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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.

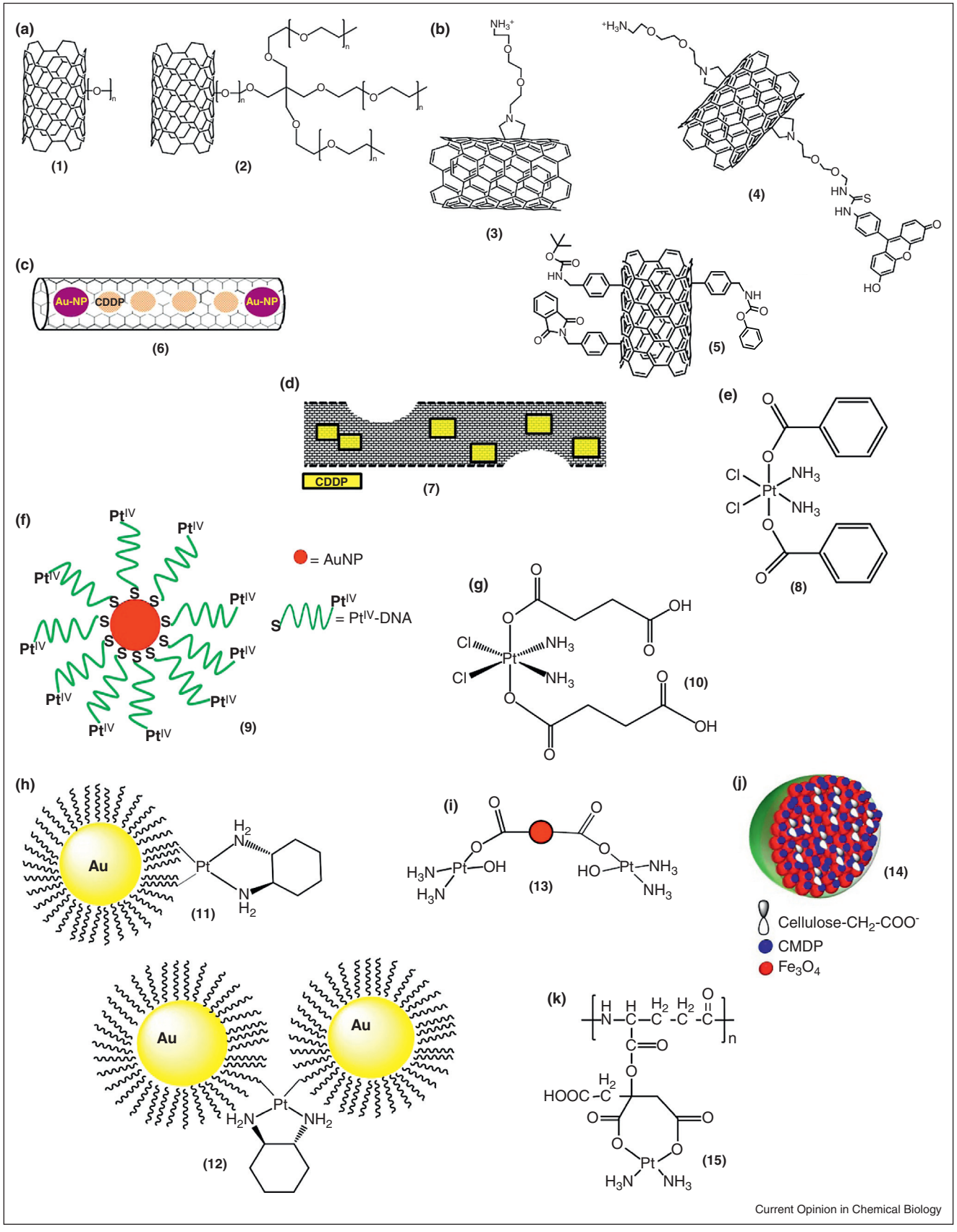
Untargeted passive drug delivery

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)
Current Opinion in Chemical Biology