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Current Opinion in Chemical Biology

Targeted delivery of platinum-based anticancer complexes

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The most widely used anticancer drugs are platinum-based. Their efficacy might be improved by carriers which can transport large numbers of Pt centres, shield the drug from premature activation, and/or deliver Pt specifically to cancer cells using vectors which recognise specific targets. We describe recent progress using functionalized carbon nanotubes (CNTs) and nanorods, hollow Prussian blue (HPB), magnetic iron oxide and gold nanoparticles, liposomes, nanogels and polymers, as well as active targeting by conjugation to biodegradable proteins and peptides (e.g. EGF, heparin, herceptin, somatostatin and TAT). Spatially targeted activation of Pt^{IV} prodrugs using light is also a promising approach. Interestingly, use of these new delivery and targeting systems for platinum drugs can lead to species with unusual reactivity which can kill cancer cells by new mechanisms.

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Introduction

Cisplatin, cis-$[PtCl_2(NH_3)_2]$ (CDDP), is well known for both its anticancer activity and systematic toxicity. Hydrolysis of cisplatin generates active Pt^{II} aqua species which induce apoptosis in cancer cells due to the formation of 1,2-d(GpG) intrastrand DNA cross-links [1]. Side-effects and deactivation may arise from the reactions of active Pt^{II} aqua species with proteins. The later generation complexes carboplatin and oxaliplatin on the one hand can exhibit less side-effects, and on the other hand, can exhibit activity against cisplatin-resistant cancers [2••]. However, targeted delivery of platinum drugs specifically to tumour cells of patients remains to be addressed. The major limitations of chemotherapeutic agents are often difficulties with solubility, formulation, biodistribution and ability to cross cell membranes. These problems have prompted the exploration of various scaffolds to act as vectors for targeted delivery of platinum-based anticancer complexes. Targeted delivery is a well-known field in which the drug carriers target tumour cells via two different processes; passive or active drug delivery. The former exploits the tumour vascular system through the enhanced permeability and retention (EPR) effect (the tendency for macromolecules and nanoparticles to accumulate more in tumour than in normal tissues), whereas, active drug delivery utilizes receptor-type conjugates which drive the drug towards the tumour cells. Wang *et al.* have discussed these processes in detail [3••]. Here we summarise recent advances in both passive and active delivery of platinum-based anticancer complexes.

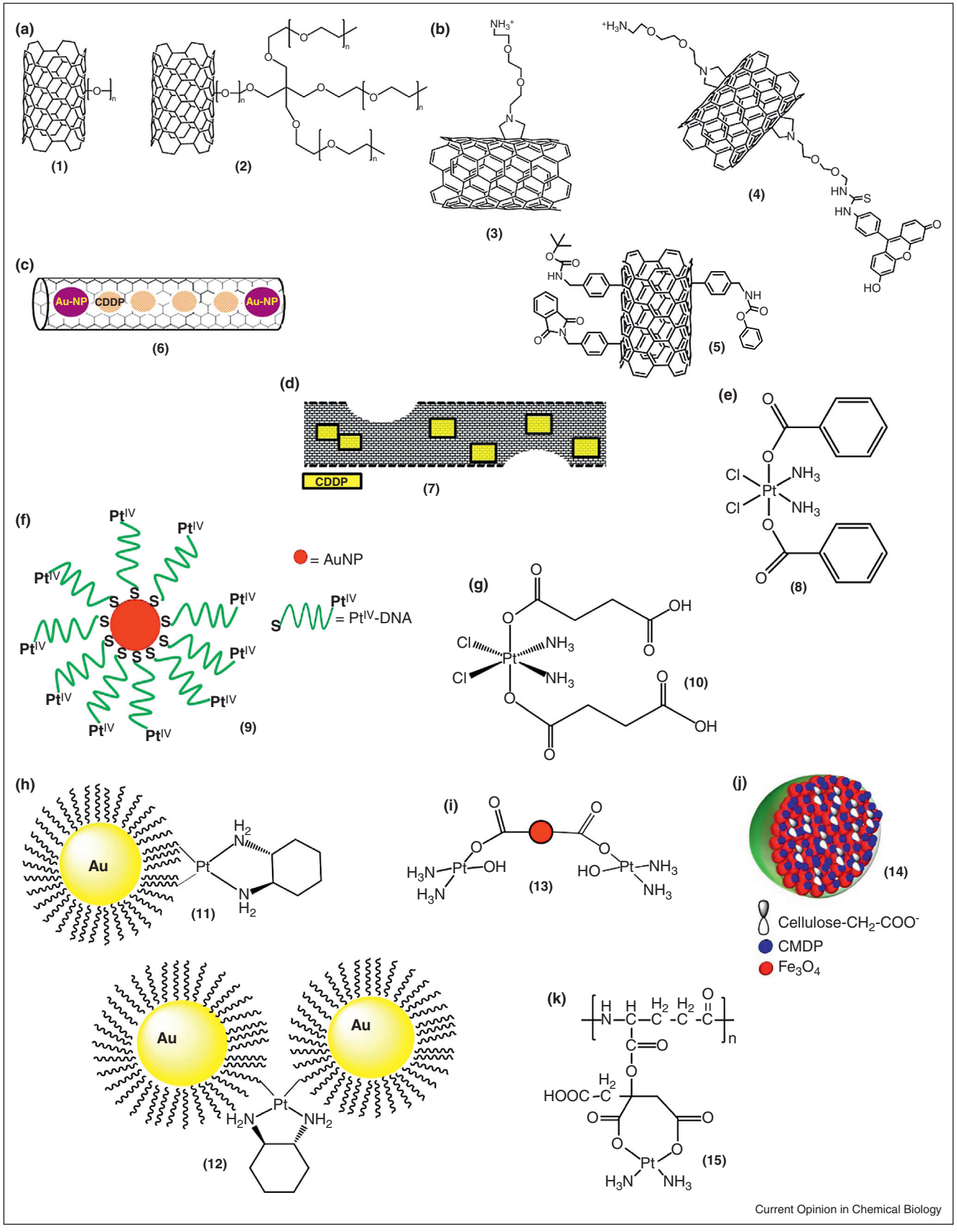
Untargeted passive drug delivery

Utilizing nanotechnology to improve drug delivery is a well-known concept, however innovative designs of nano-vectors to achieve efficient drug delivery and their complexity are emerging [4•]. Carbon nanotubes (CNTs) are the most studied. Pristine CNTs are insoluble in most solvents and bear structural resemblance to carcinogenic asbestos fibres. However, coating CNTs with linear and/or branched poly(ethylene glycol) (PEG) units (**1** and **2**, Figure 1a) renders them more hydrophilic and more suitable for biomedical applications [5]. The toxic nature of pristine (non-functionalised) multi-walled and single-walled CNTs and ability to induce mesothelioma have been demonstrated. Bianco *et al.* have shown that mono-functionalisation, bi-functionalisation, and tri-functionalisation of CNTs (**3**–**5**, Figure 1b) give enhanced biocompatibility and can be translocated directly into the cytoplasm of cells. Non-biodegradable CNTs have the potential to accumulate in various tissues and organs [6], however the oxidative enzyme horseradish peroxidase (HRP) can catalytically degrade *f*-CNTs [7].

Tripisciano *et al.* have encapsulated CDDP into functionalised single-walled carbon nanotubes (SWCNTs). CDDP-SWCNTs are more cytotoxic than free CDDP towards PC3 cancer cells, but less potent than CDDP towards DU145 cells [8]. Recently, Li *et al.* capped multi-walled carbon nanotubes (MWCNTs) with functionalized 1-octadecanethiol (ODT) gold nanoparticles (*f*-GNPs) to facilitate the effective delivery of CDDP (**6**). The presence of the *f*-GNP at the tip of the MWCNTs hinders the encapsulated CDDP from leaving the narrow passage of the MWCNTs. The *in vivo* activity of CDDP in capped CDDP-MWCNTs towards MCF-7 breast cancer cells was enhanced (IC_{50} 7.7 μM), compared to uncapped CDDP-MWCNTs (IC_{50} 11.7 μM). These results suggest that *f*-GNP MWCNTs may be effective drug depots [9].

Reducing the size of the CNTs renders them more likely to pass into the cell, as seen for SWCNTs of 1–2 nm

Figure 1


(a)
(1)
(2)
(b)
(3)
(4)
(c)
Au-NP
CDDP
Au-NP
(6)
(5)
(d)
CDDP
(7)
(e)
(8)
(f)
= AuNP
= PtIV-DNA
(9)
(g)
(10)
(h)
Au
(11)
(i)
(13)
(j)
(14)
Cellulose-CH2-COO-
CMDP
Fe3O4
(k)
(15)
Au
Au
(12)
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diameter. Guven *et al.* have synthesised ultra-short carbon nanotubes (USCNTs) of ca. 1.4 nm diameter in which CDDP was encapsulated (**7**) and then wrapped with a surfactant. The CDDP-USCNTs were more potent than free CDDP in two breast cancer cell lines (MCF7 and MDA-MB-231) after 24 hours. Wrapping of USCNTs with a surfactant retards release of CDDP resulting in its higher cytotoxicity. For *in vivo* use, the surfactant molecules could be replaced with a cancer-specific protein [10].

Li *et al.* have entrapped a hydrophobic Pt^{IV} complex (**8**) within the inner cavity of MWCNTs. Chemical reduction converted the Pt^{IV} prodrug to its hydrophilic and cytotoxic Pt^{II} form triggering its release from the MWCNTs. Incubation of **8**-MWCNTs in the presence of deoxyguanosine monophosphate (dGMP) did not produce any Pt^{II}-DNA adducts in the absence of the bio-reductant ascorbic acid. These results indicated that chemical reduction was required for the formation of the Pt^{II} species which bind to DNA. *In vitro* studies showed that **8**-MWCNTs were efficiently delivered into A2780 human ovarian carcinoma cancer cells in comparison to the free Pt^{IV} prodrug which was readily dissipated into the ambient environment [11]. Ajima *et al.* have incorporated cisplatin into single-wall carbon nanohorns (SWCNHox). SWCNHox offer various advantages over conventional CNTs. The *in vitro* cytotoxicity of cisplatin in SWCNHox was ca. four to six fold greater than free CDDP towards human lung cells, NCI-H460 [12].

Dhar *et al.* have tethered a Pt^{IV} complex via amide linkages to AuNPs functionalised with thiolated 28-mer oligonucleotides (**9**). Pt-DNA-Au nanoparticles were most active in A549 lung cancer cells, displaying cytotoxicity ca. 12-fold higher than free CDDP [13••]. Min *et al.* have conjugated a Pt^{IV} prodrug (**10**) to amine-functionalised PEGylated gold nanorods (AuNRs); it is reduced to Pt^{II} by cellular reductants. Nanorods possess longer circulation times than nanoparticles rendering their accumulation more efficient within tumour cells. The Pt^{IV}-PEG-AuNRs were most active in the MCF-7 breast cancer cells, exhibiting an IC_{50} of 0.18 μM, significantly more potent than free cisplatin IC_{50} of 11.8 μM [14].

In similar work, Brown *et al.* functionalised AuNPs with thiolated PEG tethered to the active fragment of oxaliplatin, $\{Pt(R,R\text{-dach})\}^{2+}$ (**11** and **12**, Figure 1h). Similarly, these Pt-AuNPs were almost 6x more active towards A549 lung cancer cells than free oxaliplatin but ca. 5x more active, or as active, as free oxaliplatin in various colon cancer cell lines [15]. These results demonstrate increased potency of platinum complexes conjugated to gold nanoparticles/rods.

Use of inorganic nanoparticles to overcome multidrug resistance is being explored [16]. Treatment of T24 bladder cancer cells with aqueous CDDP loaded into hollow Prussian blue (HPB) nanoparticles results in breakage of the cell membrane and changes in cell morphology indicative of cell death. HPB nanoparticles show potential as future vectors owing to their biocompatibility, although their size needs to be optimised to allow a higher percentage of loaded cisplatin to be released [17].

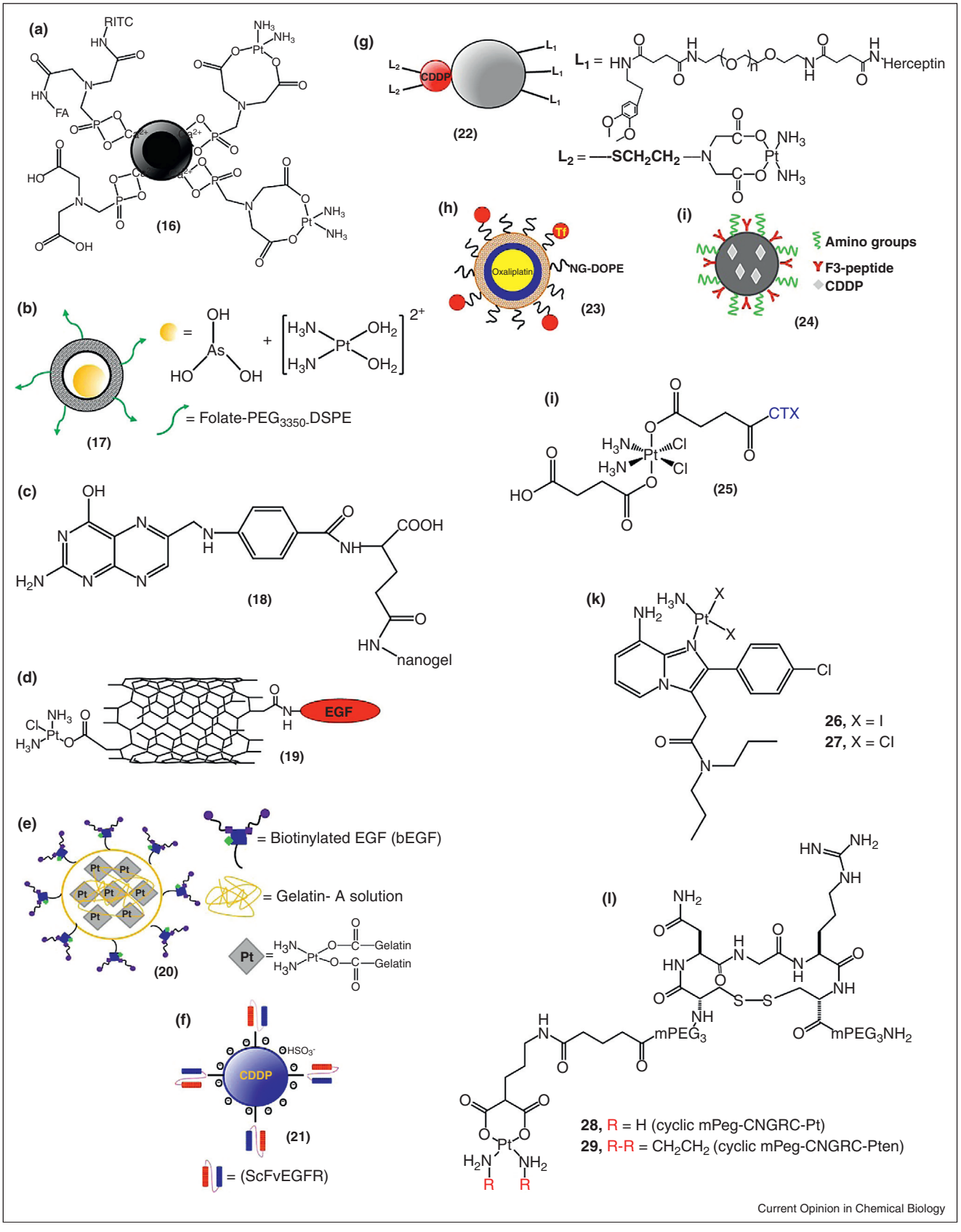
Likhitkar *et al.* have developed a novel method for the synthesis of superparamagnetic (SPM) nanoparticles impregnated with nano-sized iron oxide loaded with aqueous cisplatin (**13**). Cisplatin was released in both the absence and presence of a magnetic field through a controlled diffusion pathway. However, the quantity of cisplatin released was influenced by pH and temperature of the medium in addition to the presence of an external magnetic field [18].

Xing *et al.* have synthesized superparamagnetic magnetite nanocrystal clusters modified with carboxymethylcellulose (CMC) in which $\{PtCl(NH_3)_2\}^+$ was tethered through carboxylate groups on the surface (**14**). The CMC-SPM clusters were non-toxic towards both human cervical (HeLa) and hepatocarcinoma (HepG2) cells. While, CMDP–CMC–SPM clusters were more active (0.9 μM) than CDDP (2.6 μM) towards HeLa cells, in HepG2 the CMDP–CMC–SPM clusters were only 1.2-fold more active than CDDP. Similar to other platinum delivery systems, the release of the platinum pharamacophore from the CMDP-CMC-SPMNC is facilitated by the acidic environment of the tumour [19].

Superparamagnetic iron oxide nanoparticles (SPIONs) are biocompatible, biogradable, have good aqueous solubility and magnetic properties. Pectin is a suitable drug carrier for colon-specific drug delivery owing to its resistance to both protease and amylase. Dutta *et al.* have encapsulated both SPIONs and oxaliplatin *in situ* into pectin cross-linked with Ca^{2+} forming pectin nanocarriers. These magnetic nanocarriers exhibited cytotoxicity 10-fold higher than free oxaliplatin towards MIA-PaCa-2 pancreatic cancer cells [20].

(a) PEGylated carbon nanotubes, linear (**1**) and branched (**2**). **(b)** Mono-functionalised (**3**), bi-functionalised (**4**) and tri-functionalised (**5**) carbon nanotubes. **(c)** Carbon nanobottle with encapsulated CDDP capped with *f*-AuNPs (**6**). **(d)** Encapsulation of cisplatin by single-walled carbon nanotubes (**7**). **(e)** Hydrophobic Pt^{IV} complex (**8**). **(f)** Encapsulation of Pt^{IV} complex within AuNP functionalised with oligonucleotides (**9**). **(g)** Pt^{IV} prodrug complex (**10**). **(h)** Active component of oxaliplatin tethered to AuNP functionalised with PEG linker (**11**, **12**). **(i)** Monohydroxido cisplatin conjugated to iron oxide nanoparticles impregnated with starch (**13**). **(j)** CDMP encapsulated within superparamagnetic iron oxide nanoparticles modified with sodium carboxymethylcellulose (**14**). **(k)** Poly(γ,L-glutamic acid)–citric acid conjugated to *cis*-diammine Pt^{II} (**15**).

Figure 2


(a)
RITC
FA
(16)
(b)
= Folate-PEG3350-DSPE
(17)
(c)
(18)
nanogel
(d)
EGF
(19)
(e)
= Biotinylated EGF (bEGF)
= Gelatin- A solution
(20)
(f)
CDDP
(21)
= (ScFvEGFR)
(g)
(22)
L1 = Herceptin
(h)
Oxaliplatin
NG-DOPE
(23)
(i)
Amino groups
F3-peptide
CDDP
(24)
(i)
CTX
(25)
(k)
26, X = I
27, X = Cl
(l)
mPEG3
mPEG3NH2
28, R = H (cyclic mPeg-CNGRC-Pt)
29, R-R = CH2CH2 (cyclic mPeg-CNGRC-Pten)
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The cisplatin nanoconjugate, γ-PGA-CA-CDDP is a hydro-soluble polymer of γ-polyglutamic acid (γ-PGA) modified with citric acid (CA) conjugated with diaqua cisplatin (**15**, Figure 1k). Sustained release of the nanoconjugate indicated its improved selectivity and efficiency. However, **15** was less potent than free CDDP towards both BcaP-37 human breast and Bel-7402 liver cancer cell lines [21].

Targeted active drug delivery through cancer-cell specific vectors

While delivery of anticancer agents via nanocarriers is efficient for reaching the tumour site through the EPR effect, correct attachment of receptor-binding molecules (particularly for receptors overexpressed in cancer tissues) on the surface of NPs can enhance the uptake of the nanocarrier into the tumour cell through receptor-mediated internalisation. The most common receptors targeted in nanotechnology include the folate (FR), epidermal growth factor (EGF) and transferrin (TfR) receptors.

Rout *et al.* have conjugated *cis*-diaquadiammine Pt^{II}, folic acid (FA) and rhodamine B isothiocyanate onto magnetic calcium phosphate nanoparticles for the targeted delivery of CDDP into HeLa human cervical cancer cells (**16**). The cytotoxicity of **16** towards both HeLa (FR +ve) and L929 (FR −ve) human cervical cancer cells was ca. fourfold and onefold, respectively, more active compared to free CDDP, indicating that the nano-agent selectively targeted the HeLa cells through receptor mediated endocytosis [22]. Coencapsulation of As^{III}-based and cisplatin-based anticancer complexes in a folate-functionalised liposome, referred as a ''nanobin'' (**17**), provided efficient drug delivery and uptake in KB human nasopharyngeal cells (FR +ve), but not in MCF-7 breast cancer cells (FR −ve) [23].

Nanogels are swollen polymers containing ca. 95% water suitable for trapping a range of chemical and biological agents. Nukolova *et al.* have investigated the antitumour activity of nanogels conjugated with folic acid (**18**) and loaded with CDDP. Uptake into A2780 human ovarian carcinoma cells (FR +ve) depended on whether CDDP was loaded before or after folate attachment. In contrast, for A549 lung cancer cells (FR −ve), the uptake was independent on the sequence of loading. The FR-nanogel-CDDP displayed superior antitumour activity towards A2780 xenografts in contrast to free CDDP [24].

The intracellular delivery of carboplatin has been investigated by coupling i.p. administration with a folate-receptor-targeted liposomal system. The cytotoxicity is enhanced (twofold) in comparison to carboplatin itself towards human ovarian IGROV-I (FR +ve) cancer cells. Mice bearing the i.p.-grown human IGROV-1 ovarian tumour xenografts treated with FRT-carboplatin liposomes had an 83% survival rate [25].

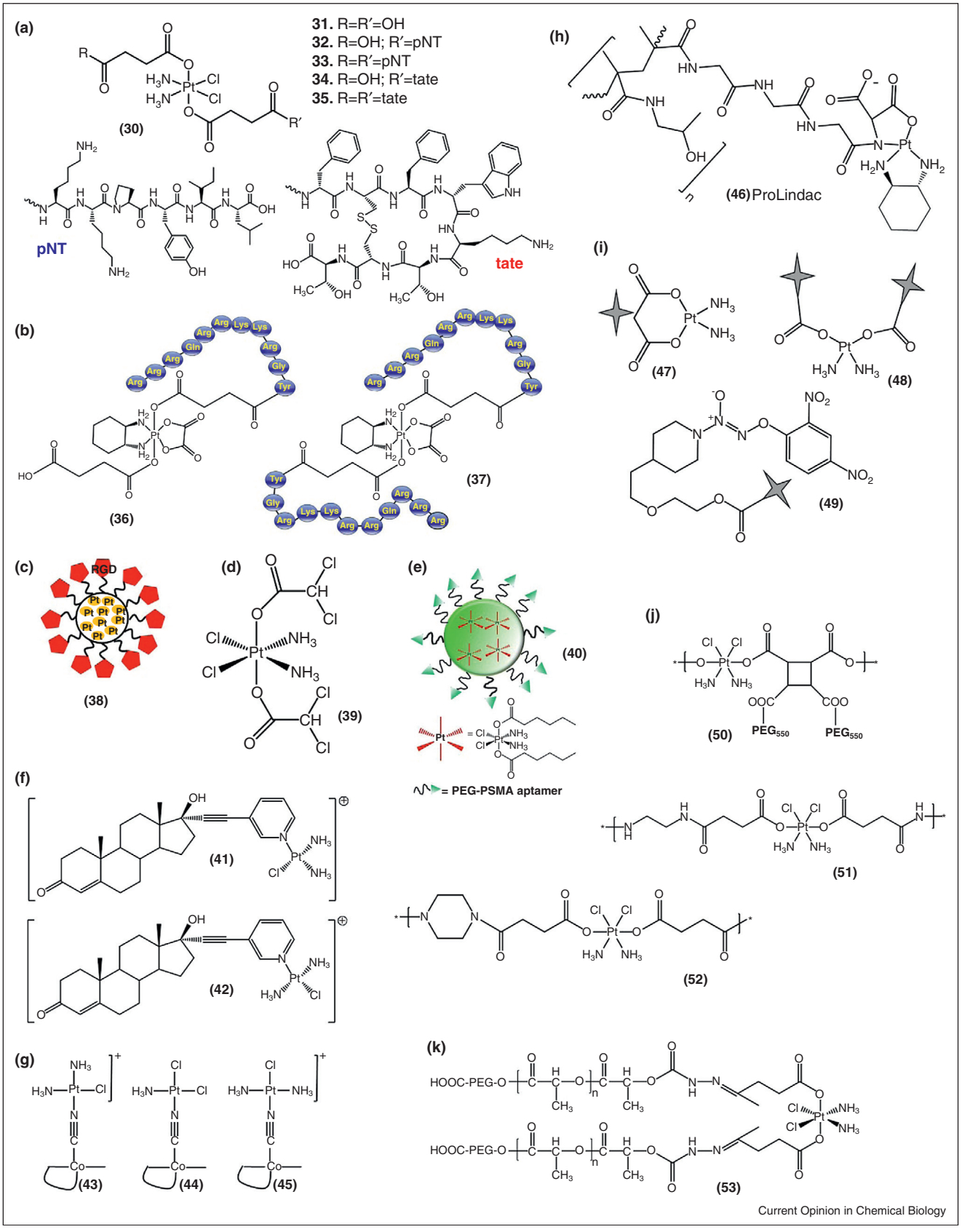
EGF is another potential targeting ligand due to the overexpression of the EGF receptor in human tumours, in particular NSCLC non-small cell lung cancer. Bhirde *et al.* have attached cisplatin (dissolved in DMSO) and EGF to oxidised SWCNTs to target squamous cancer. *In vivo* studies revealed SWCNT–CDDP–EGF (**19**) were selective towards HNSCC head and neck squamous cell carcinoma. Tumour growth regression was significant in mice treated with SWCNT–CDDP–EGF bearing HNSCC xenografts in contrast to mice treated with SWCNT–CDDP [26•]. Biotinylated epidermal growth factor (bEGF) conjugated to a $\{Pt(NH_3)_2\}^{2+}$-gelatin nanocomplex (GP-Pt-bEGF, **20**) gives rise to a twofold higher Pt concentration in A549 human adenocarcinoma (EGF +ve) compared to HFL1 lung fibroblasts (EGF −ve). Immunodeficient mice injected with an A549 cell suspension treated with GP-Pt-bEGF nanoparticles displayed a reduction in tumour volume compared to mice treated with free CDDP which the tumour volume grew rapidly [27••].

The high molecular weight of full length EGFR monoclonal antibody if used as a targeting ligand may hinder its penetration into tumour cells; furthermore interaction with the Fc receptor on normal tissues may disturb its specific targeting. Therefore, single-chain antibodies against the EGFR (ScFvEGFR) lacking the Fc receptor have been conjugated onto the surface of ScFvEGFR-heparin-CDDP nanoparticles (with $\{Pt(NH_3)_2\}^{2+}$ bound to carboxylates, **21**). Nanoparticle conjugate **21** was most potent towards H292 (EGF +ve) human lung cancer cells with an IC_{50} of 1.1 μM. Kidneys from mice treated with **21** showed no change in either blood urea nitrogen (BUN) or creatine (CRE) levels, in contrast to CDDP which gave significant changes consistent with impaired renal function [28••].

Xu *et al.* have coupled a $\{Pt(NH_3)_2\}$-herceptin (L_2, Figure 2g) dicarboxylato binding ligand onto dumbbell-like Au-Fe_3O_4 nanoparticles (**22**) to act as nanocarriers to deliver the platinum pharamacophore into SK-Br3 breast

(a) Conjugation of cisplatin, folic acid and rhodamine B isothiocyanate to amorphous calcium phosphate/$CoFe_2O_4$ nanoparticles (**16**). **(b)** Coencapsulation of arsenic and platinum into a folate-PEGylated functionalised liposome (**17**). **(c)** Folate functionalised nanogel (**18**). **(d)** SWCNT bioconjugated with cisplatin and epidermal growth factor (**19**). **(e)** Gelatin-Pt nanoparticles with biotinylated EGF (**20**). **(f)** EGF-targeted heparin nanoparticles with encapsulated CDDP (**21**). **(g)** Dumbbell gold-iron oxide nanoparticles coupled with herceptin and CDDP (**22**). **(h)** Oxaliplatin encapsulated within liposomes functionalised with Tf and DOPE (**23**). **(i)** CDDP-F3-targeted nanoparticles (**24**). **(j)** Pt^{IV}-chlorotoxin conjugate (**25**). **(k)** Platinum-TSPO-binding ligand conjugates with various X groups (**26**, **27**). **(l)** Pt^{II} peptide conjugates (**28**, **29**).

Figure 3


(a)
31. R=R′=OH
32. R=OH; R′=pNT
33. R=R′=pNT
34. R=OH; R′=tate
35. R=R′=tate
(30)
pNT
tate
(b)
(36)
(37)
(c)
RGD
(38)
(d)
(39)
(e)
(40)
= PEG-PSMA aptamer
(f)
(41)
(42)
(g)
(43)
(44)
(45)
(h)
(46) ProLindac
(i)
(47)
(48)
(49)
(j)
(50)
PEG550
PEG550
(51)
(52)
(k)
HOOC-PEG-O
HOOC-PEG-O
(53)
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cancer (HER2 +ve) cells. Without the targeting agent, the platin-Au-Fe_3O_4-NPs were still active, but less than CDDP. Thus, herceptin enhances Pt uptake in SK-Br3 cells giving greater cytotoxicity owing to the specific targeting. The platin-Au-Fe_3O_4-herceptin NPs did not display any improvement in cytotoxicity towards MCF-7 breast cancer (HER2 −ve) cells [29].

Krieger *et al.* have synthesised both transferrin-targeted and non-targeted PEGylated cisplatin-containing liposomes. Free CDDP displayed strong differences in cytotoxicity towards A2780 and resistant A2780cis breast cancer cells, whereas the liposomes all displayed comparable cytotoxicity in both cell lines. Thus, these liposomes are potential carriers to treat cisplatin-resistant tumours [30]. Liposomes encapsulating oxaliplatin and with bound human transferrin (**23**) show potency *in vitro* towards colon, pancreatic and neuroendocrine human cancer cells [31].

Peptides

The F3 peptide is a 31-residue fragment of the high mobility group protein (HMGN2) which has potential to bind to the nucleolin protein expressed on both the surface of endothelial and tumour cells. Winer *et al.* have encapsulated CDDP in a polyacrylamide nanoparticle functionalised with the F3 peptide. Complex **24** displayed significant cytotoxicity towards tumour endothethial cells (TECs). Using a model of human tumour vasculature, it was shown that the F3-Cis-NPs bind to human tumour vessels [32]. These results suggest the safety of F3-Cis-Nps and effectiveness for targeting TECs.

Various peptide sequences can bind preferentially to tumour cells and thus can act as cancer targeting ligands. For example, chlorotoxin (CTX), a 36-amino acid peptide which blocks small-conductance chloride channels, binds to functional proteins such as matrix metalloproteinase-2 (MMP2) (overexpressed in glioma and related cancers) and chloride ion channels overexpressed in different types of cancers. CTX has been conjugated to a Pt^{IV}-succinato complex (**25**) as a prodrug for delivery of cisplatin. The cytotoxicity of **25** towards MCF-7 breast, A549 lung and HeLa cervical cancer cells was less than CDDP but greater than both the Pt^{IV} precursor and CTX alone. The kinetic inertness of the Pt^{IV} complex probably contributes to its reduced activity [33•].

Translocator proteins (TSPOs) are peripheral benzodiazepine receptors (PBRs) overexpressed in both human and rat glioma cells. Margiotta *et al.* have conjugated *cis*-$\{Pt^{II}(NH_3)(X)_2\}$ to TSPO-binding ligands (Figure 2k). Such conjugates showed potency equivalent to that of cisplatin through apoptosis. The iodido complex **26** was slightly more potent than the chlorido derivative **27**; however, unlike CDDP, both complexes were equally active towards sensitive A2780 and resistant A2780cis breast cancer cells [34•].

The targeting sequence NGR (Asn-Gly-Arg) can bind specifically to murine breast cancer cells. Two peptide conjugates of the type cyclic mPEG-CNGRC-Pt and cyclic mPEG-CNGRC-Pten (Figure 2l, **28** and **29**) showed selective delivery and more effective destruction of PC-3 prostate (CD13 +ve) cells than the untargeted platinum complex, carboplatin [35].

The 13-amino acid peptide neurotensin (pNT) and NT1 and NT3 receptors are upregulated in colon, pancreatic and prostate cancers. Somatostatin (growth-inhibiting hormone) is a cyclic tetradecapeptide overexpressed in a variety of neoplastic tumours, but has a short natural lifetime. Analogues such as octreotate (tate) a cyclic octapeptide, possess longer lifetimes owing to the presence of D-amino acids. Gaviglio *et al.* have prepared four conjugates of a Pt^{IV}-succinato complex (**10**, as a CDDP prodrug) with both pNT and tate peptides (Figure 3a). All four conjugates (**31-35**) displayed similar IC_{50} values to that of the precursor in the MCF-7 breast cancer cells. Additionally, in the HepG2 human hepatocytes and PT45 pancreatic cell lines, the presence of an extra tate residue (**35**) did not enhance interaction with the SSTR2 receptor [36••].

Cell penetrating peptides (CPPs) are another well-known class of drug carriers due to their ability to pass through cell membranes. The TAT peptide is a widely studied CPP. Conjugates of the TAT peptide (YGRKKRRQRRR) with a Pt^{IV} analogue of oxaliplatin generated complexes (**36** and **37**, Figure 3b) were >4× more potent in ovarian, colon and lung cancer cells lines than the free Pt^{IV} analogues of oxaliplatin. The diconjugate **37** displayed slightly lower cytotoxicity, indicating that an extra TAT peptide does not enhance the cytotoxicity [37].

Integrins, heterodimeric cell-adhesion proteins associated with tumour angiogenesis and metastasis, are upregulated in tumour cells compared to low levels in normal endothelial cells. Polymer NPs with a Pt^{IV} cisplatin prodrug (**38**, Figure 3c) encapsulated in the core and

(a) Platinum(IV)-succinato peptide conjugates (**31**–**35**). **(b)** Oxaliplatin-TAT mono-peptide (**36**) and di-peptide (**37**) conjugates. **(c)** Nanoparticles functionalised with PLGA-PEG with CDDP encapsulated in the core (**38**). **(d)** Mitaplatin (**39**). **(e)** Platinum(IV) prodrug encapsulated within nanoparticles functionalised with PSMA aptamer and PEG (**40**). **(f)** Example of *cis* (**41**) and *trans* (**42**) steroidal platinum(II) complexes. **(g)** Vitamin B_{12}-platinum(II) complexes (**43**–**45**). **(h)** ProLindac™ (**46**). **(i)** Platinum (**47** and **48**) and NO-prodrug (**49**) poly(acrylic acid) star conjugates. **(k)** Platinum(IV) polymer conjugates (**50**–**52**). **(j)** Bi(PEG-PLGA)-platinum(IV) polymer prodrug conjugate (**53**).

targeted to $\alpha_v\beta_3$ integrin-expressing cells using the cyclic pentapeptide c(RGDfk) (**38**) showed a 6-fold enhancement in the *in vitro* cytotoxicity towards MCF-7 breast cancer cell lines compared to CDDP. *In vivo* studies revealed equivalent tumour growth inhibition (ca. 60%) by both **38** and cisplatin in mice bearing A2780 xenografts [38••].

The Warburg effect, the ability of cancer cells to produce energy through a high rate of glycolysis, helps tumours cells survive. The FDA-approved anticancer agent dichloroacetate (DCA) can reverse the Warburg effect. The Pt^{IV} prodrug Mitaplatin (**39**) contains two DCA units, and once internalised is reduced to cisplatin which can attack nuclear DNA, while the DCA can attack mitochondria selectively. Mitaplatin alters the mitochondrial membrane potential of cancer cells, promoting apoptosis by releasing cytochrome c and translocating apoptosis-inducing factor from mitochondria to the nucleus. The cytotoxicity of **39** is equivalent or exceeds most well-known Pt^{IV} complexes and is comparable to CDDP [39•].

Phase I, II and III trials of Lipoplatin^{TM} (composed of 8.9% cisplatin and 91.1% lipids, w/w, with an average diameter of 110 nm) have reported no renal toxicity. Stathopoulos *et al.* have investigated the use of lipoplatin as both a mono-therapy and in combination with taxanes in cancer patients with renal insufficiency. The lack of increase in CRE levels suggest a potential future use for lipoplatin in patients with renal insufficiency [40].

With the aim of targeting prostate cancer (PCa), a Pt^{IV} prodrug (for CDDP) has been encapsulated into aptamer (Apt)-targeted poly (D,L-lactic-co-glycolic acid)-b-poly(-ethylene glycol) (PLGA-b-PEG) nanoparticles (NPs) forming a Pt-PLGA-b-PEG-Apt-NP conjugate (**40**) engineered to target the prostate-specific membrane antigen (PSMA). These nanoparticles demonstrated enhanced *in vivo* pharmacokinetics (PK), biodistribution, tolerability and efficacy. The maximum tolerated dose (MTD) for Pt-PLGA-*b*-PEG-NP was 40 mg/kg while that of CDDP and the prodrug alone was 20 mg/kg. The Pt in **40** remained in systemic circulation one hour post-administration [41••], longer than for cisplatin itself.

Since the androgen receptor (AR) is upregulated in breast, ovarian and prostate tumour cells, Huxley *et al.* have designed multiple androgenic steroidal ligands with various nitrogen-containing heterocyclic rings conjugated to either *cis*-platin *or trans*-platin (**41** and **42**, Figure 3d) as platinum drug delivery vectors. These $[Pt^{II}(NH_3)_2Cl(steroid)]$ conjugates were 2–12-fold more cytotoxic than the non-steroidal complexes, but with a similar activity range as CDDP. Interestingly, the *cis*-complex conjugates displayed two to threefold higher activity than their *trans* analogues. Conjugation to lipophilic testosterone appears to help the cationic complexes through the cell membrane [42].

Many proliferating cells have a high demand for cobalamin (Cbl, coenzyme vitamin B_{12}) making it an attractive carrier. Enzymatic reduction of complexes of the type B_{12}-CN-Pt^{II} (Figure 3g) releases Pt^{II} diammine complexes. Complex **43** was the most active but still with an IC_{50} ca. 27-fold higher than free CDDP; conjugates **44** and **45** were ca. 180-fold less active than free cisplatin towards A2780 ovarian and MCF-7 breast cancer cell lines. The reduced cytotoxicity was attributed to a low receptor-mediated response [43].

Polymer carriers

Nowotnik *et al.* have reviewed the nano-polymer, ProLindac^{TM} (**46**), consisting of the active $\{Pt(R,R\text{-dach})\}^{2+}$ fragment of oxaliplatin bound to hydroxypropylmethacryl-amide (HMPA). Release of the active platinum pharamacophore was ca. seven-times greater at pH 5.4 in comparison to pH 7.4 after 24 hours. The superior activity of ProLindac^{TM} over oxaliplatin was shown in both human and mouse xenograft models, while the cytotoxicity profile of **46** was similar to oxaliplatin [2,44].

Release of nitric oxide (NO) from prodrugs is usually activated by glutathione reductase in tumour cells resulting in growth inhibition of cancerous tissues. Duan *et al.* have synthesised both hydrophilic poly(acrylic)-*cis*-$[Pt(NH_3)_2(carboxylate)_2]$ (**47** and **48**) and hydrophobic NO-donating (**49**) prodrugs (Figure 3h) combining NO prodrug therapy with Pt based-therapy. The extended life-times of both prodrugs suggest potential future use in combination therapy. The Pt-prodrugs exhibited lower cytotoxicity compared to free CDDP, attributable to the slow release of the Pt^{IV} complex from the polymer conjugate [45].

Yang *et al.* have synthesised various Pt^{IV} coordinated polymers which incorporate mPEG550 to increase polymer solubility (Figure 3i). Conjugates **51** and **52** displayed higher cytotoxicity towards MDA-MB-468 breast carcinoma cells in comparison to the starting monomer [46]. Aryal *et al.* have synthesized an acid-responsive polymer-conjugated to a Pt^{IV} prodrug, Bi(PEG-PLA)-Pt^{IV}(Figure 3j) for the delivery of cisplatin to tumour cells. Polymer conjugate **53** was cytotoxic towards A2780 human ovarian cancer cells. The release of CDDP from the polymer conjugate is pH dependent, activated only in acidic environments [47].

Vieira *et al.* sandwiched (aquated) cisplatin between two oppositely charged polyelectrolytes, chitosan (CH) and CMC to deliver cisplatin effectively to SK-mel-28 human melanoma cells. The degree of acetylation of glucosamine monomers in the CH was modified. *In vitro* CDDP-CMC-CH75 (75% deacetylated) was 10-fold more active towards SK-mel-28 cells than CDDP, whereas CDDP-CMC-CH25 (25% deacetylated) was only 1.6-fold more active. The 10-fold activity of the CDDP-CMC-CH75

conjugate illustrates the enhanced activity and potential for the use of these polyelectrolytes as carriers [48].

Micelle carriers

Xiao *et al.* have synthesised a biodegradable di-block amphiphilic copolymer (mPEG-b-P(LA-co-MCC) bearing carboxylate groups for Pt^{II} chelation (**54**). The cytotoxicity of **54** towards EMT6 breast cancer cells was lower than that of cisplatin, but comparable to oxaliplatin. The reduced side effects associated with targeted delivery suggest potential use of this polymer conjugate as a targeted carrier vehicle [49].

Duong *et al.* have conjugated a Pt^{IV}-succinato prodrug to a polymer backbone while simultaneously cross-linking the core of the micellar structure (**55**). The release of cisplatin from **55** was 80% within three weeks in the presence of sodium ascorbate (5 mM) as a reductant at 37 °C. The copolymer was inactive towards A549 lung cancer cells, whereas both the Pt^{IV} prodrug and **55** displayed comparable activity. However, their cytotoxic activities are difficult to compare on account of their different mechanisms of action [50].

Huynh *et al.* synthesised platinum amphiphilic block copolymers (micelles, **56**), by conjugating aquated CDDP to the deprotected monomer 1,1-di-*tert*-buty; 3-2(2-methacryloyloxy)ethyl) butane-1,1,3-tricarboxylate (MAETC). Before conjugation with CDDP, the polymers were non-toxic to A549 lung cancer cells. The polymer bearing the shortest block length displayed the highest activity, perhaps due to fast release of CDDP [51]. Developing on this work, Huynh *et al.* generated three different block copolymers by varying the spacer lengths and chain extension. Conjugation with aqueous CDDP produced macromolecular drugs related to carboplatin. Activity was tested against three cancer cell lines, A549 lung, OVCAR3 and SKOV3 ovarian cancer cells with only the block copolymer with the longest spacer length having an IC_{50} (10.3 μM) comparable to free cisplatin (7.2 μM) [52].

Preclinical evaluation of the drug delivery micelles NC-6004, composed of PEG, a hydrophilic chain, PGA and carboxylate-bound $\{cis\text{-}Pt(NH_3)_2\}^{2+}$ fragments (**57**) has confirmed a long blood retention time for the platinum-conjugate in comparison to free cisplatin; the maximum Pt accumulation for **57** occurred at 48 hours compared to 10 min for cisplatin. The cytotoxicity of **57** was comparable to free cisplatin in mice implanted with MKN-45 human gastric cancer cells [53].

Xue *et al.* have synthesised polymer–Pt complex nanomicelles from folate-conjugated PEG-graft-α,β-poly[(N-amino acidyl)-aspartamide] (FA-PEG-g-PAAsp) and aqueous CDDP(**58**), also with conjugation to various amino acids FA-PEG-g-PAsp-X (X = aminomalonate, Ami; L-glutamate, Glu; L-aspartate, Asp). Cellular uptake was higher for the folate-conjugated-Ami-CDDP towards KB (FR +ve) epidermoid carcinoma cells in contrast to the non-targeted Ami-CDDP micelles. All the FA-conjugated amino acid-CDDP micelles were less potent than free CDDP, but their reduced toxicity makes them potentially attractive drug carriers [54].

Liposomes possess a number of drawbacks limiting their translation into the clinic, including drug release in plasma, non-targeting, and non-uniform composition. In contrast, dendrimers can have defined structures in which the core consists of a functional monomer with a minimum of two functional groups to allow additional layers, so called generations. Haririan *et al.* have synthesised two dendrimers (with a PEG unit as the core and citric acid CA on the periphery) G1 with MW ~1000 Da and G2 with MW ~2000 Da conjugated to cisplatin forming G1 + CDDP and G2 + CDDP. G2 + CDDP showed greater cytotoxicity towards both sensitive and resistant HT1080 human fibrosarcoma cells, CT26 fibroblasts and SKOV3 human ovarian cells compared to the parent cisplatin drug, while G1 + CDDP demonstrated greater cytotoxicity towards HT1080 and CT26 cell lines. Enhanced cytotoxicity of both conjugates over CDDP is encouraging for the potential use of platinum-dendrimer conjugates as drug carriers [55].

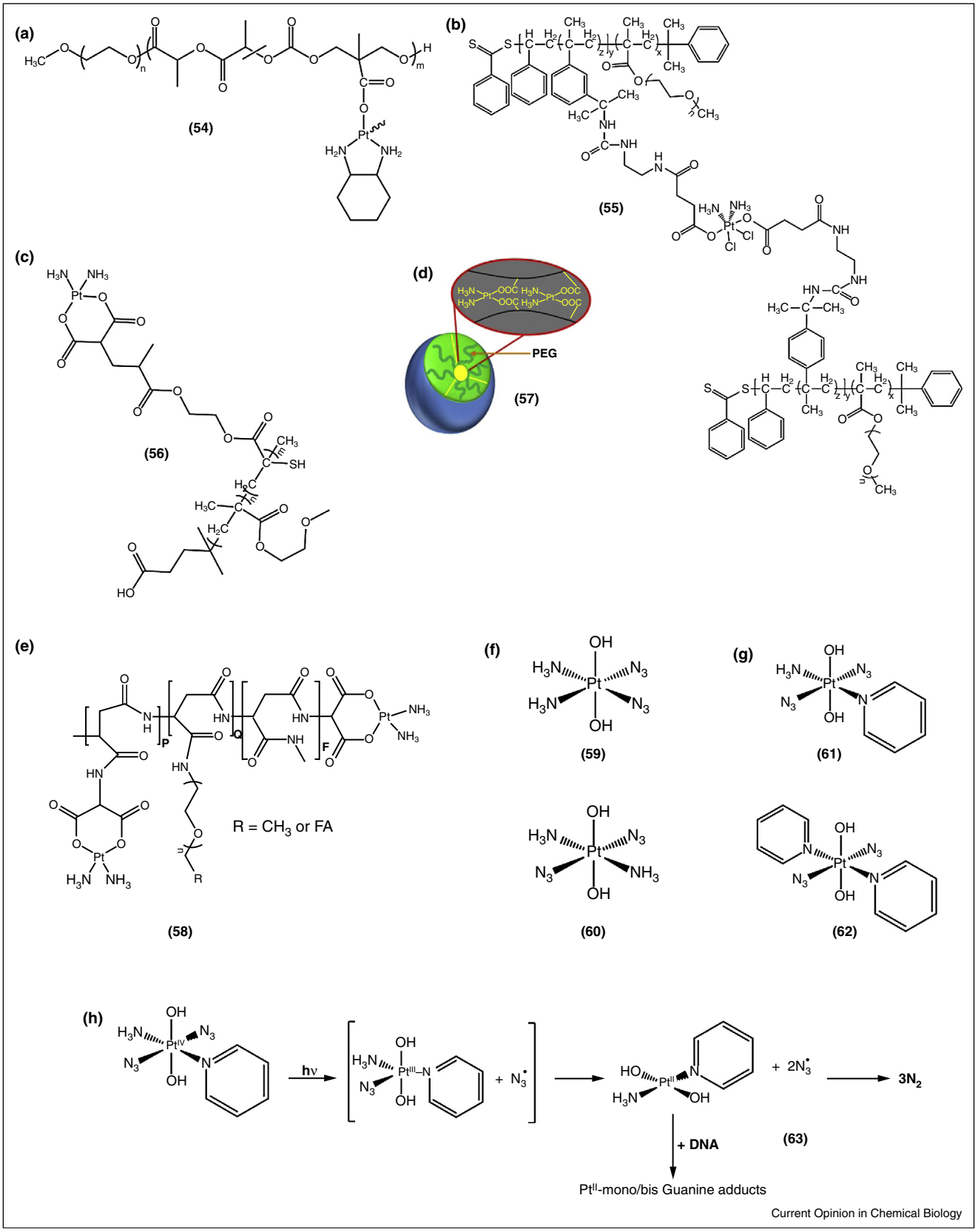
Radiation-activated prodrugs — photoactivation

Another way of avoiding unnecessary damage to normal tissues and delivering the active drug mainly to the tumour itself is by the use of spatially directed radiation to enhance activity or activate the drug specifically in the cancer cells. One approach involves the use of high energy radiation such as x-rays. Administration of a radiosensitiser can potentially overcome the resistance of cancer cells towards radiotherapy on account of their low O_2 content (hypoxia). Several platinum complexes including CDDP are known to be radiosensitisers. It is possible to enhance the effects of radiation by the use of less toxic platinum complexes. We shall not discuss this mode of targeting further here, although it is still of interest clinically.

Recent interest has focussed on the use of light for spatially directed drug activation. Current clinical use of photodynamic therapy involves administration of a photosensitiser such as a porphyrin ('Photofrin') which absorbs red light and converts ground state $^3O_2$ into excited state $^1O_2$ which is highly damaging to cancer cells [56•]. Hence, as with radiosensitisation, this is less effective when cells are hypoxic. One class of platinum complexes which do not appear to rely on oxygen for activity are Pt^{IV} diazides.

Dihydroxidodiam(m)ine platinum(IV) diazido complexes (e.g. **59** and **60**, Figure 4f) are relatively inert in the dark and importantly are not readily reduced by the thiol tripeptide glutathione, present in most cells at millimolar concentrations. These Pt^{IV} complexes possess intense

Figure 4


(a)
(54)
(b)
(55)
(c)
(56)
(d)
PEG
(57)
(e)
R = CH3 or FA
(58)
(f)
(59)
(60)
(g)
(61)
(62)
(h)
hν
+ DNA
(63)
3N2
PtII-mono/bis Guanine adducts
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ligan-(azide)-to-Pt^{IV} charge-transfer bands suitable for photoactivation. The excited states (which are populated in femto/pico-seconds) can have different geometries including lengthened and weakened Pt–ligand bonds [57]. Interestingly, the *trans* diam(m)ine diazido complexes (**60**) appear to be more effective as photoactivatable anticancer agents than the *cis* isomers [58]. These complexes are also more effective than cisplatin when used under conditions appropriate for clinical phototherapeutic drugs (short treatment times and short irradiation times).

Introduction of pyridine ligands instead of ammonia leads to a marked increase in potency and activity at longer wavelengths (**61**). For example, the *trans* di-pyridine complex **62** is active with UVA, blue and green light against a range of cancer cells at low micromolar doses [59•]. Longer wavelengths are of special interest because they penetrate more deeply into tissue than short wavelengths. Activating platinum complexes which do not possess long wavelength absorption bands is possible using two photons of red light as fast laser pulses [60].

The activity of the complex *trans,trans,trans*-$[Pt(N_3)_2(OH)_2(NH_3)(pyridine)]$ (**62**) towards oesophageal cancer is enhanced *in vivo* when irradiated with blue light [61•]. The mechanism of action appears distinct from that of conventional platinum drugs such as cisplatin. One route of photodecomposition involves two one-electron transfers from the azido ligands generating N_2 and Pt^{II} (Figure 4h) which can then form DNA lesions. These lesions can be interstrand (e.g. *trans* bis-guanine) and different from those formed by cisplatin.

Recent work suggests that there may be a role for the released azidyl radicals in the mechanism of action. Such radicals can be readily trapped and characterised by EPR and quenched by the amino acid tryptophan which can protect cancer cells *in vitro* [62•]. Furthermore, Pracharova *et al*. assessed the importance of DNA binding for the cytotoxicity induced by photoactivated **62**. Major DNA adducts of photoactivated **62** are able to stall RNA polymerase II more efficiently than cisplatin, suggesting that transcription inhibition may contribute to the cytotoxicity of photoactivated Pt^{IV} complexes [63].

Carboplatin irradiated with UVA (365 nm) is more potent (>10-fold) than non-photoactivated carboplatin in A2780 ovarian cancer cells. Short UVA-irradiation of carboplatin (30 min) resulted in 74% mono-functional DNA adducts while prolonged irradiation for four hours converted all mono adducts to bi-functional adducts [64].

Conclusions

Platinum drugs cisplatin, carboplatin and oxaliplatin are currently successful for treating some types of cancer, but have problems associated with toxic side-effects, the development of resistance and lack of tumour selectivity. Promising current work shows that these problems can be overcome to some extent by improved delivery and targeting. For example, platinum complexes can be encapsulated in nanotubes, liposomes, biodegradable proteins and other polymers and attached to the surfaces of nanotubes, nanorods and other nanoparticles. Encapsulation can be accompanied by wrapping and capping. One advantage of using carriers is that they can be multifunctional, containing not only the Pt drug or prodrug but also targeting molecules such as cell-penetrating peptides, aptamers, antibodies and various overexpressed receptors. Some nanoparticles can also be made magnetic or can be activated thermally. Encapsulation can also protect reactive platinum complexes from activation before they reach the target site. Initial data indicate that such polymer and nanoparticle supports can be well-tolerated by cells. The preparation (homogeneity) and characterisation of such multi-functionalised platinated systems, which unlike small Pt complexes cannot be crystallised, presents a challenge for translation into the clinical use. Targeting by spatially directed activation of photoactivatable Pt^{IV} prodrugs using light is also a promising way of avoiding damage to non-tumour tissue. Moreover, it is evident that these new designs of transport and delivery systems for Pt prodrugs can lead to the release of novel species which can kill cancer cells by new mechanisms, itself a potentially useful way of combating resistance and extending the spectrum of anticancer activity.

Conflict of interest

P.J. Sadler has ownership interest by patent application GB0120618.

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(a) Pt^{II} micelle conjugate (**54**). **(b)** Platinum(IV) cross-linked within a highly functionalised micelle carrier (POEGMA-b-PSTY-co-PTMI) (**55**). **(c)** Amphiphilic platinum(II) block copolymers (**56**). **(d)** NC-6004 Pt polymeric micelle (**57**). **(e)** Platinum(II) micelles with folate and without folate (**58**). **(f)** Dihydroxidodiam(m)ine platinum(IV) diazido complexes, *cis* (**59**) and *trans* (**60**). **(g)** Mono-pyridine (**61**) and di-pyridine (**62**) dihydroxido platinum(IV) diazido complexes. **(h)** Schematic photodecomposition pathway for dihydroxidodiam(m)ine platinum(IV) diazido complexes (**63**).

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