

## Exploration of the medical periodic table: towards new targets†

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Metallo drugs offer potential for unique mechanisms of drug action based on the choice of the metal, its oxidation state, the types and number of coordinated ligands and the coordination geometry. We discuss recent progress in identifying new target sites and elucidating the mechanisms of action of anti-cancer, anti-bacterial, anti-viral, anti-parasitic, anti-inflammatory, and anti-neurodegenerative agents, as well as in the design of metal-based diagnostic agents. Progress in identifying and defining target sites has been accelerated recently by advances in proteomics, genomics and metal speciation analysis. Examples of metal compounds and chelating agents (enzyme inhibitors) currently in clinical use, clinical trials or preclinical development are highlighted.

### Introduction

A significant number of clinical trials now involve metal compounds, metal-chelating agents (metalloenzyme inhibitors) or other agents which interfere with metabolic pathways for metals, both for therapy and for diagnosis. Some of the areas of current clinical interest are listed in Table 1.

These areas have been stimulated by recent successes with platinum anticancer drugs (used as a component of nearly 50% of all cancer treatments), with gadolinium complexes as MRI contrast agents (about 20 million doses administered per year) and 99m-technetium radiopharmaceuticals for  $\gamma$ -ray imaging (used in about 20 million radiodiagnostic procedures each year). However, many other diseases and conditions are of current interest including neurodegeneration, microbial and parasitic (and other neglected tropical diseases) infections and inflammation.<sup>1–4</sup> About 24 elements are essential for man, Fig. 1. In principle, we should consider the roles of all essential elements in therapy (control of homeostasis), but this is

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**Table 1** Some examples of industries/sponsors with metallodrugs or chelating agents in development or clinical trials or approved for clinical use. In many cases more details can be found on the clinical trials website: <http://www.clinicaltrials.gov/>

Industry/sponsor	Drug	Use	Stage
<b>Metal-based anticancer therapeutics</b>			
Bioplatin AG	Dicycloplatin (Pt)	Bronchial carcinoma Liver cancer	China Phase I
Blend Therapeutics	Pt complexes including nanoparticles	Targeted and combination therapy	Pre-clinical
Regulon Inc.	Lipoplatin (Pt) (liposomal cisplatin)	Lung cancer	Phase III
Sanofi	Lipoxal (Pt) (liposomal oxaliplatin)	Colorectal cancer	Phase II
Cell Therapeutics Inc.	Oxaliplatin (Eloxatin) (Pt)	Colorectal cancer	Approved
	Dinuclear-platinum complex CT-47463	Various cancers	Pre-clinical
Solasia Pharma K.K.	Darinaparsin (As) (Z10-101/SP-02)	Peripheral T-cell lymphoma	Approved US and some other countries
Ziopharm/Teva	Trisenox (As)	Solid tumours (oral) Acute promyelocytic leukaemia Lung and others	Phase I Approved Phase II
Cancer Research UK	GSAO (As)	Advanced solid tumours that have not responded to therapy	Phase I
Sigea	NAMI-A (Ru) in combination with gemcitabine	Anti-metastatic agent	Phase I/II accomplished
NIKIPHARMA	NKP-1339 (Ru)	Various cancers, e.g. neuroendocrine and NSCLC	Phase I
	NKP-2235 (Ga)	Cancers with high incidence of bone metastases e.g. NSCLC, breast and prostate cancers, and multiple myeloma	Phase I
Virginia Commonwealth University	Belinostat (PXD101): histone deacetylase inhibitor (chelates Zn)	Relapsed or refractory acute leukaemia or myelodysplastic syndrome	Phase I
Patheon Inc.	Vorinostat: HDAC inhibitor (chelates Zn)	Cutaneous T cell lymphoma	Approved
Asan Medical Center		Gastric cancer	Phase I
Ohio State University		Advanced staged oropharyngeal squamous cell carcinoma	Phase I
Comprehensive Cancer Center		Brain cancer	Phase I
Genentech		Chronic myeloproliferative neoplasms	Phase II
Italfarmaco	Givinostat: HDAC inhibitor (chelates Zn)		
Boneca Corporation	Boronophenylalanine-based boron neutron capture therapy in combination with cetuximab (B)	Head and neck cancer	Phase I
Weill Medical College of Cornell University	Tetrathiomolybdate (Mo)	Breast cancer	Phase II
University of Michigan Cancer Center		Esophageal carcinoma	Phase II
Sanofi	Mozobil (plerixafor): (potential chelator-Zn)	Stem cell mobilisation	Approved
Viamet Pharmaceuticals, Inc.	VT-464 (lyase selective metallo-enzyme inhibitor (Fe in CYP17))	Prostate cancer	Phase I
Mayo Clinic	Auranofin (Au)	Recurrent fallopian tube, ovarian epithelial, peritoneal cavity cancer	Pilot
Univ Kansas		Chronic lymphocytic leukaemia (CLL) Small lymphocytic lymphoma Prolymphocytic leukaemia	Phase II
<b>Other metal-based therapeutics</b>			
Sanofi	Ferroquine (Fe) (SSR97193)	Antimalarial	Phase II
VPS-1, Inc.	VT-1161 (lanosterol demethylase metalloenzyme (CYP51) inhibitor)	Antifungal	Phase I
Prana Biotechnology	PBT2: hydroxyquinoline derivative – metal chelator	Alzheimer's Huntington's	Phase II
Shire Pharmaceuticals	Lanthanum carbonate (Fosrenol) (La)	Hyperphosphatemia	Approved
Smith & Nephew	Acticoat Absorbant™ Silver Eluting Dressing (Ag)	Prevention of lower extremity revascularization wound complications	Phase IV
Ceva (Nature Vet Pty Ltd)	Cu-Algesic (Cu <sup>II</sup> indomethacin) (Cu)	Anti-inflammatory (veterinary-horses, dogs)	Approved
Redox Pharmaceutical Corporation	Doxovir (CTC-96) Co <sup>III</sup> bis(2-methylimidazole) acacen complex (Co)	Ophthalmic herpetic keratitis and adenoviral conjunctivitis	Phase I completed
The University of Texas Health Science Center	Bismuth subcitrate potassium, metronidazole, tetracycline hydrochloride and omeprazole (Bi)	Herpes labialis <i>Helicobacter pylori</i> infection	Phase II completed Phase IV
UCSF/UC San Diego	Auranofin (Au)	Treatment of amoebiasis and parasite <i>Giardia intestinalis</i>	Trials planned



Table 1 (continued)

Industry/sponsor	Drug	Use	Stage
<b>Photodynamic therapy agents</b>			
Steba Biotech S.A. University of Oxford/Steba Biotech S.A.	Palladium bacteriophosphoride photosensitizer TOOKAD (Pd)	Localised prostate cancer Predetermined small renal tumour targets	Phase III Phase I/II
<b>Diagnostic radiopharmaceuticals</b>			
American College of Radiology Imaging Network Lantheus	Copper Cu 64-ATSM and PET/CT Scan (Cu) Cardiolite ( <sup>99m</sup> Tc-sestamibi) (Tc) Neurite ( <sup>99m</sup> Tc-disicate) (Tc) Etarfolatide (EC20- <sup>99m</sup> Tc) (Tc) <sup>99m</sup> Tc-MIP-1404 (Tc)	Cervical cancer Folate-receptor-positive tumours Folate-receptor-positive tumours Prostate cancer	Phase II Approved Phase III Phase II
Endocyte Inc. Molecular Insight Pharmaceuticals, Inc. Peking Union Medical College Hospital Vanderbilt University	<sup>68</sup> Ga-DOTA-TATE PET/CT Scan (Ga)	Mesenchymal tumours Oncogenic osteomalacia Neuroendocrine Cancer	Phase 0 In development Phase I
<b>Therapeutic radiopharmaceuticals</b>			
Actinium Pharmaceuticals	Actinium-225-Labeled Humanized Anti-CD33 Monoclonal Antibody HuM195 (Ac) Lintuzumab-Ac225 (Ac) Lintuzumab-Bi213 (Bi) Alpharadin ( <sup>223</sup> Ra chloride) (Ra)	Leukaemia myelodysplastic syndrome Acute myeloid leukaemia Acute myeloid leukaemia Bone metastasis from castration-resistant prostate cancer Prostate cancer	Phase I Phase I/II Phase II Phase I/II
Algeta ASA (Bayer)			
Radiation therapy oncology group and National Cancer Institute UMC Utrecht	Samarium-153-lexidronam pentasodium (Sm) Holmium-166 polylactic microspheres (Ho)	Prostate cancer Liver neoplasms	Phase II Phase II
Centre René Gauducheau	Radiation: IMP-288-lutetium (Lu)	Small cell lung cancer	Phase II
<b>Contrast agents and others</b>			
OHSU Knight Cancer Institute	Ferumoxytol and gadolinium magnetic resonance imaging (Fe, Gd)	Malignant brain tumours	Phase II
Lantheus Medical Imaging	BMS753951 (Gd)	MRI contrast for coronary arterial wall imaging	Development
Pharmacyclics	Motexafin gadolinium (Gd)	Radiation and chemotherapy sensitiser	Development
Alexion Pharmaceuticals	Cyclic pyranopterin mono- phosphate replacement therapy (precursor to Mo cofactor)	Markers for Mo cofactor deficiency Isolated SOX deficiency	Development

currently hampered in many cases (*e.g.* Si, V, Ni, Sn) because their natural biochemistry is poorly understood and we do not know how to diagnose conditions associated with their metabolism. For some elements it is already possible to use genomics to understand medical conditions related to them (*e.g.* Fe, Cu, Zn), but in other cases it is not clear how, or if, genomes code for these elements. Genomes do not code for the elements themselves, but for particular chemical forms (*e.g.* vitamin B<sub>12</sub> for cobalt). Genomic codes for metals are usually codes for proteins, proteins which are highly, but not totally, selective for particular metal ions. As is evident from the above examples of Pt, Gd and Tc, inorganic medicinal chemistry can make use of non-essential as well as essential elements for the design of drugs and diagnostic agents, Fig. 1.<sup>4</sup>

For many centuries the use of metallodrugs has been driven by empiricism. Whilst random screening is still a useful weapon in drug discovery, these days it should be guided largely by rational design. This implies that target sites (usually gene products – proteins) should be identified and verified early in the design process. Immediately this presents

challenges for medicinal metal coordination chemistry: either the synthesised complexes need to be inert to redox and ligand substitution reactions, or these reactions need to be controlled under biological conditions en route to the target. In turn, metal- and/or ligand-centred redox reactions provide a unique platform for drug design with concepts quite distinct from those for purely organic drugs.

In this article we highlight some areas of current interest in metallodrugs. We focus especially on their interactions with (proposed) target sites, including DNA and proteins. Despite the fact that successful clinical platinum anticancer drugs have DNA as their major target, DNA is nowadays not considered to be a favoured target site. This is partly because DNA is also likely to be attacked in normal healthy cells as well as in cancer cells. However, downstream processing of platinated DNA can differ in normal and cancer cells so differential cytotoxicity can still be achieved. Moreover, it is becoming evident that anticancer drugs that target a single protein or enzyme are not always successful, since cells readily become resistant to such drugs and utilise alternative metabolic pathways.



**Fig. 1** A medical periodic table: essential elements for man (symbols in white font); medical radioisotopes (green fill); elements currently used in therapy (blue fill) or diagnosis (orange fill). The entries (limited to 2 fill colours, illustrative and not comprehensive) are mainly restricted to elements/compounds which are clinically approved or on current clinical trials (e.g. as listed on <http://www.clinicaltrials.gov/>). Some entries for implants are included (e.g. Ti, Ta). The basis for some of the entries is given in Table S1 (ESI†).

Metallo-anticancer drugs have the potential advantage of attacking several sites (multi-targeting), which can be a highly effective strategy. It is important to identify these target sites and elucidate the molecular mechanisms of action. As we shall see, a range of new target sites are being proposed for metallo-drugs but there is still much progress to be made on target-site validation. Tailoring the design of metallodrugs to treat specific diseases and conditions is likely to be a major part of future personalised medicine, which will include genomic and proteomic profiling of individuals.

## 1. Metal-based anticancer drugs

### 1.1. DNA targeting

#### 1.1.1. A traditional approach for designing metallodrugs

**1.1.1.1. Direct coordinative DNA binding.** It is well established that the target site for the anticancer drug cisplatin (1), *cis*-[PtCl<sub>2</sub>(NH<sub>3</sub>)<sub>2</sub>] (Chart 1, FDA approval 1978), is nuclear DNA.<sup>5–15</sup> More than 4000 Pt compounds have now been tested as potential anticancer drugs, with the worldwide approval for clinical use of carboplatin (2, 1989) and oxaliplatin (3, 2002), and of three others – nedaplatin (4), lobaplatin (5) and heptaplatin (6) (Chart 1) for clinical use only in Japan, China and South Korea, respectively. The ability to form DNA adducts is important for the activity of all of these drugs. Table 2 lists the X-ray structures of *cis*-diam(m)ine Pt–DNA adducts registered in the Protein Data Bank by January 2013. Dicycloplatin (7) is a new complex developed at the University of Beijing by Yang *et al.* that has passed through Chinese clinical phase I trials. This compound is composed of one molecule of carboplatin and one molecule of cyclobutane-1,1-dicarboxylic acid interacting *via* hydrogen bonds (see Chart 1).<sup>16</sup> The mechanism by which the presence of free ligand affects the activity of this platinum drug is not clear.

Compounds based on *cis*-diam(m)ine Pt<sup>II</sup> structures tend to produce very similar types of adduct on target DNA – as exemplified in Table 2. It is therefore not surprising that they



**Chart 1** Molecular structures of some platinum anticancer drugs that are approved or undergoing clinical trials.

induce similar biological consequences, although protein recognition of the DNA adducts is dependent on the ligands. This consideration led to the hypothesis that development of Pt compounds structurally different from cisplatin which form different types of DNA–Pt adducts, may lead to a different spectrum of biological activity, perhaps complementary to cisplatin.<sup>36</sup> In the late 1980s, Farrell began a fruitful investigation of linear multi-platinum complexes, where the platinum centres are separated by aliphatic chains, and the chlorido ligands are *cis* or *trans* at the extremities of the complex.<sup>37–40</sup> These poly-platinum complexes are generally highly positively-charged. This leads to a stronger initial electrostatic recognition of DNA in comparison with monomeric species. Another critical feature of these multinuclear complexes is flexibility. The potent multi-platinum complex  $[(trans\text{-PtCl}(\text{NH}_3)_2)_2\text{-}\{\mu\text{-trans-Pt}(\text{NH}_3)_2(\text{NH}_2(\text{CH}_2)_6\text{NH}_2)_2\}]^{4+}$ , BBR3464 (8, Chart 2),<sup>41</sup> completed a phase I trial,<sup>42</sup> but failed phase II due to instability in blood.<sup>43–47</sup>



**Table 2** X-ray and solution NMR structures of coordinative platinum *cis*-diam(m)ine Pt<sup>II</sup>-DNA adducts registered in the Protein Data Bank in January 2013

Platinum complex	Type of Pt–DNA adduct	DNA structural changes	PDB ID and Ref.
Cisplatin	1,2- <i>cis</i> -{Pt(NH <sub>3</sub> ) <sub>2</sub> } <sup>2+</sup> -d(GpG) intrastrand cross-link	Bending (kinking) of duplex; rolling of the adjacent guanines; unwinding of the helix at platination site; widening and flattening of the minor groove opposite the platinum adduct	3LPV; <sup>17</sup> 3M9M, 3M9N, 3M9O; <sup>18</sup> 2R8J, 2R8K; <sup>19</sup> 2R7Z; <sup>20</sup> 1AIO; <sup>21</sup> 1A84; <sup>22</sup> 1AU5 <sup>23</sup>
	1,3- <i>cis</i> -{Pt(NH <sub>3</sub> ) <sub>2</sub> } <sup>2+</sup> -d(GpTpG) intrastrand cross-link		2WTF; <sup>24</sup> 1KSB; <sup>25</sup> 1DA4, 1DA5 <sup>26</sup>
	1,3- <i>cis</i> -{Pt(NH <sub>3</sub> ) <sub>2</sub> } <sup>2+</sup> -d(GpTpG) intrastrand cross-link in a nucleosome		3O62 <sup>27</sup>
	Interstrand cross-link		1A2E; <sup>28</sup> 1DDP <sup>29</sup>
Oxaliplatin	1,2-{Pt(dach)} <sup>2+</sup> -d(GpG) intrastrand cross-link	Stronger duplex bending than with cisplatin <sup>30</sup>	2K0T, 2K0U, 2K0V; <sup>31</sup> 1PG9, 1PGC; <sup>32</sup> 1IHH <sup>33</sup>
Pyriplatin	Monofunctional platinum–DNA adduct (Pt–N7G binding)	Markedly different transcription inhibition mechanism compared to cisplatin or oxaliplatin	3CO3 <sup>34</sup>
[PtCl(en) (ACRAMTU-S)] (NO <sub>3</sub> ) <sub>2</sub>	Dual mode	Platinum–N7G binding in the major groove + ACRAMTU intercalation leading to inhibition of damaged DNA transcription by RNA polymerase II	1XRW <sup>35</sup>

**Chart 2** Molecular structure of complex 8.

It seems to be the only Pt compound not based on the cisplatin chemotype to have entered human clinical trials.<sup>48</sup> Hydrolysis of BBR3464 and DNA adduct formation are well documented.<sup>49,50</sup> In general polynuclear platinum compounds bind rapidly to DNA ( $t_{1/2}$  ca. 40 min).<sup>47</sup> The most relevant feature of the special BBR3464–DNA binding is the lack of severe DNA distortions such as a kink, or significant unwinding of the helix, which are characteristics of DNA adducts of mononuclear platinum complexes. One of the direct consequences of this mild Pt-induced DNA conformational change is that these adducts are poor substrates for recognition by proteins, such as those containing the HMG domain, which binds to rigidly-bent DNA, as induced by cisplatin.<sup>51</sup> Overviews of multi-nuclear platinum drugs<sup>52,53</sup> and DNA binding to polynuclear platinum complexes<sup>54</sup> have been published.

Low-spin octahedral 5d<sup>6</sup> Pt<sup>IV</sup> complexes have potential advantages as anticancer drugs because they are more inert to substitution reactions than square-planar Pt<sup>II</sup> complexes and so are expected to undergo fewer side reactions en route to the tumour. Also they often have higher aqueous solubility, a feature exploited long ago by Tobe *et al.* who synthesised iroplatin (CHIP, JM9, *cis,trans,cis*-[PtCl<sub>2</sub>(OH)<sub>2</sub>(isopropylamine)<sub>2</sub>]).<sup>55</sup> Iroplatin entered phase I and II clinical trials,<sup>56,57</sup> and even phase III,<sup>58</sup> but ultimately was found to be less active than cisplatin and so not registered for clinical use.<sup>59</sup> Tetraplatin (ormaplatin) [PtCl<sub>4</sub>(D,L-cyclohexane-1,2-diamine)], also showed promise in preclinical studies but caused severe neurotoxicity in treated patients, and trials were subsequently abandoned at phase I.<sup>60</sup> The unpredictability of the rate, extent and localisation of *in vivo* reduction of these Pt<sup>IV</sup> complexes to the active Pt<sup>II</sup> species may be a complication in clinical use.

The need to overcome platinum resistance, to reduce toxic side-effects and broaden the spectrum of activity has also focussed attention on the potential of anticancer drugs containing other metals. Among them, Ru-based-drugs are promising.<sup>61</sup> The Ru<sup>III</sup> anticancer drug imidazolium-*trans*-dimethylsulfoxide-imidazole-tetrachlororuthenate (NAMI-A) (9) developed in Trieste by Mestroni, Alessio, *et al.* has reached phase I/II trials in combination with gemcitabine. Another octahedral Ru<sup>III</sup> complex indazolium-*trans*-bis(1*H*-indazole)-tetrachlororuthenate (KP1019) (10), developed by Keppler *et al.* in Vienna (Chart 3), has completed phase I clinical trials.<sup>62,63</sup> Organometallic arene Ru<sup>II</sup> complexes such as [(η<sup>6</sup>-biphenyl)Ru(en)Cl]<sup>+</sup> (en = ethylenediamine)<sup>61</sup> (11) and [(η<sup>6</sup>-*p*-cymene)Ru(PTA)Cl<sub>2</sub>]<sup>+</sup> (*p*-cymene = *para*-cymene and PTA = 1,3,5-triaza-7-phosphaadamantane) (12) (see Chart 3) have been widely studied and several others also show promise.<sup>65–76</sup>

The antimetastatic activity of NAMI-A is thought to be due to combined effects on the control of angiogenesis (possibly because it interferes with NO metabolism)<sup>77,78</sup> and anti-invasive properties towards tumour cells and blood vessels, and not to interaction with nucleic acids, although it can interact with DNA *in vitro*.<sup>79</sup> DNA has been proposed as one of the biological targets of KP1019, and it also triggers apoptosis.<sup>80</sup> However, the cellular mechanism of the activation of apoptosis is not understood.<sup>81</sup> These Ru<sup>III</sup> complexes may undergo activation by reduction to Ru<sup>II</sup> *in vivo*.<sup>82</sup>

Different mechanisms of action have been investigated for explaining the anticancer activity of arene ruthenium complexes. Interactions between complexes containing reactive Ru–Cl and nuclear DNA can occur, through the formation of intermediary aqua complexes able to ruthenate DNA specifically at guanine residues.<sup>83,84</sup> If the arene is extended (*e.g.* biphenyl, dihydroanthracene), DNA binding can involve not only direct coordination to G bases but also arene intercalation (see Section 1.1.1.3.). Ligand oxidation can provide a way to activate thiolato complexes of Ru<sup>II</sup> arenes, which may be of importance when the intracellular thiol glutathione binds to them. Mono- (to give the sulfenate) and bis- (sulfinate) oxygenation appear to be facile, but surprisingly do not weaken the Ru–S bond<sup>85</sup> even though





**Chart 3** Molecular structures of Ru<sup>III</sup> anticancer complexes **9** and **10**, and Ru<sup>II</sup> arene complexes **11** and **12**.

this provides a route to nucleobase binding.<sup>86</sup> Protonation of the sulfonate oxygen on the other hand does labilise this bond.<sup>87</sup>

Osmium, the heavier congener of ruthenium and a third row transition metal, commonly exhibits slower kinetics than ruthenium, and is often considered to be relatively inert. However, it is possible to tune the biochemical reactivity of the arene Os<sup>II</sup> complexes through understanding their aqueous solution chemistry. The rates of hydrolysis of  $[(\eta^6\text{-arene})\text{Os}(\text{XY})\text{Cl}]^{2+}$  complexes can be controlled by the choice of the chelating ligand XY (faster for XY = O,O, followed by O,N and slowest for N-donor chelating ligands, especially when N,N is a strong  $\pi$ -acceptor such as azopyridine). The  $\text{pK}_a$  values of the aqua adducts also follow this order, being highest for O,O ligands, with coordinated water tending to be more reactive than coordinated hydroxide.<sup>88</sup> Ligand substitution rates on arene Os<sup>II</sup> are often *ca.* 100 $\times$  slower than for Ru<sup>II</sup> and coordinated aqua ligands *ca.* 1.5  $\text{pK}_a$  units more acidic. Thus, active arene Os<sup>II</sup> complexes have been designed.<sup>89–99</sup> In particular chlorido Os<sup>II</sup> picolinate complexes can bind to DNA, but interestingly some inert iodido Os<sup>II</sup> azopyridine complexes exhibit nanomolar potency to a wide range of cancer cells and are also active *in vivo*.<sup>100</sup> The azopyridine complexes appear to have redox mechanisms of action.<sup>101</sup> Interestingly injected OsO<sub>4</sub> has a long history of use in therapy in Scandinavia for chemical synovectomy in the treatment of chronic synovitis.<sup>102</sup>

In addition to binding to DNA,<sup>103</sup> Ir<sup>III</sup> Cp\* anticancer complexes can also have redox mechanisms of action, readily forming hydride complexes on reaction with coenzyme NADH, and even producing H<sub>2</sub> catalytically.<sup>104</sup> These findings highlight the existence of new potential targets for such complexes.

**1.1.1.2. Non-covalent DNA binders.** Metal complexes of an appropriate shape and polarity can intercalate between DNA base pairs.<sup>105</sup> Intercalators can be potent mutagens, due to their ability to induce structural and therefore functional changes in duplex DNA, leading to inhibition of transcription, replication and DNA repair processes. Intercalators are potential antibiotics, antibacterials, trypanocides, schistosomicides, and antitumour agents.<sup>106,107</sup> Several metallo-intercalator complexes have been reported recently, Table 3.

Besides intercalation and groove binding, highly charged multinuclear complexes can bind strongly to the phosphate backbone of DNA, forming a “phosphate clamp”. The trinuclear complex triplatinNC  $[\{trans\text{-Pt}(\text{NH}_3)_2(\text{NH}_2(\text{CH}_2)_6(\text{NH}_3))_2\}\mu\text{-}\{trans\text{-Pt}(\text{NH}_3)_2(\text{NH}_2(\text{CH}_2)_6(\text{NH}_2)_2\}]\text{(NO}_3)_8$  (**13**, see Chart 4) exclusively utilises backbone functional groups to interact with DNA, and can associate with DNA even in the absence of direct coordination to DNA bases.<sup>129</sup>

**1.1.1.3. Coordination plus intercalation: dual mode DNA binders.** Metal complexes with  $\sigma$ -bonded aromatic side arms

**Table 3** Examples of DNA-intercalators and groove-binding metal complexes reported in 2011 and 2012

Metal	Ligands
Zn <sup>II</sup>	Schiff bases; <sup>108</sup> trihydroxy-isoflavones <sup>109</sup>
Au <sup>III</sup>	Liriodenines <sup>110</sup>
Au <sup>I</sup>	Phosphines <sup>111</sup>
Ag <sup>I</sup>	bis-Benzimidazole ligands <sup>112</sup>
Cu <sup>II</sup>	Dipyrido-phenazine and glycinate ligands; <sup>113</sup> (phenyl(pyridine-2-yl)methylidene)-benzohydrazides; <sup>114</sup> trihydroxy-isoflavones; <sup>109</sup> terpyridine ligands <sup>115</sup>
Cu <sup>II</sup> -Pb <sup>IV</sup>	Phenanthroline derivatives <sup>116</sup>
Pt <sup>II</sup>	Carbenes; <sup>117</sup> ethylenediamine, diaminocyclohexane and phenanthroline derivatives; <sup>118</sup> phenylpyridine; <sup>119</sup> bipyridyl-thiourea ligands; <sup>120</sup> phenanthroline derivatives <sup>121</sup>
Ni <sup>II</sup>	Trihydroxy-isoflavones; <sup>109</sup> (phenyl(pyridine-2-yl)methylidene)-benzohydrazides; <sup>114</sup> phenanthroline derivatives <sup>122</sup>
Ir <sup>III</sup>	Polypyridine ligands; <sup>126,127</sup> cyclopentadienyl ligands <sup>123</sup>
Rh <sup>III</sup>	Polypyridine ligands <sup>124</sup>
Co <sup>III</sup>	(Phenyl(pyridine-2-yl)methylidene)-benzohydrazides; <sup>114</sup> quinoline derivatives; <sup>125</sup> phenanthroline derivatives <sup>122</sup>
Ru <sup>II</sup>	Dppz <sup>a</sup> ligands; <sup>131,132</sup> allopyranoside-grafted ruthenium(ii) complex; <sup>126</sup> quinone derivatives; <sup>127</sup> phenanthroline derivatives <sup>118,119,128</sup>

<sup>a</sup> dppz = dipyrido[3,2-a:2',3'-c]-phenazine.



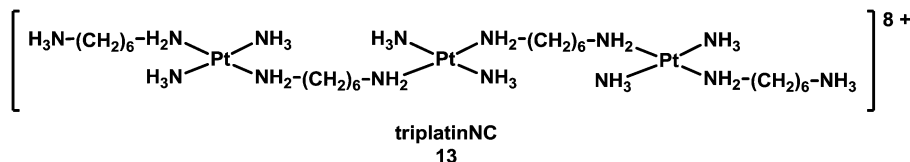


Chart 4 Molecular structure of triplatinNC.

or organometallic complexes with extended  $\pi$ -bonded arenes can act as dual-function complexes, binding to DNA both by direct metal coordination to a DNA base and intercalation between DNA bases through an attached aromatic ligand.<sup>105</sup> The utilisation of  $\sigma$ -bonded side arm-containing platinum complexes acting as intercalators was reported in the late 1980s.<sup>130,131</sup> For example, Pt complexes incorporating planar aromatic ligands such as acridine orange, 9-aminoacridine, ethidium bromide, and acridinylthiourea (ACRAMTU) bind to DNA by both coordination and intercalation.<sup>131–133</sup> The dual mode interaction causes a strong structural modification by increasing the length and unwinding the DNA duplex. On the other hand, helical bending, C3'-endo deoxyribose puckering and rolling are not observed, which distinguishes the dual mode-induced damage from intrastrand cross-link damage.<sup>35</sup> The adducts formed by the potent complex [PtCl(en)(ACRAMTU-S)](NO<sub>3</sub>)<sub>2</sub> (**14**) (Fig. 2) inhibit transcription of the damaged DNA by RNA polymerase II.<sup>134</sup>

Additionally, biphenyl Ru<sup>II</sup> complex **11** (Chart 3) not only binds strongly and preferentially to G bases in DNA but also intercalates *via* the phenyl substituent on the  $\eta^6$ -arene.<sup>135,136</sup> In monofunctional adducts of  $\{(\eta^6\text{-biphenyl})\text{Ru}(\text{en})\}^{2+}$  with the 14-mer (ATACATGGTACATA)-(TATG\*TACCATGTAT) ruthenation occurs at N7 of each guanine residue. At one site (G\*), not only was intercalation of the arene between G\* and adjacent T observed, but also stacking of a non-intercalated arene on a tilted adjacent thymine on the surface of the major groove.<sup>137</sup> Other dual-function coordination complexes have also been investigated,<sup>138,139</sup> such as the di-Rh<sup>II</sup> complex *cis*-[Rh<sub>2</sub>(dap)( $\mu$ -O<sub>2</sub>CCH<sub>3</sub>)<sub>2</sub>( $\eta^1$ -O<sub>2</sub>CCH<sub>3</sub>)(CH<sub>3</sub>OH)](O<sub>2</sub>CCH<sub>3</sub>) (dap = 1,12-diazaperylene).



Fig. 2 X-ray crystal structure showing the dual mode coordination/intercalation interaction between complex **14** and DNA (PDB ID 1XRW). Adapted from ref. 35.

A series of low-spin 5d<sup>6</sup> cyclopentadienyl Ir<sup>III</sup> organometallic half-sandwich complexes has been shown to form adducts with 9-ethylguanine and/or 9-ethyladenine readily, depending on the chelating ligands. Moreover, in the case of complexes incorporating extended Cp\* ligands, the ability to intercalate into DNA appears to contribute to the anticancer potency of these Ir<sup>III</sup> complexes.<sup>123</sup>

Combining Pt and other metal ions also provides a strategy for designing complexes able to bind DNA both by coordination and by intercalation. For example, in heterobimetallic complexes containing Pt and Ru centres joined by a linker,<sup>140</sup> Pt<sup>II</sup> offers coordinative binding through ligand substitution, and octahedral Ru<sup>II</sup> chelated by terpyridine or extended pyridyl ligands can act as an intercalator as well as possessing useful optical properties.<sup>140</sup> Alternatively, the Pt unit is capable of interacting with DNA by  $\pi$ - $\pi$  stacking or coordination through Cl substitution, and the Ru unit can bind to DNA by electrostatic or surface binding, or partial intercalation.<sup>141</sup>

**1.1.1.4. G-quadruplex binders.** Telomeres in human genes contain many repeats of the sequence d(GGTTAG) (G-quartets) and are responsible for maintaining cell division. In these G-rich strands, four-stranded G-quadruplexes can be formed consisting of planar G-quartets stabilised by K<sup>+</sup> or Na<sup>+</sup>. These inhibit the enzyme telomerase. Targeting either telomerase or stabilising G-quartets is an effective strategy for the design of anticancer agents.

The first, and only example to date, of an X-ray crystal structure of human telomeric G-quadruplex DNA bound to a metal complex was reported in 2012.<sup>142</sup> Nickel<sup>II</sup> and copper<sup>II</sup> salphen metal complexes were co-crystallised in the presence of human telomeric DNA and the effective binding of these metal-salphen complexes to human telomeric quadruplexes by direct end-stacking was demonstrated (see Fig. 3). Other methods have also been used to demonstrate the binding of metal complexes to quadruplex DNA. Table 4 lists examples of coordinative and non-coordinative metal-based G-quadruplex DNA binders reported between 2009 and 2012.

### 1.1.2. Selective DNA-targeting

**1.1.2.1. Metallodrugs with sequence specificity.** New metal drug candidates should (ideally) interact with a specific biological target. For DNA, incorporation of ligands possessing sequence specificity can provide a strategy to enhance the selectivity of binding. For example, mononuclear and dinuclear Pt<sup>II</sup> complexes incorporating linear and hairpin polyamide ligands (imidazole, pyrrole and  $\beta$ -alanine subunits, see Chart 5) are capable of recognising sequences up to seven base-pairs in length, providing a foundation for the synthesis of hairpin





**Fig. 3** X-ray crystal structure of human telomeric G-quadruplex DNA bound to a salphen-Ni<sup>II</sup> complex (PDB ID 3QSF). Adapted from ref. 142.

polyamides with multiple platinum groups leading to high DNA-sequence-selectivity, water-solubility and potentially highly active complexes.<sup>165,166</sup>

Specific recognition of DNA sequences can be also used to overcome side-effects and resistance to platinum drugs. Similarly incorporation of an oligonucleotide into a Pt complex allows sequence recognition within double stranded DNA by the formation of triple helices.<sup>167</sup> Various pathways to metal-containing oligonucleotides have been designed, such as conjugation of an end-functionalised oligonucleotide, chelation of an oligonucleotide to the metal or incorporation of metal-containing phosphoramidites or hydrogenophosphonates. Oligodeoxynucleotide-tethered bifunctional *cis*-dichlorido Pt complexes<sup>168</sup> can retain cross-linking ability.

**1.1.2.2. Protein-mediated DNA recognition.** The design of metallodrugs incorporating groups capable of interacting specifically with DNA sequences is a challenge. An elegant strategy is to use a presenter protein and a small molecule that can bind to both protein and target.<sup>169</sup> The formation of such ternary complexes has been described for organic drugs, such as the immunosuppressive antibiotic rapamycin,<sup>170</sup> and has

been illustrated as a concept for metallodrugs by an arene-Ru-biotin derivative<sup>171</sup> embedded in the tetrameric streptavidin protein (Fig. 4).<sup>172</sup> The supramolecular structure binds G-quadruplex DNA with selectivity towards DNA telomeres, even in the presence of competing targets (such as glutathione). However, because of a poor cellular uptake, the *in vivo* activity of the system was not investigated.

## 1.2. Protein targeting

A number of proteins (*e.g.* kinases, bacterial Zn enzymes) have been proposed as potential biological targets for metal complexes or chelating agents in the case of metalloprotein targets.<sup>173–187</sup> Modern bioanalytical techniques with high sensitivity and selectivity have facilitated the discovery of potential protein targets for metal complexes.<sup>188</sup> However, as for DNA, the ability of a metallodrug to interact with amino acids, peptides or proteins *in vitro* does not necessarily imply a direct involvement in the cellular mechanism of action of this metallodrug. The involvement of particular targets has to be validated (*e.g.* by knockdown experiments, silencing gene expression by RNAi techniques). This involves blocking production of the protein in the cell and observing the effects on the activity of the drug candidate. So far, this has been rarely done for metallodrugs. Correlations of activity with protein binding (including inverse) can be useful for structure–activity relationships.<sup>189</sup>

We now illustrate recent work on interactions of metallodrugs with potential protein targets. The examples are illustrative and not comprehensive.

**1.2.1. Hormone receptors.** Prostate cancer is the most common cancer for men and the second killing-cancer after lung cancer. The majority of prostate cancers are initially androgen-dependent and might be treatable by hormone therapy. This therapy aims to block androgen receptors (AR) by binding antagonists (antiandrogens) to these receptors instead of the endogenous testosterone.<sup>190</sup> Three are currently in clinical use for treatment of prostate cancer: flutamide,<sup>191</sup> nilutamide,<sup>192</sup> and bicalutamide,<sup>193</sup> (Chart 6). Despite promising results, resistance acquired by cancer cells (possibly due to mutations of the androgen receptor) is one of the major limitations of the use of hormone therapy.<sup>194</sup> The discovery of new antiandrogen compounds effective for both hormone-dependent

**Table 4** Coordinative and non-coordinative metal complexes which bind to G-quadruplex DNA

Metal	Ligands/ref.
Au <sup>III</sup>	Porphyrins; <sup>143</sup> pyrazolylpyridine <sup>144</sup>
Cu <sup>II</sup>	Salphen derivatives; <sup>142</sup> terpyridine-based ligands <sup>145</sup>
Pt <sup>II</sup>	Carboxamide phenanthrolines and bis-carboxamide pyridines; <sup>146</sup> terpyridines; <sup>145,147,148</sup> Schiff bases; <sup>149</sup> phenanthroimidazoles; <sup>150</sup> triarylpyridines; <sup>151</sup> perylene derivatives <sup>152</sup>
Tetranuclear Pt <sup>II</sup>	Quinoxalines <sup>153</sup>
Pt <sup>II</sup> –Zn <sup>II</sup>	Porphyrazine derivatives <sup>154</sup>
Dimetallic Cu <sup>II</sup> , Pt <sup>II</sup> and Zn <sup>II</sup>	Terpyridine-based ligands <sup>155</sup>
Pd <sup>II</sup>	Terpyridine-based ligands; <sup>145</sup> carboxamide phenanthrolines and bis-carboxamide pyridines <sup>146</sup>
Ni <sup>II</sup>	Salphen derivatives <sup>142</sup>
Ir <sup>III</sup>	2,2-Biquinolines <sup>156</sup>
Co <sup>III</sup> , Mn <sup>III</sup> , Octanuclear Ru <sup>II</sup>	Porphyrins <sup>157,158</sup>
Ru <sup>II</sup>	Polypyridyl ligands; <sup>159</sup> phenanthroline derivatives; <sup>160,161</sup> Dppz ligands <sup>162</sup>
Ru <sup>II</sup>	Phenanthroline derivatives
Dinuclear Ru <sup>II</sup>	Bipyridines and tetrapyrido-phenazines; <sup>163</sup> tetraazaphenanthrenes and tetrapyridoacridines <sup>164</sup>







**Chart 6** Molecular structures of flutamide, nilutamide, bicalutamide, tamoxifen, and hydroxyferrocifen.

irreversible and leads to rapid decomposition of the organo-metallic entity.<sup>197</sup> Similarly, cyclopentadienyl Re analogues do not exhibit antiproliferative activity, ( $\{CpRe(CO)_3\}$  acting as a spectator group).<sup>200</sup> Therefore, the redox activity of the ferrocenyl group is of central importance, along with the antiestrogenic properties of the hydroxytamoxifen derivative, for providing a unique dual mechanism of action of these ferrocenyl tamoxifen derivatives.

The anticancer activity of titanocene dichloride has been known for decades, but its efficacy in Phase II clinical trials in patients with metastatic renal cell carcinoma<sup>201</sup> or metastatic breast cancer<sup>202</sup> was too low to be pursued. The titanocenyl-derivative of tamoxifen<sup>203</sup> has estrogenic effects on hormone-dependent breast cancer cells in the nanomolar range. Unfortunately, hydrolysis of the titanocene fragment leads to the generation of  $Ti^{IV}$  species that behave in a similar way to estradiol towards the estrogen receptor. This explains the estrogenic effect observed for  $Cp_2TiCl_2$  and precludes the use of  $Cp_2TiCl_2$  derivatives of tamoxifen as drug candidates for the treatment of breast cancer. It also poses the problem of the possible role of titanium salts as endocrine disruptors.<sup>197</sup> Nonetheless, the recent development of highly active water-soluble ring-substituted cationic titanocene dichloride derivatives has reactivated interest in such organometallic complexes.<sup>204–206</sup>

Another promising way of targeting hormonal receptors is utilisation of carboranes as estrogen receptor agonists and antagonists. Estrogen receptors are over-expressed in estrogen-receptor-positive tumours, such as in some breast cancers.<sup>207</sup> Carboranes are versatile pharmacophores and possess unique properties that make them useful in inorganic chemistry.<sup>208,209</sup> Compounds incorporating carborane cages structurally close to estradiol,<sup>210</sup> can act as efficient estrogen receptor agonists.<sup>211</sup> *Closo* carborane tamoxifen is more stable than tamoxifen itself,

and the *Z* carborane tamoxifen isomer exhibits similar inhibition properties as tamoxifen.

**1.2.2. Mitochondrial protein targeting.** Mitochondria in cells regulate energy production and modulate redox potentials as well as generating reactive oxygen species (ROS *e.g.*  $O_2^{\bullet-}$  and  $H_2O_2$ ). In cancer cells, mitochondria have hyperpolarised membranes and over-produce ROS. Their defective function in cancer cells makes them potential targets for anticancer drugs.

Mitochondrial proteins are potential targets for arsenic compounds which can bind strongly to vicinal (Cys) thiol groups, increase ROS production and induce apoptotic signalling pathways. Several studies have highlighted the potential of arsenic metallodrugs in cancer therapy. Arsenic(III) trioxide ( $As_2O_3$ ) has been used as a therapeutic agent for over 2000 years.<sup>212–214</sup> More recently Ehrlich screened hundreds of organoarsenic compounds for biological activity and in 1910 introduced Salvarsan (arsphenamine) for the treatment of syphilis. Currently,  $As_2O_3$ , (ATO, 'Trisenox', Table 1) is the most effective single agent for the treatment of acute promyelocytic leukaemia.<sup>215</sup> In aqueous solution ATO exists as the trihydroxide  $As(OH)_3$ , and is taken up into cells *via* the aquaporins (especially aquaglyceroporins<sup>216</sup>)-membrane transport proteins.

GSAO (4-(*N*-(*S*-glutathionylacetyl)amino) phenylarsonous acid) is a promising new compound, known to inhibit adenine nucleotide translocase (ANT) in the inner membrane of mitochondria. A phase I clinical study is in progress in patients with solid tumours refractory to standard therapy (Table 1).<sup>217</sup> Metabolism of GSAO is required for biological activity. This metabolism involves a two-step mechanism, first cleavage by  $\gamma$ -glutamyltranspeptidase at the cell surface to give GCAO (4-(*N*-(*S*-cysteinylglycylacetyl)amino) phenylarsonous acid). Then GCAO enters cells *via* an organic ion transporter and is metabolised by dipeptidases to CAO (4-(*N*-(*S*-cysteinylacetyl)amino) phenylarsonous acid) in the cytosol (Fig. 5). Finally, CAO enters





Fig. 5 Metabolism of GSAO and molecular structure of PENAO. Adapted from ref. 218.

the mitochondrial matrix and As<sup>III</sup> cross-links cysteine residues 57 and 257 of human ANT1,<sup>218</sup> so inhibiting this enzyme.

The analogue of CAO, PENAO (4-(*N*-(*S*-penicillaminylacetyl)-amino) phenylarsonous acid) (Fig. 5), is accumulated in cells *ca.* 85-fold faster than GSAO, has a 44× higher antiproliferative activity and 20× higher antitumour efficiency in mice. In 2012, patients with solid tumours refractory to standard therapy were recruited for Phase I/IIa dose escalation studies.<sup>218</sup>

In general, many positively-charged lipophilic complexes are taken up by mitochondria, for example cationic gold(i) phosphines and carbenes.<sup>219,220</sup> Another example is inert polypyridyl Ru<sup>II</sup> complexes which target mitochondrial function and induce apoptosis. A strategy for combinatorial parallel coordination chemistry has been recently used, giving access to a library of more than 500 monocationic polypyridyl ruthenium complexes.<sup>221</sup> These complexes were screened for cytotoxicity towards cancer cells, and structure–activity relationships led to the discovery of a lead complex [Ru(<sup>t</sup>Bu<sub>2</sub>bpy)<sub>2</sub>(phox)]PF<sub>6</sub> (<sup>t</sup>Bu<sub>2</sub>bpy = 4,4'-di-*tert*-buty-2,2'-bipyridine and Hphox = 2-(2'-hydroxyphenyl)oxazoline) (15, Chart 7), which is active at submicromolar concentrations in clinically relevant Burkitt-like lymphoma cells. This complex strongly reduces the mitochondrial membrane potential, suggesting involvement of the intrinsic pathway of programmed cell death. These complexes are chiral,

but all compounds in this study were formed as mixtures of enantiomers or diastereoisomers. It would be interesting to test the separated enantiomers for activity.

Another example of mitochondrial targeting is the complex [Ru(dppz)<sub>2</sub>(CppH)]<sup>2+</sup> (CppH = 2-(2'-pyridyl)pyrimidine-4-carboxylic acid; dppz = dipyrido[3,2-*a*:2',3'-*c*]phenazine, 16, Chart 7), which impairs the mitochondrial membrane potential in HeLa cells as early as 2 h after treatment and induces apoptosis.<sup>222</sup>

**1.2.3. Kinases, TNF-α and thioredoxin.** The selective targeting of enzyme kinases is a particularly complex task, since more than 500 proteins belong to this family, although they all possess highly conserved ATP binding sites.<sup>223</sup> Inert octahedral metal complexes are emerging as promising scaffolds for targeting kinase active sites,<sup>224</sup> thanks to their rigid and globular shapes, and high synthetic versatility.<sup>225</sup> Meggers and co-workers have demonstrated that specific Ru<sup>II</sup>,<sup>226</sup> Os<sup>II</sup>,<sup>227</sup> Rh<sup>III</sup>,<sup>228</sup> and Ir<sup>III</sup> (ref. 229) complexes can serve as highly potent (micromolar to nanomolar range) and selective inhibitors of kinases. In most cases, the racemic complexes were resolved into the enantiomers by chiral HPLC (*Δ/Δ*-, or *R/S*-enantiomers), and the individual isomers were tested against different kinase enzymes. The affinities of the isomers for kinase ATP-binding sites are markedly different (for instance, the *Δ*-enantiomer of a ruthenium complex (FL-172) 27-fold more potent for kinase PAK1 compared to the *Λ*-enantiomer<sup>226</sup>). The Ru centre is not involved in any direct interactions and has solely a structural role.<sup>230</sup> A striking example of this work is the crystal structure of PIM2 (a serine/threonine kinase over-expressed in human leukaemia and lymphomas) with a bound *R*-configuration organoruthenium inhibitor (17, see Fig. 6 for molecular structure), which shows the good shape complementarity between the Ru complex and the ATP site of kinase PIM2, Fig. 6. An interesting strategy is the combination of kinase inhibition and photoactivity demonstrated for an angiogenic octahedral organoiridium complex. This can undergo substitution of a selenocyanate ligand on irradiation with visible light and induces apoptosis in cancer cells.<sup>231</sup> There are good prospects for further improving the selectivity of photo-activated metallodrugs by conjugation to targeting vectors such as peptides.<sup>232</sup>



Chart 7 Molecular structures of complexes 15 and 16. Only one enantiomer is shown.





**Fig. 6** Molecular structure of complex **17** and X-ray crystal structure showing its interactions in the ATP pocket of PIM2 kinase (PDB ID 2IWI). Adapted from ref. 233.

Aberrant activity of tumour necrosis factor- $\alpha$  (TNF- $\alpha$ , a pro-inflammatory cytokine involved in the regulation of many key biological processes, *e.g.* haematopoiesis, immunity, and inflammation)<sup>234</sup> is associated with a number of diseases, such as diabetes, tumorigenesis, and autoinflammatory diseases. Clinical trials in ovarian cancer suggest that synthetic therapeutic antibodies (*e.g.* infliximab), which bind directly to TNF- $\alpha$ , may be effective in blocking its interaction with the tumour necrosis factor receptor (TNFR).<sup>235–237</sup> Despite this success, synthetic antibodies suffer from limitations, such as development of anti-antibody response, which has led to the search of alternative small-molecule-based therapies as inhibitors of TNF- $\alpha$ . Based on the approach developed for kinase inhibition, inert octahedral metal complexes, such as the cyclometalated biquinoline iridium(III) complex **18** (see Chart 8), hold potential as direct TNF- $\alpha$  inhibitors.<sup>238</sup>

Interest in targeting the thioredoxin system – including thioredoxin (Trx), thioredoxin reductase (TrxR) and NADPH – led in 2006, to the submission of a New Drug Application to the FDA for Motexafin gadolinium, an inhibitor of thioredoxin



**Chart 8** Molecular structure of complex **18**. One enantiomer is shown.

**Table 5** Recent examples of metal (and metalloid) complexes which interact with isolated thioredoxin reductase

Metal	Compound/ligands
Se	Organic selenium-containing amino acids <sup>245</sup>
As	Arsenic trioxide <sup>246</sup>
Hg	Methylmercury <sup>247</sup>
Au <sup>I</sup>	Carbene derivatives; <sup>240,242,248,249</sup> Auranofin; <sup>250</sup> thiosemicarbazones; <sup>242</sup> Benzimidazol-2-ylidene; <sup>251</sup> <i>N,N'</i> -disubstituted cyclic thiourea <sup>252</sup>
Au <sup>I</sup> and Au <sup>III</sup>	Glyoxaldehyde-bis(thiosemicarbazones) <sup>253</sup>
Ag <sup>I</sup>	Carbene derivatives; <sup>249</sup> silver-nanoparticles <sup>254</sup>
Pt <sup>II</sup>	Nedaplatin <sup>255</sup>
Pt <sup>IV</sup>	<i>cis</i> -[Pt(NH <sub>3</sub> ) <sub>2</sub> Cl <sub>2</sub> ] and <i>trans</i> -[PtCl <sub>2</sub> (CN) <sub>4</sub> ] <sup>2–</sup> ; <sup>256</sup>
Pd	K <sub>2</sub> PdCl <sub>4</sub> , and K <sub>2</sub> PdCl <sub>6</sub> <sup>257</sup>
Ru <sup>II</sup>	Carbene derivatives <sup>258</sup>
Cr <sup>VI</sup>	Chromates <sup>259</sup>

reductase and ribonucleotide reductase, for the treatment of lung cancers with brain metastases. This compound is currently in clinical development as a radiation and chemotherapy sensitizer (Table 1). Thioredoxin reductase remains an attractive target for metallodrugs (Table 5), particularly for gold complexes,<sup>239–243</sup> although there is a need to validate this as a target for these metal complexes *in vivo*. Thioredoxin reductase (TrxR) contains FAD and NADPH binding domains and a redox-active disulphide (Cys–Cys) bond in its active site. It transfers electrons to thioredoxin which, in turn, reduces disulphide bonds and other substrates. Mammalian TrxRs contain a second redox-active site, a C-terminal –Cys–SeCys– (where SeCys is selenocysteine).<sup>244</sup>

### 1.3. Metallodrug delivery and activation

**1.3.1. Light activation of Pt<sup>IV</sup> prodrugs.** Spatially-targeted activation by light is a possible way of increasing the efficiency of Pt<sup>IV</sup> prodrugs, avoiding unnecessary damage to normal tissues, and delivering the active drug mainly to the tumour itself to enhance activity or activate the drug specifically in the cancer cells.<sup>260</sup> The metal complexes used are generally stable to thermal activation so that they reach the target site intact. However the excited singlet and triplet states (which are often reached very quickly, in pico-nano seconds) have different electron distributions to the ground state and hence different geometries and different reactivities.<sup>261</sup> Excited state drugs offer the prospect of novel mechanisms of action.<sup>262</sup> The wavelength of activation is important because longer wavelengths (*e.g.* red light) penetrate tissues more deeply than shorter wavelengths (*e.g.* blue light).

Platinum(IV) complexes of the type [Pt(OH)<sub>2</sub>(N<sub>3</sub>)<sub>2</sub>(amine1)-(amine2)] have strong azide-to-Pt<sup>IV</sup> charge-transfer bands, are stable in the dark, and towards the intracellular reducing agent glutathione.<sup>263</sup> After short treatment and short irradiation times (*e.g.* 1 h), they react rapidly with DNA bases such as guanine and are potently cytotoxic. Interestingly, the *trans* diam(m)ine diazido complexes appear to be more effective as photoactivatable anticancer agents than the *cis* isomers (Fig. 7).<sup>264</sup> These complexes are also more effective than cisplatin when used under conditions appropriate for clinical phototherapeutic drugs (short treatment times, short irradiation times).





**Fig. 7** Photocytotoxicity of *trans*-diam(mine) Pt<sup>IV</sup> diazido complexes versus their *cis*-isomers, with associated IC<sub>50</sub> values.

The DNA lesions are unusual and include interstrand cross-links. *Trans,trans,trans*-[Pt(OH)<sub>2</sub>(N<sub>3</sub>)<sub>2</sub>(NH<sub>3</sub>)(py)] is active *in vivo* on activation with blue light in an oesophageal cancer model.<sup>265</sup> *Trans,trans,trans*-[Pt(OH)<sub>2</sub>(N<sub>3</sub>)<sub>2</sub>(py)<sub>2</sub>] (py = pyridine) undergoes photoreduction when irradiated by UVA, blue or green light,<sup>266</sup> and also produces azidyl radicals which can be quenched by L-Trp.<sup>267</sup> Therefore these diazido complexes may have a dual mechanism of action involving the production of reactive Pt<sup>II</sup> and radicals from the Pt<sup>IV</sup> prodrug. Unlike conventional photosensitizers (which convert <sup>3</sup>O<sub>2</sub> to excited <sup>1</sup>O<sub>2</sub>; photodynamic therapy), these complexes would not rely on O<sub>2</sub> for activity, a potential advantage since tumours are often relatively hypoxic.

Other metal complexes are potent light activated anticancer agents. For instance, strained octahedral tris-bipyridyl ruthenium(II) complexes have been shown to be inert until triggered by visible light.<sup>268</sup> Under irradiation, a light-activated ligand release mechanism occurs, leading to DNA binding, and to an increase in cytotoxicity of 2 orders of magnitude in cancer cells (with potencies superior to cisplatin against 3D tumour spheroids). The use of intramolecular strain is a promising strategy for developing light-activated Ru complexes for PDT applications.

### 1.3.2. Photo-release of biologically-active small molecules.

Photoactivation is also a promising strategy for the release of biologically-active small molecules such as NO, CO, and H<sub>2</sub>S. NO is an important signalling molecule with a wide range of functions in the cardiovascular, nervous, and immune systems.<sup>269</sup> The interactions of NO with metal complexes *in vivo* – heme and non-heme Fe in particular – are of prime importance to its physiological role. Metal complexes show promise for both controlled release and scavenging of NO.<sup>270</sup> Examples include [Ru(terpy)(bdqi)NO]<sup>3+</sup> (terpy = terpyridine, bdqi = 1,2-benzoquinone diimine) which can release NO on irradiation with visible light. This complex can be delivered in lipid nanoparticles *via* topical administration and provides a possible treatment for skin cancer.<sup>271</sup>

CO is also a natural signalling molecule which can be released from a metal centre by light activation,<sup>272</sup> and metal carbonyls have been extensively investigated as potential CO-donating pharmaceuticals.<sup>273,274</sup> *In vivo*, CO appears to have a role as a messenger, has anti-inflammatory properties and an ability to suppress organ graft rejection. The design of metal complexes that can release CO at a predictable rate is therefore valuable as a relatively non-toxic source of CO. Cell viability studies of HT29 colon cancer cells treated with

the CO-releasing compound [Mn(CO)<sub>3</sub>(tpm)]PF<sub>6</sub> (tpm = tris-(pyrazolyl)methane) have revealed a significant photoinduced cytotoxicity, comparable to that of the established anticancer agent 5-fluorouracil.<sup>275</sup>

**1.3.3. Anticancer platinum drug delivery.** The limitations of Pt<sup>IV</sup> drug candidates might also be overcome by the utilisation of drug cargos. In principle, these transporters can carry a large number of platinum centres, shield the drug from premature activation, and deliver platinum specifically to cancer cells. Moreover, cancer cells divide rapidly and have a higher demand for nutrients than normal cells. Because of this need for nutrients, the vascular endothelial growth factor (VEGF) is expressed and induces angiogenesis (formation of new blood vessels for the tumour cells) which increases the permeability of the cell membrane. The increased permeability leads to a higher uptake of large molecules and proteins. However the major difference from normal cells resides in the lymphatic drainage, which is severely impaired for cancer cells, thus leading to the retention of large molecules and lipids inside the cell.<sup>276</sup> This enhanced permeability and retention (EPR) effect of cancer cells is an excellent target for the development of anti-cancer agents.<sup>277</sup> Large molecules might be selectively taken up by cancer cells and retained whereas excretion by normal cells through their healthy lymphatic system might occur.

A large number of carrier systems have been developed in recent years, spanning functionalised carbon nanotubes, nanorods, metal-organic frameworks, metalla-cages, nanoparticles, liposomes, nanogels, proteins, and polymers. This wide diversity of systems offers an interesting pool of carriers, and each system possesses unique advantages.<sup>260</sup> The delivery system can also influence the activity of metallodrugs. For example, a Pt<sup>IV</sup> complex has been recently tethered *via* amide linkages to gold nanoparticles (AuNPs) functionalized with thiolated oligonucleotides. The resulting systems exhibit 12-fold higher activity than free cisplatin towards A549 lung cancer cells.<sup>278</sup> The delivery of a lethal dose of cisplatin to prostate cancer cells by the encapsulation of Pt<sup>IV</sup> prodrug in prostate-specific membrane nanoparticles (NPs) has also been recently reported.<sup>279</sup> The utilisation of prostate-specific membrane antigen to target aptamers overexpressed in tumour cells, allows a specific delivery of the active drug into cancer cells. The release of the Pt<sup>IV</sup> complex from the nanoparticles is followed by reduction to Pt<sup>II</sup> (cisplatin), which can subsequently form 1,2-d(GpG) intrastrand cross-links on nuclear DNA.

Ruthenium metalla-cages also show promise as drug delivery systems. Supramolecular metalla-prisms based on arene ruthenium complexes can encapsulate square-planar acetylacetonato Pd<sup>II</sup> and Pt<sup>II</sup> complexes in their cavities and deliver them into cells, (*e.g.* [19]<sup>6+</sup>, see Chart 9).<sup>280,281</sup> The activity of these carceplexes towards human ovarian cancer cell lines is more than an order of magnitude higher than the empty metalla-cage.<sup>281</sup> Metalla-prisms can be synthesised with larger portal sizes (*e.g.* [20]<sup>6+</sup>, [21]<sup>6+</sup>, and [22]<sup>6+</sup>, see Chart 9).<sup>282,283</sup> The guest can be released from such metalla-cages without rupture of the cage,<sup>284-288</sup> and the extent of drug release correlates with the portal size of the cage.<sup>289</sup> The host-guest





Chart 9 Molecular structures of metalla-cages [19]<sup>6+</sup>, [20]<sup>6+</sup>, [21]<sup>6+</sup>, and [22]<sup>6+</sup>.

capability of these systems has been used for encapsulating hydrophobic pyrenyl-cycloplatin complexes,<sup>290</sup> pyrenyl-containing dendrimers of different generations, for targeting cancer cells *via* the EPR effect,<sup>291–293</sup> and for incorporating guests having affinity for G-quadruplex DNA.<sup>294</sup> They can also be used as vehicles for intracellular delivery of photosensitisers, with possible use in photodynamic therapy.<sup>295</sup> These systems being robust, highly water-soluble, and versatile are promising for drug delivery.

## 2. Anti-viral, anti-microbial and anti-diabetic metallodrugs

### 2.1. Anti-viral metallodrugs

**2.1.1. Hepatitis.** According to The World Health Organization, hepatitis C viral infection (HCV) affects 150 million people with consequences spanning from a mild illness lasting a few weeks to a serious, lifelong condition that can lead to cirrhosis of the liver or liver cancer. Every year, more than 350 000 people die from hepatitis.<sup>296</sup> This disease can be treated by combination therapy involving pegylated recombinant interferon and ribavirin. However, interferon is not always well tolerated, some HCV genotypes respond better to interferon than others, and both interferon and ribavirin are not selective for HCV or viral disease in general.<sup>297</sup> Moreover, the absence of an effective vaccine is stimulating the search for new drugs. A possible strategy for such development is to target specifically the critical RNA sequences present in hepatitis C virus but rare in the genome of infected host cells. For instance, the synthesis of a catalytic metallodrug that targets stem-loop IIb of the internal ribosomal entry site (IRES) RNA of hepatitis C virus has been recently reported.<sup>298</sup> This metal complex incorporates an amino-terminal copper and nickel binding motif (ATCUN) that is found naturally at the N-terminus of many albumins<sup>299</sup> as well as natural peptides such as histatin 5<sup>300</sup> and neuromedin,<sup>301</sup> and which binds copper and nickel with very high affinity.<sup>302</sup> The ATCUN ligand provides a stabilisation of the redox states Cu(III)/Cu(II) and prevents the formation of the labile Cu(I) state. A C-terminal tetrapeptide (YrFK-amide) targeting domain is also coordinated to the metal centre in order to provide a selective recognition of the HCV IRES stem-loop IIb domain (Chart 10). Interestingly, neither the targeting peptide alone YrFK-amide, lacking the metal binding ATCUN motif, nor the metal binding ATCUN domain alone show any cellular efficacy. However, the



Chart 10 Molecular structure of Cu(II)-YrFK-amide complex.

complex reacts *in vitro* with the HCV IRES stem-loop IIb domain and inactivates catalytically and irreversibly the replication of hepatitis C virus with a turnover number of about 32.<sup>298</sup> Despite this low turnover number, this preliminary study represents a promising new approach to the design of anti-hepatitis drugs.

**2.1.2. Human immunodeficiency virus.** Drugs for treatment of the Human Immunodeficiency Virus (HIV) are targeted to various pathways and enzymes: nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, and integrase inhibitors.<sup>303</sup>

The enzyme integrase (IN) catalyses the integration of viral DNA into the host cell DNA and is a particularly interesting target for HIV inhibitors. The active centre of the enzyme possesses two Mg<sup>II</sup> ions held in place by a triad of protein carboxylate side chains, as well as an HHCC zinc finger site. Ligands which can chelate to the Mg<sup>II</sup> ions might be effective enzyme inhibitors and drugs. Such a drug is raltegravir, approved by the FDA in 2007 (see Fig. 8). Despite its clinical success it suffers from an overall dose burden, and a lack of potency. To help to overcome rising raltegravir resistance, Cohen *et al.* have synthesised a series of raltegravir-chelator derivatives (RCD) as HIV integrase inhibitors in order to assess the role of the metal-binding group.<sup>304</sup> The binding mode for this series of RCD molecules was elucidated by docking simulations, based on a crystal structure of prototype foamy virus (PFV) integrase in complex with raltegravir (PDB ID 3OYA). The docking of raltegravir and of RCD-1 (structure in Fig. 8) into PFV IN gives identical binding modes (Fig. 8), showing that the O,O,O donor atom triad of both raltegravir and RCD can bind to the Mg<sup>II</sup> ions, forming 5- and 6-membered chelate rings.





**Fig. 8** Molecular structures of raltegravir and RCD-1. Comparison of the computational docking of RCD-1 (magenta) in the PFV IN versus the reported crystal structure of raltegravir (green) bound to PFV IN (PDB ID 3OYA). Adapted from ref. 304.

Carbamoyl pyridine scaffolds can also chelate two  $Mg^{II}$  ions in the active site of HIV-1 IN with nanomolar affinity.<sup>305</sup> Carcelli *et al.* have shown that incorporation of  $Ru^{II}$  arene substituents can increase the potency of quinolone and hydroxypyrimidine-carboxamide HIV-1 IN inhibitors.<sup>306</sup>

An effective anti-HIV strategy is to target the membrane protein CXCR-4, a seven-helix transmembrane G-protein-coupled receptor and one of the several chemokine receptors that HIV uses to infect CD4+ T cells. The bis-macrocyclic xylyl-bicyclam has potent anti-HIV activity but its use in the treatment of HIV was hindered by its lack of oral availability and cardiac disturbances.<sup>307</sup> During clinical trials, its effectiveness in mobilising stem cells from the bone marrow was discovered, which led to clinical approval by the FDA in 2008 for this purpose (*e.g.* in transplant therapy) as the drug Mozobil.<sup>308</sup>

Metal ions such as  $Zn^{II}$  and  $Cu^{II}$  bind to cyclam strongly<sup>309</sup> and relatively rapidly,<sup>310</sup> and it seems likely that metal complexation by xylyl-bicyclam is involved in the mechanism of action of the drug *in vivo*. The affinity of xylyl-bicyclam for the CXCR4 receptor is enhanced by factors of 7, 36, and 50 by incorporation of  $Cu^{II}$ ,  $Zn^{II}$ , or  $Ni^{II}$ , respectively, into the cyclam rings. Dizinc xylyl-bicyclam tetraacetate forms the unusual folded *cis-V* configuration with an acetate carboxylate bound to  $Zn^{II}$  on one side of the cyclam ring and acetate forming a double H-bond to cyclam NH groups on the other side of the ring.<sup>311</sup> In a model of the Zn drug docked onto human CXCR4, a similar coordination can be achieved involving the carboxylates of Asp171, Asp162 and Glu288. Hydrophobic interactions involving Trp side chains and the periphery of the cyclam rings together with metal-carboxylate binding and H-bonding are observed in the X-ray crystal structure of  $Cu^{II}$ -cyclam and  $Cu^{II}_2$ -bicyclam adducts of the protein lysozyme (Fig. 9).<sup>312</sup>

Configurational constrained metal-cyclam complexes have potential as even more potent antiHIV agents. For example,  $Zn^{II}$



**Fig. 9** X-ray crystal structure of a  $Cu^{II}$ -cyclam adduct of lysozyme (PDB ID 1YIK). A different viewing point is adopted in the enlargement on the right side, for clarity. Adapted from ref. 312.

hexyl-dimethyl-cyclam complexes are active, but more active are  $Zn_2((5-5'-(1,4\text{-phenylenebis(methylene)})\text{-bis}(1,5,8,12\text{-tetraazabicyclo}[10.2.2]\text{hexadecane}))(\text{OAc})_4)$ ,<sup>313</sup> and  $Ni_2(1-[4\text{-aminomethylbenzyl}]-1,4,8,11\text{-tetraazabicyclo}[10.2.2]\text{hexadecane})(\text{NO}_3)_2$ .<sup>314</sup> These studies illustrate that direct metal coordination, H-bonding and hydrophobic interactions with the ligands can all play important roles in metallodrug-protein target recognition.

## 2.2. Anti-microbial agents

**2.2.1. Tuberculosis.** Tuberculosis (TB) remains a major global health problem, with almost 9 million new cases in 2011 and 1.4 million TB deaths (990 000 among HIV-negative people and 430 000 HIV-associated TB deaths).<sup>315</sup> Moreover, 27 000 cases of extremely drug-resistant TB in both developed and underdeveloped countries were reported in 2005; The most recently developed anti-tuberculosis drug is more than 40 years old. New anti-tuberculosis drugs with different



biological mechanisms are needed, and although metal complexes might provide efficient alternatives, very few examples of such complexes have been reported, and in most cases, their mechanisms of action have rarely been thoroughly studied.

Nonetheless, some recent studies have demonstrated the potential of metal-based drugs for the development of anti-tuberculosis agents. Among them, the redox activation of isoniazid iron(II) complexes is of interest.<sup>316</sup> Indeed, isoniazid has been used as a front-line drug in the treatment of TB, although resistant TB strains have limited its use. Isoniazid is a prodrug that needs to be activated by an electron transfer reaction. This reaction is catalysed by the catalase-peroxidase KatG, and leads to the formation of an intermediate isonicotinic acyl radical that promptly reacts with NADH, generating a NAD-isoniazid adduct. This adduct is an efficient inhibitor of the enoyl reductase enzyme InhA, a major target for anti-*Mycobacterium tuberculosis* agents.<sup>317</sup>

About 50% of isolated isoniazid-resistant strains have either a deletion or mutations in the *katG* gene and this KatG enzyme disruption (blocking electron transfer reactions) has been shown to be the major cause of isoniazid resistance.<sup>318</sup> For overcoming such resistance, the coordination of isoniazid to metal complexes (e.g. cyanoferrates) might allow a rapid oxidation of the metal centre, triggering isoniazid activation intramolecularly, independently of the activation by KatG enzymes (see Fig. 10 for a possible mechanism of action). This hypothetical mechanism still needs to be supported by experimental evidence, but preliminary studies on an isoniazid-containing pentacyanoferrate complex show that an inner-sphere electron transfer reaction occurs between the metal and isoniazid, thereby activating this prodrug and overcoming the necessity for KatG. This metal complex inhibits both wild-type InhA and its isoniazid-resistant mutant InhA I21V, even in the absence of KatG and NADH, bypassing the enzymatic activation.



**Fig. 10** Possible mechanism for overcoming isoniazid resistance using an Fe<sup>II</sup> complex. Based on ref. 316.

Interestingly, the ruthenium analogue (isoniazid)pentacyanoruthenate(II) complex does not inhibit InhA, probably because its very high electrochemical potential is outside the biological range.

**2.2.2. Other anti-microbial agents.** Many metal compounds show appreciable antimicrobial activity, some established examples are based on silver, bismuth, mercury, arsenic, and antimony. For instance, the arsenic-based antimicrobial agent Salvarsan ((AsR)<sub>n</sub>, R = 3-amino-4-hydroxyphenyl, where *n* = 3 and 5 are the most abundant species in solution) was used historically to treat syphilis and trypanosomiasis, although in recent times it has been replaced. It is suggested that oxidation *in vivo* generates the active form of the drug, such that Salvarsan serves as a slow-release source of RAs(OH)<sub>2</sub> (oxidation from As<sup>I</sup> to As<sup>III</sup>).<sup>319</sup> The importance and historical role of inorganic and organometallic complexes as antimicrobial agents have been recently reviewed.<sup>320,321</sup>

A wide range of inorganic compounds from organometallic complexes to metal organic frameworks, nanoparticles or metallic surfaces have also been recently investigated for killing or inhibiting microbial growth, including mercury,<sup>322</sup> silver,<sup>323</sup> gold wires<sup>324</sup> and nanoparticles,<sup>325</sup> copper,<sup>326</sup> cobalt,<sup>327</sup> platinum,<sup>326</sup> palladium,<sup>328</sup> ruthenium,<sup>329</sup> iron (chelation therapy),<sup>330,331</sup> manganese complexes,<sup>332</sup> titanium dioxide nanoparticles,<sup>333</sup> noble metal nanoparticles,<sup>334,335</sup> and nanostructures as anti-bacterial drug delivery systems.<sup>336</sup>

### 2.3. Anti-diabetic metallodrugs

Diabetes mellitus (DM) is a group of chronic metabolic diseases characterised by persistent hyperglycaemia associated with absolute or relative deficiency in insulin secretion from the beta cells of pancreas. The dysfunction of insulin receptors might also be associated with diabetes. The current (285 million patients worldwide) and dramatically-increasing incidence of this disease is stimulating the search for new anti-diabetic agents.<sup>337</sup> Potential insulin mimetic metallodrugs have received much interest in the last two decades. The aim of developing new oral insulin mimetic drugs that act independently of insulin, for both insulin-dependent and insulin-independent diabetes, is to overcome side effects such as hyperinsulinemic hypoglycaemia due to current insulin preparations and synthetic drugs used in clinic.

Zinc and vanadium complexes have been widely studied as potential metallopharmaceutics for treating diabetes mellitus. Zinc plays an essential role in the physiology, structure and function of insulin,<sup>338</sup> and vanadium is also an essential element. The complex bis(maltolato)oxovanadium(IV) (BMOV, Chart 11), underwent phase II clinical trials but failed due to effects on the kidneys of patients. To reduce toxicity, Wei *et al.* have synthesised a vanadium complex which incorporates a modified pyranone derivative (BBOV, Chart 11).<sup>339</sup> BBOV has low *in vivo* toxicity and oral administration of this complex to STZ-induced diabetic rats leads to a dramatic reduction of hyperglycaemia, along with an increase of the impaired glucose tolerance activity.

A third metal of interest for development of anti-diabetic drugs is chromium, an element for which there is now no good





**Chart 11** Molecular structures of vanadyl anti-diabetic drug candidates BMOV and BBOV.

**Table 6** Examples of anti-diabetic Cr<sup>III</sup> complexes

Cr <sup>III</sup> ligands	Activity
Nicotinates, phenylalanines, histidinates	Decrease of blood glucose level <sup>342–345</sup>
Polysaccharides	No positive effect <sup>346</sup>
Picolinates	Improvement of serum lipid metabolism Improvement of glucose metabolism <sup>347,348</sup>
Propionates	Amelioration of insulin resistance symptoms <sup>349</sup>
Rutin, folate and stachyose ligands	Control of blood glucose <sup>350</sup>
Malate	Control of blood glucose level, liver glycogen level, and of the activities of aspartate transaminase, alanine transaminase, and alkaline phosphatase <sup>351</sup>

evidence that it is essential.<sup>340,341</sup> Table 6 summarises recent examples of anti-diabetic Cr<sup>III</sup> complexes and their activity.

Tetrahedral vanadate, molybdate, and tungstate complexes can compete with phosphate substrates for binding to phosphatases,<sup>352</sup> and are potent inhibitors of muscle glycogen phosphorylases by competing with glucose-1-phosphate.<sup>353</sup> Sodium tungstate Na<sub>2</sub>WO<sub>4</sub> has been particularly investigated, due to the restoration of hepatic glucose metabolism by the stable oxoanion [WO<sub>4</sub>]<sup>2-</sup>.<sup>354</sup> Moreover, [WO<sub>4</sub>]<sup>2-</sup> appears to mimic most of the metabolic effects of insulin and stimulate insulin output.<sup>355</sup> The Keggin anion [PW<sub>12</sub>O<sub>40</sub>]<sup>3-</sup> has been also investigated for its ability to mimic insulin.<sup>356–358</sup> Sodium molybdate Na<sub>2</sub>MoO<sub>4</sub> is similarly effective for preventing or treating of diabetic mellitus in the early stages of the disease.<sup>359</sup> However none of these compounds has yet received clinical approval as a new antidiabetic drug.

There is also increasing interest in the potential use of vanadium compounds for treating leishmaniasis, Chagas' disease and amoebiasis, and viral infections.<sup>360</sup>

### 3. Anti-parasitic, anti-inflammatory and anti-neurodegenerative metallodrugs

#### 3.1. Anti-parasitic metallodrugs

**3.1.1. Malaria.** The absence of a vaccine for the prevention and/or treatment of malaria is one of the major factors stimulating the search for new anti-malarial therapeutics. Malaria is treated mainly with a combination of chloroquine and antifolate drugs, or by artemisinin derivatives. Innovative drugs having new biological mechanisms of action are needed, due to the emergence of a high number of drug-resistant *Plasmodium* strains. In this context, metallodrugs are a promising class of compounds that might lead to a breakthrough in antimalarial therapy.

*Plasmodium falciparum* is one of the five species of *Plasmodium* parasite that causes the most lethal form of malaria. *Plasmodium falciparum* is particularly sensitive to oxidative stress,<sup>361</sup>



**Fig. 11** Molecular structure of auranofin. Docked conformation of {Au(PET<sub>3</sub>)}<sup>+</sup> in truncated SmTGR. FAD is in violet sticks. The gold atom is a yellow sphere. Residues interacting with the gold atom are in sticks. Adapted from ref. 364.

and targeting of thioredoxin reductase is an approach that is being widely studied.<sup>362</sup> Auranofin (Fig. 11) and a few related gold complexes strongly inhibit *Plasmodium falciparum* growth, probably due to a direct inhibition of *Plasmodium falciparum* thioredoxin reductase. In 2012, based on studies demonstrating that auranofin is a pro-drug giving rise to the active fragment {Au(PET<sub>3</sub>)}<sup>+</sup> (while the tetraacetylthioglucose ligand is excreted *in vivo*),<sup>363</sup> molecular docking experiments<sup>364</sup> were carried out and suggest that {Au(PET<sub>3</sub>)}<sup>+</sup> can bind to a N atom of an histidine in the active site of *Plasmodium falciparum* thioredoxin reductase, Fig. 11. This mode of binding to a protein His sidechain (despite the presence of Cys thiol sulfurs) was observed previously for {Au(PET<sub>3</sub>)}<sup>+</sup> in the X-ray structure of cyclophilin-3.<sup>365</sup> Gold(I) also has a high affinity for seleno-cysteine which provides selectivity for inhibition of thioredoxin reductase over glutathione reductase.<sup>251</sup>

Another approach for designing metallodrugs with potency against malaria is to coordinate biologically-active quinolone derivatives to metal centres. The ferrocene–quinoline conjugate ferroquine has been on clinical trials (Chart 12, Table 1).<sup>366</sup>

Chloroquine is thought to interfere with the digestion of haemoglobin in the blood stages of the malaria life cycle. Even though some similarities between the biological mode of action





**Chart 12** Molecular structures of chloroquine, ferroquine, and ruthenoquine. The intramolecular hydrogen bond facilitating membrane permeability of ruthenoquine is shown.

of chloroquine and ferroquine have been observed,<sup>367</sup> ferroquine exhibits additional mechanisms.<sup>368</sup> In particular, ferrocene can undergo a one-electron oxidation, yielding the ferrocenium cation, which may generate hydroxyl radicals under physiological solutions,<sup>369,370</sup> leading to potential DNA<sup>371</sup> and cell membrane damage.<sup>372</sup> Moreover, the weaker base properties and higher lipophilicity at physiological pH of ferroquine compared to chloroquine, as well as intramolecular H-bonding with the lateral side chain of ferroquine (in non polar conditions) leads to the improved ability of ferroquine to cross membranes and a higher accumulation in the digestive vacuole.<sup>373</sup>

Ferroquine and ruthenoquine analogues possess slightly different mechanisms of action, Ruthenoquine does not produce reactive oxygen species (ROS) under the oxidative conditions of the parasitic digestive vacuole of *Plasmodium falciparum*.<sup>374</sup> However, both compounds are active against drug-susceptible and drug-resistant strains of *Plasmodium falciparum*.<sup>375</sup> Ruthenocenic derivatives of chloroquine with and without an intramolecular hydrogen bond have been used to study the localisation and quantification of ruthenoquine in *Plasmodium falciparum*-infected erythrocytes.<sup>374</sup> This study suggested that the presence of intramolecular H-bonding (Chart 12) substantially improves the membrane permeability and transport of the drug to its target.

**3.1.2. Amoebiasis.** Amoebiasis is an infection of the intestine caused by the parasite *Entamoeba histolytica*, responsible for about 70 000 deaths a year.<sup>376</sup> The World Health Organisation estimates that amoebiasis is the fourth leading cause of death due to protozoan infections (after malaria, Chagas disease, and trichomoniasis). Current medications for the treatment of amoebiasis are based on nitroimidazole derivatives, such as metronidazole, and tinidazole. However, the appearance of resistant *E. histolytica* strains<sup>377</sup> and side effects associated to these drugs, are strong limitations for this family of compounds. New drugs are therefore needed with new mechanisms of action.

Metal complexes of active anti-amoebiasis drugs have been investigated including Au<sup>I</sup>, Ru<sup>II</sup> and Cu<sup>II</sup> complexes of metronidazole ([1-(2-hydroxyethyl)-2-methyl-5-nitro-1*H*-imidazole]) which

have higher activity than uncomplexed metronidazole.<sup>378</sup> Cyclooctadiene Ru<sup>II</sup> complexes of thiosemicarbazone derivatives are also more active than metronidazole.<sup>379</sup> Recently, an automated, high-throughput screen has been developed to facilitate drug screening for *Entamoeba histolytica*.<sup>380</sup> Interestingly, this screening identified that auranofin is 10× more potent against *E. histolytica* than metronidazole. The capability of this drug to inhibit *E. histolytica* thioredoxin reductase prevents the reduction of thioredoxin and enhances the sensitivity of trophozoites to reactive oxygen-mediated killing. This new use of auranofin represents a promising therapy for amoebiasis, and the drug has been granted orphan-drug status by the FDA (Table 1).

### 3.2. Anti-inflammatory metallo drugs

**3.2.1. Arthritis.** Chrysotherapy (utilisation of metallic gold and its complexes in medicine) has been used for the treatment of various diseases for many centuries. For instance, Au<sup>I</sup> cyanide was used to treat tuberculosis in the early 20th century and was replaced by Au<sup>I</sup> thiolates such as the polymer aurothiomalate. French physicians first used injectable Au<sup>I</sup> compounds to treat rheumatoid arthritis in 1929.<sup>381</sup> In 1985 the Au<sup>I</sup> triethylphosphine complex auranofin (Fig. 11) was approved by the FDA as an oral antiarthritic agent. The mechanism of action of this compound is still not understood,<sup>382</sup> although recent studies have shown that cathepsin B is inhibited by Au<sup>I</sup> complexes.<sup>383</sup> Auranofin is also highly cytotoxic to cancer cells and clinical trials for certain cancers are now in progress (Table 1).

**3.2.2. Ulcers.** Similarly to gold, utilisation of bismuth is traditional, both in Chinese and occidental medicines. Dyspepsia, syphilis, colitis, wound infections and quartan malaria are examples of diseases in which bismuth is effective. Yang and Sun comprehensively reviewed the biological chemistry of bismuth in 2011.<sup>384</sup> However, the use of bismuth in therapy has found its main application for the inhibition of *Helicobacter pylori*,<sup>385,386</sup> a bacterium that can prevent ulcers from healing.<sup>387</sup> Due to the development of antibiotic drug resistance by *H. pylori*, triple<sup>388</sup> and quadruple<sup>389</sup> regimens based on two antibiotics, plus an acid-suppressing agent, plus bismuth salts are nowadays investigated for the treatment of this bacterium. Time-resolved ICP-MS studies of the uptake of bismuth-based drugs suggest a competitive Fe<sup>III</sup>/Bi<sup>III</sup> transport pathway into *H. pylori*.<sup>390</sup> Homoleptic *tri*-substituted bismuth(III) sulfonate complexes possess interesting bactericidal activity towards three laboratory strains of *H. pylori* (B128, 26 695 and 251), with minimum inhibitory concentration (MIC) values in the nanomolar range.

In the blood, the Fe<sup>III</sup> binding site of transferrin is also a strong site for Bi<sup>III</sup>.<sup>391</sup> The recent 2.4 Å X-ray crystal structure of human transferrin with Bi in the N-lobe and Fe in the C-lobe shows Bi bound in a partially-opened cleft *via* only one of the two binding cleft Tyr side-chains together with nitrilotriacetate, carbonate and water.<sup>392</sup>

### 3.3. Neurodegenerative diseases

Neurodegenerative diseases (NDs), the progressive loss of structure or function of neurons – are attracting much



attention due to the global increase of life expectancy in modern societies; 35 million people currently live with dementia; Alzheimer's disease (AD), Parkinson's disease (PD), and prion diseases (PrDs) are the most prevalent NDs.<sup>393</sup> However the lack of knowledge of the origins, mechanisms, and development factors for these diseases results in poorly efficient drugs, which treat symptoms at best (for ADs and PDs, but no medication available for PrDs),<sup>394</sup> and do not reverse or slow down disease progression.

Senile plaques, neurofibrillary tangles, neutrophil threads, amyloid- $\beta$  peptide (A $\beta$ ) deposition, selective loss of neurons and decreased synaptic density in post-mortem brains are the pathognomonic indicators of Alzheimer's disease. Aberrant metal biochemistry in the pathogenesis of AD has been demonstrated.<sup>395,396</sup> Related to the synaptic activity, Cu and Zn are of importance, since millimolar concentrations of Zn are released upon neuronal activation, whilst Cu is involved in the regulation of synaptic functions. Amyloid- $\beta$  peptide (A $\beta$ ) is released upon neuronal activation, and A $\beta$  deposition and oxidative stress may be attributed to interactions between A $\beta$  and metal ions. Bush *et al.* have recently reported the post-hoc analysis of a Phase IIa double-blind, randomised, placebo-controlled clinical trial for a copper/zinc ionophore, PBT2,<sup>397</sup> an hydroxyquinoline derivative that facilitates the clearance of A $\beta$  aggregates in the cortex by targeting the zinc and copper ions that mediate the assembly of these aggregates in amyloid and diffuse deposits, effectively detoxifying the A $\beta$ .<sup>398</sup> The output of this study shows clear improvement for treated patients compared to placebo group.<sup>397</sup>

In 2012, the bioinorganic chemistry of Alzheimer's disease was surveyed by Kepp,<sup>399</sup> and the role that metal-A $\beta$  association species play in AD was comprehensively reviewed by Pithadia and Lim.<sup>400</sup> Inhibition of the interactions between A $\beta$  and metal ions is a promising therapeutic approach for developing new and effective anti-AD agents. This inhibition may be achieved by utilisation of competitive agents (for occupying the metal binding site on A $\beta$ ), or by using chelating agents. Chelation therapy is a powerful tool for metal depletion and excretion and has been extensively studied in recent years for the treatment of Wilson's disease and neurodegenerative diseases.<sup>401,402</sup>

Metal chelators, especially inhibitors of histone deacetylases (HDACs), are also of much interest in anticancer therapy, as exemplified by suberoylanilide hydroxamic acid (SAHA, vorinostat, Zolinza) which inhibits Zn(II)-dependent class I and class II histone deacetylases (HDACs). Histone acetylation plays a key role in controlling the affinity of histones for DNA and gene expression. Deacetylation of Lys on histones produces a positive charge on its side chain and increases DNA affinity.

In 2013, Telpoukhovskaia and Orvig, surveyed how coordination chemistry might play a role in anti-neurodegenerative drug development, by understanding the binding preferences of metal ions for key proteins involved in the propagation of NDs, and by using the tools of inorganic chemistry for investigating the competition of synthetic ligands with proteins for metal ions.<sup>403</sup>

## 4. Diagnostic and therapeutic radiopharmaceuticals

There is an increasing interest in the development of both diagnostic and therapeutic radiopharmaceuticals (Fig. 1), as illustrated by the large number of ongoing clinical trials worldwide (Table 1). The development of radiopharmaceuticals is aided by their rapid passage from the laboratory into the clinic, since very small doses are usually administered, posing a negligible toxicity hazard.

Therapeutic radiopharmaceuticals are useful for delivering locally cytotoxic doses of ionising radiation. The radionuclides used emit  $\beta^-$ -particles (electrons) or  $\alpha$ -particles (used in targeted  $\alpha$ -therapy (TAT)). Most radiotherapeutic nuclides in the clinic are  $\beta^-$  emitters, such <sup>32</sup>P, <sup>47</sup>Sc, <sup>64</sup>Cu, <sup>67</sup>Cu, <sup>89</sup>Sr, <sup>90</sup>Y, <sup>105</sup>Rh, <sup>111</sup>Ag, <sup>117m</sup>Sn, <sup>131</sup>I, <sup>149</sup>Pm, <sup>153</sup>Sm, <sup>166</sup>Ho, <sup>177</sup>Lu, <sup>186</sup>Re, <sup>188</sup>Re.<sup>404</sup> Recent advances in this field include the first clinical trial using an  $\alpha$ -particle emitting <sup>225</sup>Ac complex, labelled with a humanised antibody, lintuzumab, which targets the CD33 antigen expressed on the blast cells of most cases of acute myeloid leukaemia. The phase I clinical trial was initiated by the Scheinberg group at Memorial Sloan-Kettering Cancer Center with a primary goal to define both safety and the maximum tolerated dose of <sup>225</sup>Ac TAT in patients with advanced myeloid leukaemia (AML) through a dose escalation series.<sup>405</sup> Promising results have led to the ongoing phase I/II clinical trial, sponsored by Actinium Pharmaceuticals (Table 1). This complex is also undergoing a phase I clinical trial for the treatment of leukaemia myelodysplastic syndrome. The Scheinberg group reported the first proof-of-concept <sup>213</sup>Bi TAT clinical trial, again targeting CD33 with antibody lintuzumab to treat 18 patients with advanced myeloid leukaemia in a phase I trial.<sup>406</sup> This compound is now undergoing a phase II clinical trials (Table 1). Jurcic *et al.* also conducted a follow up study with <sup>213</sup>Bi TAT, wherein 13 newly diagnosed patients and 18 patients with relapsed/refractory acute myeloid leukaemia were first treated with continuous cytarabine (cytosine arabinoside) infusion for 5 days.<sup>407</sup> They observed marrow blast reductions at all dose levels.

Two types of radioimaging are used in clinic: single-photon emission computed tomography (SPECT), and positron emission tomography (PET). SPECT is based on the utilisation of pharmaceuticals labeled with a  $\gamma$ -emitting radionuclide, while PET requires a radiopharmaceutical labeled with a positron  $\beta^+$ -emitting radionuclide. Useful  $\gamma$ -emitting nuclides include <sup>99m</sup>Tc, <sup>67</sup>Ga, <sup>111</sup>In, and <sup>201</sup>Tl; useful  $\beta^+$ -emitting nuclides include <sup>55</sup>Co, <sup>64</sup>Cu, <sup>66</sup>Ga, <sup>68</sup>Ga, <sup>82</sup>Rb, <sup>86</sup>Y.<sup>404</sup> Recent clinical developments of such radioimaging agents include for instance <sup>68</sup>Ga-DOTA-TATE<sup>408</sup> and <sup>64</sup>Cu-ATSM for PET/CT scans<sup>409</sup> (Table 1, and Chart 13 for the molecular structure of <sup>68</sup>Ga-DOTA-TATE).

Multimodality imaging (positron emission tomography-computed tomography (PET-CT)) has been used in clinic for more than a decade, and is nowadays one of the main cancer imaging techniques.<sup>410</sup> Following this clinical success, combined PET/magnetic resonance (MR) systems for clinical use have been recently developed. Ga-DOTATOC PET/MR imaging





Chart 13 Molecular structure of  $^{68}\text{Ga}$ -DOTA-TATE.

is feasible in patients, with a good diagnostic image quality (average visual rating PET/CT, 2.83; PET/MR, 2.08). Moreover, detectability of focal PET lesions is equivalent to PET/CT on a patient basis and organ-system basis.<sup>411</sup> The clinical value of Ga-DOTATOC PET/MR with additional diagnostic MR protocols needs to be evaluated against PET/CT with multiphase contrast-enhanced CT protocols in future studies.

## Conclusions

The exploration of the medical periodic table presents exciting challenges. Inorganic compounds, and metal complexes in particular, offer mechanisms of drug action that can be quite distinct from those of organic drugs. About 13 metal ions are essential for mammalian life, which can all be used in therapy. However, not only can essential metals be used, but also non-essential metals, a strategy that might be particularly important for fighting bacteria which are becoming increasingly resistant to organic drugs. Also radionuclides with suitable ligands offer targeted agents both for diagnosis and therapy. The ligands can play critical roles in the activity of all metallodrugs and diagnostic agents. It is important to identify the parts of metallodrugs which are critical for activity (the pharmacophores).

We have tried to focus here particularly on the discovery of new targets for metallodrugs. These days an understanding of targets and mechanisms of action is essential if a drug is to receive approval for clinical use. Such understanding will eventually become important when patients can be screened on a personal-medicine basis for the optimum drug to treat their particular conditions. There are signs that rapid progress is currently being made, aided by advances in metal analysis and especially speciation techniques, and by the methods of modern molecular biology (proteomics and genomics), which can be fruitfully applied to the identification of target sites and understanding of metabolic pathways.

Although many new targets are currently being proposed for metallodrugs, and provide promising new leads for development, few have been validated *in vivo*. Advances in controlling metallodrug activation are also needed so that metallodrugs reach target sites and do not undergo unwanted side-reactions. From a general point of view, the field will benefit greatly from the application of the drug design principles used for the development of organic drugs. In this sense, we have tried to highlight some recent and promising strategies. Specific G-quadruplex binders, metallodrugs with DNA sequence specificity, inert polypyridyl metal complexes specifically able to target kinases, catalytic metallodrugs, and multi-labeled nanoparticle drug delivery systems are striking examples of the new strategies that can be used for designing metal-based anticancer drug candidates. The potential of inorganic and organometallic complexes as antibiotics, and for the treatment of other diseases, such as viral and parasitic diseases is also apparent.

We also have highlighted some organic drugs which are targeted to metal ions, often to the metal in a metalloenzyme. Organic drugs are often designed so they contain H-bond acceptors (lone pair donors). These acceptor atoms are also potential metal binding sites but perhaps not always recognised as such.

There is an urgent need to find new and effective therapies for a wide range of diseases and conditions. As highlighted in Table 1, there is current clinical and industrial interest in such advances.

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