The composition of budotitane is incorrectly shown in the chart. The compound is actually $[\text{Ti}(\text{CH}_3\text{COCHCOC}_6\text{H}_5)_2(\text{OCH}_2\text{CH}_3)_2]$. The ligand $\text{CH}_3\text{COCHCOC}_6\text{H}_5$ has a negative charge because of deprotonation at the center carbon (boldface). There are five possible diastereoisomeric forms for the complex, 3 cis and 2 trans forms. The material actually exists as an equilibrium mixture of the three cis isomers with no detectable amount of either of the trans forms. Because titanium(IV) is not an inert metal ion the cis interconvert and cannot be separated. These interconversion processes also mean that the enantiomeric forms that exist for each cis isomer also cannot be separated. For a determination of the isomeric composition and a discussion of the structural features of these compounds see *Inorg. Chem.* 1994, 33, 3396. The structures of the three cis isomers and their distribution in the mixture are shown below. For a discussion of antitumor activity of these and other compounds see http://www.infobiogen.fr/agora/journals/cancer/articles/11-4/krat.htm
<table>
<thead>
<tr>
<th>Compound</th>
<th>One trade name</th>
<th>Value and notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zr(IV) glycinate</td>
<td></td>
<td>Antiperspirant</td>
</tr>
<tr>
<td>Vitamin B12</td>
<td>Ca - cobalin</td>
<td>Food supplement</td>
</tr>
<tr>
<td>Ag(I) sulfadiazine</td>
<td>Flamazine</td>
<td>Antibacterial for severe burns</td>
</tr>
<tr>
<td>ZnSO$_4$$ \cdot$ H$_2$O</td>
<td>Z-span</td>
<td>Food supplement</td>
</tr>
<tr>
<td>Zn oxide or carbonate (trace of Fe$_2$O$_3$)</td>
<td>Calamine lotion</td>
<td>Antimicrobial and antifungal in skin ointments</td>
</tr>
<tr>
<td>Tc(CNR)$_6^+$ [R = CH$_2$C(CH$_3$)$_2$OMe]</td>
<td>Cardiolite</td>
<td>Used to image heart abnormalities</td>
</tr>
<tr>
<td>Tc(HMPAO)</td>
<td>Cerelec</td>
<td>Cerebral perfusion imaging</td>
</tr>
<tr>
<td>Gd(DTPA)$_2^-$</td>
<td>Magnevist</td>
<td>Improves magnetic resonance imaging scans, administered in up to 100 g doses</td>
</tr>
<tr>
<td>cis-Pt(NH$_3$)$_2$Cl$_2$</td>
<td>Cisplatin</td>
<td>Cytotoxic drug, effective in treatment of cancers of testes or ovaries</td>
</tr>
<tr>
<td></td>
<td>Carboplatin</td>
<td>Second generation less toxic cytotoxic platinum drug</td>
</tr>
<tr>
<td>cis-(CH$_3$COCHCO$_2$H)$_2$</td>
<td>Budotane</td>
<td>On trial for treatment for colon cancer, Ti delivers effective ligand</td>
</tr>
<tr>
<td>Ti(OE)$_2$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Au(CH$_2$(CO$_2$)$_2$CH(CO$_2$)$_2$S)</td>
<td>Myocresin</td>
<td>Antiarthritic</td>
</tr>
<tr>
<td></td>
<td>Auranofoin</td>
<td>Oral agent for rheumatoid arthritis</td>
</tr>
</tbody>
</table>
Anticancer metal complexes and tumour targeting strategies

F Kratz§, M.T. Schütte

Tumour Biology Center, Department of Medical Oncology, Clinical Research, Albert-Ludwigs-Universität, Freiburg im Breisgau, Postfach 1120, D-79106 Freiburg, Germany. Fax: 49 0761 2061899

§: correspondence

ABSTRACT
Cisplatin and carboplatin are at present two of the most widely used anticancer agents in the world. They show their best activity against testicular carcinomas and are also effective against ovarian carcinomas, tumours of the head and neck, and bladder tumours. The clinical responses seen with antitumour platinum complexes have incited the development of a number of non-platinum compounds with metal ions such as germanium(IV), titanium(IV), tin(IV), gallium(III) or ruthenium(III) which exhibit antitumour activity in in-vitro and in-vivo models. Some of these complexes have entered, or are about to enter, clinical trials. Although platinum and non-platinum complexes are potent antineoplastic agents, they do have serious side-effects (e.g. myelotoxicity, nephrotoxicity and neuropathy) that are due to their reactions with cellular components of healthy tissues. Hence, to improve the selectivity of metal complexes for tumour tissue, effective drug delivery systems are needed.

Appropriate carriers are low molecular weight compounds such as hormone derivatives, on the
one hand, and macromolecular carriers or microparticles, on the other. Members of this latter group that are under investigation include microparticulate delivery systems (liposomes, nano- and microparticles, emulsions) and soluble polymeric delivery systems (serum proteins, synthetic and natural polymers).

This review article describes antitumour metal complexes of preclinical and clinical interest and outlines tumour targeting concepts that use macromolecular and particulate carrier systems which aim to improve cancer chemotherapy with metal complexes.

Key words: anticancer chemotherapy, anticancer metal complexes, drug delivery systems, polymer conjugates, tumour targeting

INTRODUCTION

At the beginning of this century metal complexes emerged as potential pharmacologically active agents due to the pioneer work of Paul Ehrlich and the development of Salvarsan (1910), an arsenic-containing compound, which was the first effective drug in the treatment of syphilis. Half a century later, in 1965, a serendipitous discovery by Barnett Rosenberg paved the way for the application of platinum complexes in cancer chemotherapy. Rosenberg was investigating the influence of an electric field on the cell growth of E. coli using platinum electrodes which were submerged in a solution containing ammonium chloride (1). These conditions and the sunlight irradiating the experiment setup favoured the formation of cis-configured platinum complexes such as \(\text{cis-}\text{diamminetetrachloroplatinum(IV)}\) which produced what is known as filament growth of E. coli, the bacteria growing up to 300 times their own length without any cell division. This observation led Rosenberg to synthesize a number of simple platinum complexes among which cis-configured complexes showed remarkable antitumour efficacy in tumour-bearing animals, in contrast to the inactive trans compounds (2). Only 6 years after Rosenberg's discovery, one of these complexes, cisplatin \(\text{cis-diamminedichloroplatinum(II)}\) (Figure 1), entered clinical trials and since then has established itself as a highly effective drug in the treatment of a number of solid tumours. The clinical success of cisplatin initiated the development of further platinum complexes as well as of non-platinum complexes. A number of these have been tested in clinical trials or are now at an advanced stage of preclinical development. In the future, drug discovery strategies involving metal complexes as anticancer agents will focus on circumventing cisplatin resistance in malignant diseases, on avoiding or reducing the side-effects of antitumour metal complexes, and of broadening their field of indication. Basically, these goals can be reached through: (a) improved administration concepts, e.g. with the aid of cytoprotective agents, (b) development of novel platinum complexes, (c) development of non-platinum complexes, (d) tumour targeting.

The following sections will address these issues with emphasis on tumour targeting strategies.

ANTITUMOUR PLATINUM COMPLEXES

Cisplatin shows its best activity against testicular carcinomas (cures in most cases) and is effective against ovarian carcinomas, tumours of the head and neck as well as bladder tumours (prolongation of survival time and cures in some cases). Since its discovery by Barnett Rosenberg, a wealth of information has been published on the interactions of cisplatin with nucleotides and DNA [reviewed in
These studies have supported the theory that cisplatin enters healthy as well as tumour cells and then reacts specifically with intracellular DNA, thus inhibiting DNA and cell replication. The precise molecular nature of the different adducts formed from cisplatin and DNA have been extensively studied (see above reviews). Cisplatin favours binding to the N7 atom of the DNA base guanine which can result in inter- or intrastrand cross-linking of adjacent or opposing guanine moieties as well as cross-links between guanine and a protein molecule. 

Cisplatin, although a very potent antineoplastic agent for the above-mentioned tumours, does have serious side-effects that are due to its reactions with cellular components of healthy tissues. These include nephrotoxicity, ototoxicity (loss of high-frequency hearing), myelotoxicity, peripheral neuropathy, nausea and vomiting. Hydration using infusion of isotonic saline solutions and diuretics as well as administration strategies (e.g. continuous 24-hour infusion) have allowed the use of high doses without severe damage to the kidneys in most cases. In addition, cytoprotective agents such as amifostine can, in part, reduce its haematological toxicity and cumulative nephrotoxicity (5). The development of so-called "second generation platinum complexes" has concentrated on reducing or avoiding the toxicity of the parent compound and on finding compounds active against other cancers. Design of such compounds has in most cases been empirical, and the rule of thumb of retaining a cis-configuration in platinum analogs has been followed. Thus, thousands of new platinum complexes have been synthesised by either replacing the chlorides by other hydrolyzable groups or by changing the amine moiety (reviewed in 6). Subsequent assessment of antitumour activity has shown that "direct" analogues of cisplatin do not show a very different antitumour spectrum, but toxicity can be reduced, as in the case of carboplatin [cis-diammine(1,1-cyclobutane-dicarboxylato)platinum(II)] (Figure 2). This direct analogue, in which cyclobutanedicarboxylate replaces the chlorides, has reached the clinical stage thanks to reduced nephrotoxicity and ototoxicity (7). The dose-limiting toxicity for carboplatin is myelosuppression, mainly thrombopenia.

Besides cis- and carboplatin, a number of platinum complexes have undergone or are undergoing clinical trials (mostly clinical phase I and II studies), and those that are of current interest are shown in Figure 3. In most cases, reduced systemic toxicity, or a different toxicity profile compared to cisplatin, has been the major reason for initiating clinical trials with these platinum complexes. In some cases, however, the ability to circumvent cisplatin resistance in murine tumour models or marked activity against tumours which do not respond to cisplatin has encouraged clinical trials, for instance with oxaliplatin or transplatin. Some clinical responses have been observed in combination therapy studies with 5-fluorouracil and oxaliplatin in the treatment of colorectal tumours (8). Oxaliplatin, a diaminocyclohexane (DACH) platinum complex, has recently been approved in France for the treatment of colon cancer. Dose-limiting toxicities of oxaliplatin are neutropenia and peripheral neuropathy. The first orally administrable platinum complex, JM216, showed comparable toxicity to carboplatin in phase I studies, but did not appear to have a significant antitumour activity in a phase II study in non-small-cell lung cancer patients (9). Finally, lobaplatin is a promising new platinum complex with clinical activity against solid tumours such as ovarian and oesophageal tumours and, because of its favourable toxicity profile, its clinical development is being pursued intensively (11). Nevertheless, further trials are necessary to find out whether these platinum complexes can establish themselves in routine clinical practice. Cisplatin and carboplatin remain the standard anticancer metal complexes to which novel platinum-based complexes are compared.
NON-PLATINUM ANTITUMOUR METAL COMPLEXES

Because cisplatin and direct platinum analogues are only active against a limited number of cancers, metal complexes with non-platinum metals, e.g. germanium(IV), titanium(IV), tin(IV), ruthenium(III), gold(III), and copper(II), have been developed over the last ten years. Several exhibit high in-vitro and in-vivo antitumour activity. Those that have been extensively studied in preclinical models and/or tested in early clinical trials will be described in more detail below.

Non-platinum compounds which have entered clinical trials - Two titanium(IV) complexes, budotitane and titanocene dichloride (Figure 4), have undergone phase I studies after showing promising antitumour activity in experimental colon tumour models (11) (12). Their main side-effects are liver and kidney toxicity; their myelotoxicity is not pronounced (11) (12). Phase II trials with titanocene dichloride are scheduled in Germany under the auspices of the Arbeitsgruppe Internistische Onkologie (AIO) of the German Cancer Society.

Two other antitumour metal complexes which contain metal-carbon bonds and have undergone clinical trials are the germanium complexes germanium-132 and spirogermanium (Figures 5 et 6). In phase II studies performed in the mid-eighties, their toxicity was mild or moderate in most patients but hardly any evidence of antitumour activity was observed (13) (14).

Finally, two gallium(III) salts have undergone a number of clinical trials. Gallium trinitrate has shown antitumour activity in previously treated patients with malignant lymphoma, bladder carcinoma as well as small cell lung carcinoma and is also effective in the treatment of cancer-related hypercalcemia (15) (16). Gallium chloride potentiates the therapeutic effect of cisplatin and etoposide when administered in combination (17). Gallium salts probably exert their antitumour effect by binding to transferrin in the blood circulation and subsequently interfering with the transferrin cell cycle of tumour cells.

Non-platinum complexes at an advanced stage of preclinical development - Keppler and coworkers have developed anticancer ruthenium(III) complexes with N-heterocycles and, among these, trans-indazolium-[tetrachlorobis(2H-indazole)ruthenate(III,N1)] (HInd[RuInd2Cl4]) (Figure 7) exhibits high antitumour activity in-ivvo and low systemic toxicity (18). Kratz et al. have demonstrated a fast and specific binding of this complex to human serum transferrin and human serum albumin (19) (20). These protein adducts of HInd[RuInd2Cl4] retain the antitumour efficacy of the original complex indicating that transferrin and albumin play an important role in the biodistribution of this highly active complex (21). Because of the insufficient aqueous solubility of the original complex, which precluded a clinical formulation, an analogous ruthenium(III) indazole complex has been developed in which the indazolium ion has been replaced by sodium. Trans- Na[RuInd2Cl4] displays similar antitumour activity to trans-HInd[RuInd2Cl4] and is a prime candidate for clinical trials.

Other active ruthenium complexes are the tumour-inhibiting ruthenium dimethylsulfoxide complexes studied by Mestroni and coworkers, which show antimetastatic activity in murine tumour models (22). Finally, Crowe (23) and Gielen et al. (24) have developed a large number of organotin(IV) derivatives - either direct analogues of cisplatin or novel tetracoordinated structures - with promising in-vitro and
in-vivo antitumour activity. This work and the potential and current status of antitumour non-platinum metal complexes, have been reviewed in a recent book (25).

TUMOUR TARGETING

A major disadvantage of clinically established anticancer agents is their lack of selectivity for tumour tissue. This results in systemic toxicity, severe side-effects and low cure rates. Thus, drug delivery systems which can carry the cytotoxic agent to the tumour target, killing tumour cells while largely sparing normal tissue, are needed. A general strategy in tumour targeting has made use of both low or high molecular weight carriers and particulate systems which have an affinity for tumour tissue or for tumour cells. Antitumour metal complexes have been coupled to or associated with these different kinds of carriers, and a number of examples are described below.

Tumour targeting strategies with low molecular weight carrier molecules - Two approaches of attaching pharmacologically active metal complexes to low molecular weight carrier molecules have been described in the literature. In the work of Brunner, von Angerer, Schönenberger and coworkers, platinum complexes linked to hormone derivatives which have an affinity for hormone receptor-positive tumours (breast or prostate carcinomas) have been developed (26). In these platinum derivatives a cis-configured platinum(II) moiety is either bound to substituted 1,2-diphenylethylenediamines or to 2-phenylindole derivatives as shown in Figure 8. The antitumour activity of these complexes has been confirmed in estrogen receptor-positive tumours whereas estrogen-negative tumours did not respond (27). The mode of action seems to be an antiestrogenic one: the complexes bind to estrogen receptors on target cells displacing estrogen from its binding site. The resulting receptor complex can no longer induce transcriptional events because of interactions of the cis-configured platinum(II) moiety within the complex or within DNA. In a second approach, Keppler and coworkers have developed osteotropic platinum compounds containing phosphonates (28). Phosphonic acids are used routinely in technetium scintigraphy, against metabolic disorders of the bone (e.g. Paget's disease), and in the therapy of tumour-induced hypercalcemia (e.g. therapy with Clodronate, Ostac"). Two platinum complexes, in which a phosphonate capable of binding to hydroxylapatite is coordinated to a cis-configured platinum(II) moiety, have been intensively studied in animal models, i.e. cis-diammine[bis(methylphosphonato)(2-)- O, N1]platinum(II) (12) and cis-diammine[bis(phosphonatocarbonyl)amino)acetato(2-)-O, N1]platinum(II) (13) (Figure 9). Less toxic than cisplatin, they markedly inhibit the growth of a transplantable osteosarcoma, prolonging survival time (29). Further research is needed to evaluate whether such complexes are potential candidates for the treatment of bone malignancies.

Tumour targeting strategies with macromolecular carriers and microparticles - In recent years there has been an increasing awareness that the lack of selectivity of low molecular weight antitumour drugs could be related to their pharmacokinetic properties, i.e. their short half-life in the bloodstream and their rapid diffusion throughout the body resulting in an essentially even tissue distribution [reviewed in (30)]. Therefore, one approach to alter the pharmacokinetic behaviour and overcome the toxicity of anticancer drugs to normal tissue - thereby increasing the therapeutic index of theses agents - is to attach cytotoxic drugs to soluble macromolecules or to incorporate them into microparticulate delivery systems. World-wide a great number of macromolecular delivery systems are under investigatin with the aim of improving cancer chemotherapy, and a general classification is shown in Figure 10. Microparticulate
delivery systems, in which anticancer agents are physically incorporated into nano- or microparticles, include emulsions, liposomes and polymer microspheres. In polymeric drug delivery systems, however, the anticancer moiety is covalently linked to polymers such as proteins, polysaccharides or synthetic polymers.

The rationale for using large molecules and microparticles to deliver antitumour agents has been strengthened by recent studies on the enhanced vascular permeability of tumour tissue to macromolecules (31) (32), the so-called "enhanced permeability and retention" (EPR) effect in tumour targeting (30) (see Figure 11). Blood vessels in most normal tissues have an intact endothelial layer which allows the diffusion of small molecules but not the entry of macromolecules into the tissue. In contrast, the endothelial layer of blood vessels in tumour tissue is often leaky so that small as well as large molecules have access to malignant tissue. Since tumour tissue does not generally have a lymphatic drainage system, macromolecules are thus retained and accumulate in solid tumours. In this respect, Yuan et al. have investigated the vascular permeability of human tumour xenografts in nude mice for molecules of varying size and demonstrated that even liposomes as large as 400 nm can pass the leaky endothelial layer of tumour tissue and thus reach tumour cells (32).

Over the past 20 years, many macromolecules and microparticles have been studied as potential carriers of anticancer agents (see examples in Table I). Both microparticulate systems and polymeric drug conjugates offer exciting possibilities of improving antitumour chemotherapy. Besides selective drug delivery and reduced systemic toxicity, the advantages of attaching antitumour metal complexes to macromolecules such as serum proteins, or of incorporating them into microparticulate delivery systems such as liposomes, could be that such macromolecular complexes will be less immunogenic because the active metal complex is cloaked in a natural environment and will therefore not activate the body's immune system. Drug hypersensitivity can reduce the therapeutic effect of platinum-based chemotherapy or even induce severe anaphylaxis (33).

<table>
<thead>
<tr>
<th>macromolecular carriers</th>
<th>examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>biological macromolecular</td>
<td></td>
</tr>
<tr>
<td>proteins</td>
<td>antibodies, serum proteins</td>
</tr>
<tr>
<td>polysaccharide</td>
<td>dextran, inulin</td>
</tr>
<tr>
<td>lectins</td>
<td>concanavalin A, wheat germ agglutinin</td>
</tr>
<tr>
<td>peptide hormones</td>
<td>melanotropin, thyrotropin</td>
</tr>
<tr>
<td>nucleic acids</td>
<td>deoxyribonucleic acid (DNA)</td>
</tr>
<tr>
<td>synthetic macromolecules</td>
<td></td>
</tr>
<tr>
<td>polyamino acids</td>
<td>polylsine, polyaspartic acid</td>
</tr>
<tr>
<td>copolymers</td>
<td>styrene-maleic acid anhydride-copolymer (SMA)</td>
</tr>
<tr>
<td></td>
<td>divinylether-maleic acid anhydride-copolymer (DIVEMA)</td>
</tr>
<tr>
<td></td>
<td>N-2-hydroxypropyl)methacrylamide-copolymer (HPMA)</td>
</tr>
</tbody>
</table>
In the past, liposomes have provided a sustained release technology for some anticancer agents. Two liposomal formulations are now commercially available to the practising oncologist: DaunoXome®, a daunorubicin citrate liposome injection, and Doxil™, a Stealth™ formulation of doxorubicin. (In so-called Stealth™ formulations, the liposome surface bears grafted polyethylene glycol groups which reduce opsonization and phagocytosis, thus increasing their circulation time and the chance of their accumulation in the tumour). Both have been approved for the treatment of Kaposi’s sarcoma (8).

Polymer conjugates, however, constitute a novel class of pharmacologically active formulations which have only recently entered clinical practice.

**Microparticulate drug delivery systems with platinum complexes**

**Liposomes** - Several platinum complexes such as carboplatin, lobaplatin or the lipophilic platinum(II) complex cis-bis-neodecanoato-trans-R,R-1,2-diaminocyclohexane platinum(II) (NDDP) (Figure 12) have been encapsulated in liposomes. NDDP has been formulated within multilamellar liposomes composed of dimyristoylphosphatidylcholine and dimyristoylphosphatidylglycerol (34), and a phase I clinical study has been performed. The instability of this DACH platinum compound within liposomes has, however, prevented its widespread clinical evaluation. Reszka and coworkers have encapsulated lobaplatin and carboplatin in specially tailored liposomal systems (35). Carboplatin liposomes demonstrated a superior tumour-inhibiting effect in certain human mammary xenografts in immunodeficient mice compared to free carboplatin. Surprisingly, after encapsulation of carboplatin in particular liposomes, the myelotoxicity of the free substance could be translated into hematopoiesis.

**Cisplatin microspheres** - Several investigators have incorporated cisplatin into microspheres prepared from albumin, chitosan, polylactic acid/polyethylene glycol blend polymers or polybenzyl glutamate (36) (37) (38) (39). In general, microsphere formulations are produced by chemical cross-linking of the polymers producing a matrix in which the drug is contained. Depending on the chosen procedure, particle size of the microspheres varies from about 5 to 200 microns. Cisplatin microspheres have been developed to improve intraperitoneal chemotherapy of cancers such as ovarian tumours, and preclinical data in tumour models have shown that the survival of rats with peritoneal carcinoma is increased by this drug delivery system in comparison to cisplatin (40). In a recent pilot study, 13 patients with malignant ascites (induced by cancers of the digestive system) were treated i.p. with cisplatin incorporated in microspheres composed of lactic acid oligomers (41). Malignant ascites disappeared completely in eight patients and decreased partially in four, indicating that cisplatin microspheres are suitable for locoregional chemotherapy. Intratumoural and arterial hepatic routes of administration have also been suggested for the therapeutic use of cisplatin microspheres (36).

**Emulsions** - The therapeutic effect of an emulsion of lipiodol and cisplatin has been examined in a number of studies. Lipiodol is an oily contrast medium which is taken up by tumours, especially those of...
the liver. Studies in patients with inoperable hepatocellular carcinoma have shown a high response rate when the formulation of lipiodol and cisplatin was given as a transarterialchemoembolization (40) (41).

Polymer conjugates with platinum complexes - The development of cis-configured platinum complexes that can bind to macromolecules has recently been integrated into our drug development programme of polymer conjugates at the Tumour Biology Center, FRG. In order to bind an active cis-configured platinum(II) complex to macromolecular carriers, we have synthesised appropriate ligands which can form a complex with platinum(II) and also bind to functional groups of polymers. The general structure of such platinum(II) complexes is illustrated in Figure 13. The spacer molecule forms a chemical bond to the active moiety of the metal complex and also to a functional group of the macromolecular carrier, thus cross-linking the metal complex to the carrier.

According to our experience with polymer conjugates of organic anticancer agents, the chemical bond between the drug and the carrier plays a crucial role in in-vitro and in-vivo activity (42) (43) (44) (45). Our conjugates containing anthracyclins or alkylating agents incorporate acid-sensitive linkers which act as a predetermined breaking point. The polymer-bound drug is released either in the acidic environment of the tumour tissue or in the acidic endosomal or lysosomal compartments after cellular uptake of the conjugate by the tumour cell. In-vivo data in several animal models have shown a reduced toxicity of anthracyclin conjugates compared to the free anthracyclin at low doses with a concomitantly stable and significantly improved antitumour activity of the conjugate at high doses (44) (45). Binding of an active cis-configured platinum moiety to serum proteins or synthetic polymers is therefore a promising strategy for improving the therapeutic effect of platinum complexes. Suitable functional groups which bind specifically and selectively to sulfhydryl, amino or hydroxy groups of the macromolecular carrier are the maleimide group and the N-hydroxysuccinimide ester group. The maleimide group reacts selectively with sulfhydryl groups to form a stable thioether bridge whereas the N-hydroxysuccinimide ester reacts readily with NH₂- and HO- groups to form an amide and ester bond respectively. We have recently synthesised cis-configured platinum(II) maleimide complexes which were then bound to human serum albumin (46) or polyethylene glycols (47) in order to obtain the conjugates shown in Figure 14. In these conjugates, the point of cleavage is either an ester or an acid-sensitive carboxylic hydrazone bond. In-vitro and in-vivo studies are in progress.

In summary, it is hoped that through a combination of the outlined development strategies novel formulations of antitumour metal complexes are prepared exhibiting lox toxicity, a broader field of indication, and a targeting potential towards tumour tissue thus increasing the therapeutic index of clinically relevant metal compounds.

Acknowledgments: We would like to thank the Dr. Mildred Scheel Stiftung der Deutschen Krebshilfe, the Deutsche Forschungsgemein-schaft and the Schering Research Foundation for their support.

REFERENCES


27. von Angerer E. Platinum complexes with specific activity against hormone-dependent tumours; in Metal Complexes in Cancer Chemotherapy (BK Keppler ed.); Verlag Chemie VCH, Weinheim, pp


