conformers of the NCp7 F2 "gold finger" were identified in the gas phase using TWIM-MS, while a single conformer was identified for the Sp1 F3 "gold finger". Collision induced dissociation allowed an unequivocal assignment of the Au(I) binding sites for the major conformers obtained in each reaction. A Cys-Au-Cys coordination was identified for NCp7 F2 "gold finger", while a Cys-Au-His coordination was observed for the Sp1 F3 "gold finger".

Meier et al. studied the interaction of a series of gold(III) compounds (both organometallic and coordination, **8-12**) with biologically relevant nucleophiles by ESI-MS.[5] Compound **8** reacts readily with 9-ethylguanine (EtG). Organometallic compounds **9** and **10** show only very minor MS signals for EtG adducts even after 24 h. Readily detectable EtG adducts were observed for **11**. Compounds **11** and **12** form adducts with cytochrome c (cyt) to a greater extent than **9** and **10** do. Compound **8** did not form any adducts with either ubiquitin (ub) or cyt. Compounds **9** and **10** formed mono- and bis-adducts of the type [protein+$(L)_n$Au(III)]$^+$ (L is the respective C,N bidentate ligand; n = 1 or 2) with both proteins to a similar extent. Complexes **11** and **12** reacted similarly with both proteins, even leading to the formation of higher order adducts. Compound **8** reacted preferentially with Se-Cys, **9** with Cys, and **10** with His, whereas **11** and **12** undergo redox reactions and oxidize Cys to cystine. The molecular reactivity patterns and binding preferences correlated with the inhibition of TrxR1, i.e., Se-Cys binding leads to potent TrxR1 inhibitors and in some cases to a high antiproliferative activity. The binding preferences imply that the families of coordination and organometallic Au(III) anticancer agents follow different modes of action.

The inhibition of human aquaporin (AQP3) was evaluated by a series of Au(III) complexes (**10**, **11**, **13**, **14** and **15**) was investigated by Almeida et al. [6] The cationic complex **15** was identified as the most potent inhibitor of glycerol permeation. The neutral complex **14**, with a similar ligand system, was scarcely active. DFT studies showed a good correlation between the compound's calculated affinity to cysteine residues and their AQP3 inhibition. Electrochemistry demonstrated that AQP3 inhibition is not related to oxidative damage. Molecular Dynamics studies demonstrated that binding of the compounds to one monomer also affects substrate permeability in an adjacent one. The Au(III) complexes were also shown to be cytotoxic *in vitro* and AQP3 inhibition might contribute to the biological effects observed towards cancer cells.

Wang et al.[7] investigated the inhibition amyloid fibril formation by gold dithiocarbamate complexes. Thioflavin fluorescence assay (added to samples of the peptides PrP106-126 and hIAPP incubated with the gold compounds), supported by TEM and DLS measurements, revealed that complexes **16** and **17** effectively inhibited fibril formation. Auranofin (**3**) had only limited effects. In terms of binding sites, histidine was pointed as a potential target in both PrP106-126 and hIAPP.

A panel of Au(I) and Au(III) coordination and organometallic compounds (**2**, **3**, **8**, **18-22**) was evaluated in terms of inhibition of human and parasitic Cys-proteases (Proteasome (CT-L), Cathepsin B, Cathepsin L, Rhodesain and CPB2.8ΔCTE).[8] Compounds **8**, **19**, **20** and **22** were found to be potent inhibitors of human cathepsins (B and L) and of *L. mexicana* cysteine protease CPB2.8DCTE. The compounds showed sub-micromolar antiproliferative activity against *L. infantum*, *T. cruzi*, *T. brucei*, *T. rhodesiense* and *P. falciparum*, but were also shown to be cytotoxic against the model host cell lines MCR-5 and PMM.

Antiproliferative activities

A series of gold(I)-alkyne derivatives containing the water soluble phosphines PTA (1,3,5-triaza-7-phosphaadamantane) and DAPTA (3,7-diacetyl-1,3,7-triaza-5-phosphabicyclo[3.3.1]nonane) (compounds **23-30**) were tested against the human colon cancer cell line Caco-2 (PD7 and TC7 clones).[9] PTA-containing compounds were more cytotoxic than DAPTA-containing analogs, which correlated well with the higher cellular uptake of the former. The anticancer activity of **23** against colon cancer cell lines happens through the apoptotic pathway and induction of S-phase arrest in the cell cycle. An increase in the mean survival time and life expectancy in athymic nude mice xenografted with human HCT -116-luc2 cancer cells was observed, with moderate inhibition of tumor growth.[9]

Muenzner et al.[10] investigated the antiproliferative and antivascular properties gold(I) carbene complexes featuring 4-ferrocenyl-substituted imidazol-2-ylidene ligands (31 and 32 were selected as examples). The series had low micromolar to nanomolar IC_{50} (72 h) values against a panel of seven cancer cells. The lipophilic cationic complexes **31** and **32** caused an increase in reactive oxygen species by a ferrocene-dependent mechanism and by inhibition thioredoxin reductase. Both complexes led to a G1 phase cell cycle arrest and a retarded cell migration. Antiangiogenic effect was demonstrated by tube formation assays with endothelial cells. The biscarbene complex **32** lead to up to 80% xenograft tumor volume reduction in mice.

Antimicrobial properties

The novel heteroleptic cyclometalated complex [Au^{III}(py^b-H)(mnt)] (**33**) was tested against a panel of ten Gram-positive (belonging to the *Staphylococcus*, *Streptococcus* spp. and *Bacillus clausii*) and Gram-negative (*E. coli*, *K. pneumoniae*, *P. aeruginosa*) bacteria and three yeasts belonging to the *Candida* species. Complex **33** showed a remarkable bacteriostatic antimicrobial activity against *Staphylococci*, with Minimum Inhibitory Concentration (MIC) values of 1.56 and 3.13 μg/mL for *S. haemoliticus* and *S. aureus*, respectively. [11]

Antiparasitic properties

In a Phase **1** clinical trial, auranofin (**1**) was identified as a broad-spectrum antiparasitic drug, being effective *in vitro* and *in vivo* against *Entamoeba histolytica* and both metronidazole-sensitive and -resistant strains of *Giardia intestinalis*.[13] Both parasites are the major causes of water and foodborne diseases. Patients were treated daily with 6 mg of auranofin, which corresponds to the recommended dose for arthritis treatment. Besides the 7 days treatment period, the patients were followed for 126 days. A concentration of 13 μM (in auranofin equivalents) was found in feces at the 7th day of treatment, which corresponds to more than 25 fold the IC_{50} for *E. histolytica* and 4 fold that of *Giardia*.

3. Recent advances on Pt(II,IV) chemistry in the context of Bioinorganic Chemistry

Platinum compounds are still the leading metallodrugs and platinum chemistry with bioinorganic applications has been extensively explored. For that reason, we had to handpick the most noteworthy examples of platinum(II,

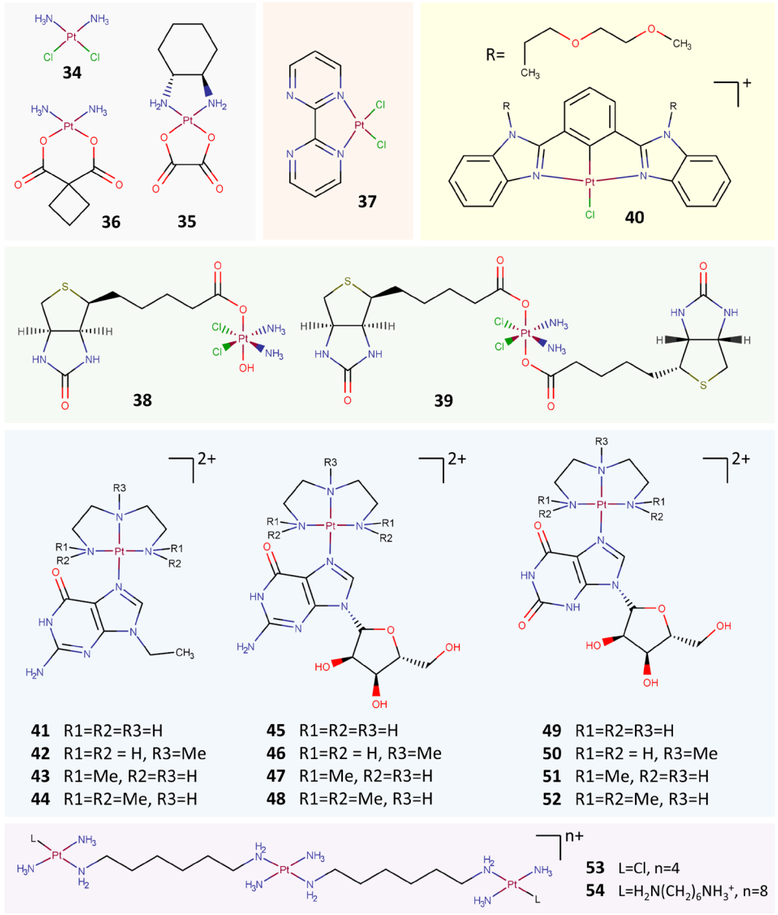

Figure 2 - Grey board: classical platinum(II) compounds cisplatin (**34**), oxaliplatin (**35**) and carboplatin (**36**). Orange board: platinum(II) complex (**37**) used by Rivilla and co-authors[19] for catalyzing 1,3-dipolar reactions of azomethine ylides with maleimides using platinated DNA systems coupled with copper(II). Green board: Platinum(IV) biotinylated systems (**38** and **39**) designed by Muhammad and co-authors as cytotoxic agents.[20] Yellow board: platinum(II) compound (**40**) designed by Zhu and co-authors[21] as probes for lipopolysaccharide endotoxin and discrimination between Gram-negative and Gram-positive bacterial strains. Blue board: platinum(II) compounds (**41-52**) designed by Tsotsoros and co-authors[22] containing the general motif [Pt(chelate)(N-donor)]$^{2+}$ and evaluated as anti-HIV agents. Purple board: Peterson and co-authors[23] demonstrated that the polynuclear platinum compounds triplatin (**53**) and triplatin NC (**54**) can bind to glycans.

has been extensively explored. For that reason, we had to handpick the most noteworthy examples of platinum(II, IV) metallodrugs published in the literature from late 2016 to late 2017 to be discussed in this minireview. Figure 2 shows the structures of the selected compounds.

Expanding on the understanding of cisplatin-like drugs

Bruno, Lippard, Hamman and co-authors demonstrated that oxaliplatin (**35**) kills cells by inducing ribosome biogenesis stress, unlike cisplatin (**34**) and carboplatin (**36**) that have the same effect through a DNA-damage response.[18] This difference in drug mechanism explains for example an observed lack of efficacy for oxaliplatin in the treatment of malignancies conventionally treated by cisplatin and suggests that alterations in the nature of the ligands in platinum complexes have deep implications for primary mechanisms of action. The final consequence is that platinum drugs might not function interchangeably with their derivatives in cancer chemotherapy. The authors suggest that the ability of oxaliplatin to cross-link DNA has questionable relevance in cytotoxicity, but it could still lead to the inhibition of rRNA synthesis, which would ultimately be responsible for ribosome biogenesis stress.

The mechanism of hypersensitivity of testicular germ cell tumors (TGCTs) to cisplatin was investigated by Awuah, Riddell, Lippard and co-authors.[24] The authors demonstrated that the high-mobility group box protein 4 (HMGB4), a transcription repressor preferentially expressed in the testes that binds cisplatin-damaged DNA, blocks excision repair of cisplatin-DNA 1,2-intrastrand cross-links, increasing the sensitivity of TGCTs to cisplatin therapy. CRISPR/Cas9-mediated gene editing was used to knockout the HMGB4 gene in a testicular human embryonic carcinoma. Cell proliferation and apoptosis assays demonstrated that loss of HMGB4 elicits resistance to cisplatin.

Bioconjugation

Rivilla, Cosío and co-authors described a novel catalytic system based on covalently modified DNA that promotes 1,3-dipolar reactions between azomethine ylides and maleimides.[19] The catalytic system makes use of the distortion of the double helix of DNA caused by platination of guanine units, similar in nature to the DNA damage caused by platinum chemotherapeutic drugs. As a proof of concept, compound **37** caused a distortion in salmon sperm DNA and an heterobimetallic system was generated *in situ* using $Cu(OTf)_2$. This system was able to catalyze (3 + 2) cycloadditions between azomethine ylidenes and maleimides.

Muhammad, Guo, Wang and co-atuthos demonstrated that tethering biotin moieties to the Pt(IV) scaffold remarkably increases the cellular uptake of Pt in breast cancer cells, but lowers its accumulation in breast epithelial cells. [20] The mono-biotinylated Pt(IV) complex (**38**) was more active than the di-biotinylated one (**39**) in terms of reactivity and cytotoxicity.

Platinum complexes as probes of biomolecules

A very interesting luminescent probe based on platinum(II) complexes of 2,6-bis(benzimidazol-20 -yl) pyridine with hexaethylene glycol methyl ether groups (compound **40**) was developed by Zhu, Yu and co-authors[21]. The compound can be used for sensing lipopolysaccharide (LPS) endotoxin and, as consequence, it can be applied in a sensor for rapid discrimination between Gram-negative and Gram-positive bacterial pathogens. In the presence of LPS, **40** binds to negatively charged LPS to form LPS–Pt(II) aggregates that enhance the intermolecular Pt/Pt and π- π stacking interactions, leading to a luminescence emission centered at 650 nm. The limit of detection of LPS was of 5.7 nM. As a proof-of-concept, the authors also demonstrated the application of **40** for rapid and washing-free discrimination of Gram-negative *E. coli* and Gram-positive *S. aureus* within 5 min.

Anti-HIV activity

Tsotsoros, Farrell and co-authors presented to the scientific community a systematic strategy to understand the interaction between platinum–nucleobase compounds and the tryptophan-containing HIV NCp7.[22] The inherent π–π stacking properties of the compound $[Pt(chelate)(N\text{-donor})]^{2+}$ were modulated by systematic variation of the tridentate ligand (diethylenetriamine and Me-substituted derivatives) and N-donor (nucleobase or nucleoside), leading to compounds **41-52**. The activity of $[Pt(dien)(9\text{-EtGua})]^{2+}$ (**41**) against HIV-1 strains BaL, NL4-3 and 91-US001 in peripheral mononuclear blood (PBMC) cells showed only modest HIV inhibitory activity for the latter with an IC_{50} = 28.61 mM. Cellular accumulation studies showed no significant correlation with lipophilicity of the compounds, but all compounds had very low cytotoxicity suggesting the potential for antiviral applications.

Novel targets

Peterson, Farrell and co-authors demonstrated that heparan sulfate acts as a ligand receptor for polynuclear platinum anti-cancer agents.[23] Masking of extracellular heparan sulfate (HS) through metalloshielding resulted in very effective inhibition of physiologically critical HS functions including catalytic heparanase (HPSE) and protein growth factor recognition. The interaction of cationic polynuclear platinum complexes with the model HS-like pentasaccharide Fondaparinux resulted in inhibition of its cleavage by the HS-related enzyme heparanase. The end-point of inhibition of HPSE activity and growth factor signaling is the prevention of cell invasion and angiogenesis, demonstrated in HCT-116 cells at sub-cytotoxic concentrations. A competition assay demonstrated that Fondaparinux can sequester the 8+ TriplatinNC from DNA, emphasizing the strength of PPC–HS interactions. Altering the profile of platinum agents from cytotoxic to anti-metastatic has consequences for future directions in the development of platinum-based chemotherapeutics.

4. Summary and Outlook

Some important contributions were made to the field of gold- and platinum-based metallodrugs throughout the year of 2017. New classes of gold compounds were explored in the field of bioinorganic chemistry, such as gold(I)-alkyne organometallic complexes.[9] A new MS-based technique, Ion Mobility Mass Spectrometry, was also employed to better characterize gold adducts to the nucleocapsid protein of the HIV-1 virus.[4] In the field of platinum chemistry, new insights were published on the mechanism of action of oxaliplatin, which surprisingly differs significantly from cisplatin and carboplatin.[18] Other exciting applications include bioconjugation for both medicinal[20] and catalytic purposes[19]. Finally, glycans were identified as a new class of biomolecular targets for polynuclear platinum complexes.[23]

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