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Platinum Group Metal Compounds in Cancer Chemotherapy

An overview of the history and the potential of anticancer pgm compounds

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It was some 50 years ago that Barnett Rosenberg and coworkers published their studies on unusual patterns of bacterial growth that led to the identification of platinum compounds as highly effective agents against some cancers, particularly those of genitourinary origin. This sparked a renewed interest around the world in the potential of metal compounds as small molecule therapeutic agents. Some of that history, particularly related to the platinum group metals (pgm) platinum and ruthenium, is described in this overview.

The First Drug – Cisplatin

The application of platinum compounds in cancer therapy was one of the most unexpected developments in pharmaceuticals in the last 50 years. Many reviews have been published previously on this topic; in this journal the most recent being by Reedijk in 2008 (1).

The potential of platinum compounds was discovered by Rosenberg in 1965 (2). He had recently taken up an interdisciplinary post as Professor of Biophysics at Michigan State University, USA. Coming from a physics background with little experience in biological sciences one of his early experiments was to study the effect of electromagnetic fields on cell division. In a fortunate combination of circumstances, he conducted a test experiment with platinum electrodes, an ammoniacal medium and *Escherichia coli* as the test organism. He observed unusual filamentous growth that he was later able to attribute to the formation of soluble platinum ammine complexes. After further study he approached the National Cancer Institute (NCI), USA, to demonstrate whether the key compound, *cis*-$PtCl_2(NH_3)_2$, could also affect the growth of cancer cells. The activity was significant and encouraged the NCI to support the clinical evaluation of cisplatin, as this compound came to be known (3). The action of cisplatin was subsequently determined to arise from its interaction with deoxyribonucleic acid (DNA), in particular forming intrastrand cross-links between neighbouring guanosine residues. Over many years much effort was put into studying the detail of this lesion and its interactions with proteins which might mediate the cell death process (4, 5).

Early clinical results were variable, with occasional patients showing very positive results while others encountered marked toxic effects such as kidney and nerve damage. While these side effects remained uncontrolled there seemed little likelihood of cisplatin achieving regulatory approval, but fortunately a new administration procedure involving pre- and post-hydration significantly reduced the kidney toxicity (but did not eliminate it) (6). This allowed somewhat higher doses to be given to patients with acceptable

toxic risk and pronounced activity in genitourinary cancers (particularly testicular and ovarian cancer) was observed. On this basis, the NCI and Research Corporation (on behalf of Michigan State University) licensed the marketing of cisplatin (**Figure 1**) to Bristol-Myers, USA, with marketing approval being gained in the USA in 1978 and many other countries, including the UK, the following year.

Second Generation – Carboplatin

To raise support for his continuing work at Michigan State University and promote interest in his discovery Professor Rosenberg toured and corresponded widely. This included contact with the platinum companies Rustenburg Platinum Mines Ltd, South Africa (pgm mining and supply), and Engelhard Corp, USA, and Johnson Matthey Plc, UK (both specialised in pgm marketing). To obtain a better understanding of this technology Johnson Matthey and Engelhard sent postgraduate researchers, Michael Cleare and James Hoeschele respectively, to work in Professor Rosenberg's research group. Cleare decided to study the structure-activity relationships of platinum complexes, resulting in the synthesis of various pgm complexes and a series of publications describing this work (see, for example (7–9)). On returning to the UK, Cleare, with Rustenburg's support, coordinated the exchange of results between a number of researchers interested in the new field. After the marketing of cisplatin, he was instrumental in linking Bristol-Myers, Johnson Matthey and the Institute of Cancer Research (ICR), UK, to identify a second generation alternative to cisplatin. The aim of the programme was to increase the therapeutic potential of the drug either by decreasing the toxicity, particularly kidney toxicity, associated with its use or by increasing the potency and thus effectiveness at lower doses.

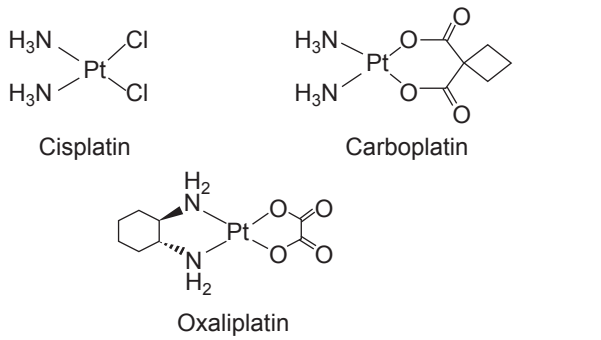

Fig. 1. Globally marketed platinum-containing drugs

Ultimately, it was the former of these targets which proved easier to achieve. From the compounds originally synthesised at Michigan State University by Cleare, diammine-1,1-cyclobutanedicarboxylatoplatinum(II), carboplatin (**Figure 1**), was found by the ICR to have the best balance of antitumour activity and low toxicity for taking forward to clinical trials (10). Due to the close links between the ICR and the Royal Marsden Hospital, London, UK, with the support of Bristol-Myers, the compound was progressed rapidly through clinical trials and granted its first marketing approval for treating ovarian cancer in 1986.

Other Second Generation Compounds – Oxaliplatin

Bristol-Myers and Johnson Matthey investigated another second generation compound, iproplatin (JM-9, **Figure 2**), in this case with the pre-clinical studies being carried out by the Roswell Park Cancer Institute, USA, in addition to work at ICR (11). In clinical trials this drug had similar activity to carboplatin but toxicities proved more difficult to control (12). Bristol-Myers also pursued the development of spiroplatin (TNO-6, **Figure 2**) a compound synthesised at the Dutch Institute of Applied Chemistry, Nederlandse Organisatie Voor Toegepast Natuurwetenschappelijk Onderzoek (TNO), The Netherlands. In this case problems were encountered with kidney toxicity and limited activity (13). Therefore, Bristol-Myers chose to concentrate its further efforts on gaining marketing approval for carboplatin.

A significant number of compounds were investigated in early stage clinical trials by other organisations, both commercial and academic (12, 14). Some examples are given in **Figure 2**. Some of these gained local market approval including nedaplatin (Aqupla™, 254-S), Shionogi Pharmaceuticals, Japan; lobaplatin, Asta Medica, China; heptaplatin (eptaplatin), SK Chemicals Life Sciences, Korea, see **Figure 3**. However, one compound that has achieved widespread use is oxaliplatin (**Figure 1**). This compound incorporates the 1,2-diaminocyclohexane ligand that was favoured in early studies by the NCI, the same ligand being incorporated into JM-82 ((1,2-diaminocyclohexane)(trimellitic acid)platinum(II)) and tetraplatin (ormaplatin, **Figure 2**) which entered clinical trials but were not marketed. Oxaliplatin (named as *l*-OHP) was first reported by Kidani and Mathé (15) who initiated clinical trials (16). Development was continued by Debiopharm Group™, a small Swiss company, with

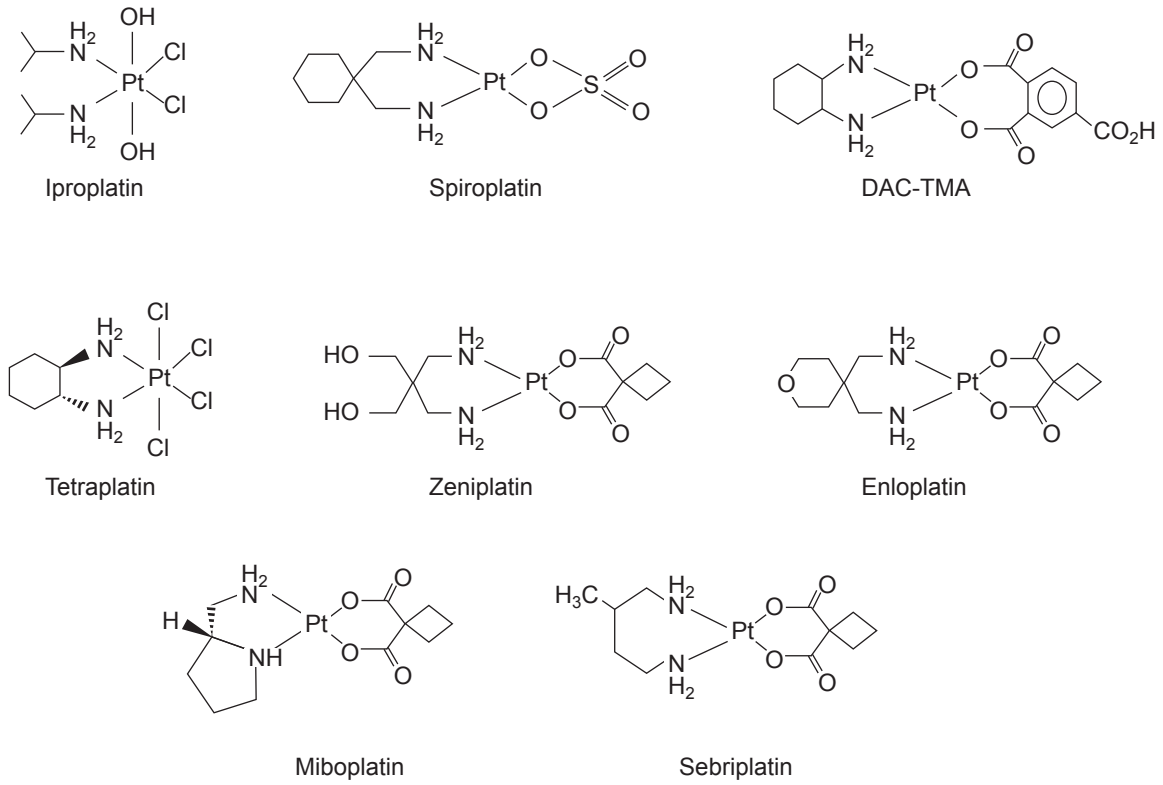

Fig. 2. Second generation platinum compounds evaluated in clinical trials

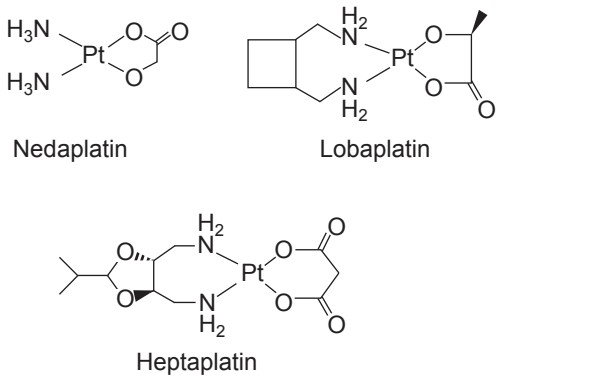

Fig. 3. Regionally marketed platinum-containing drugs

clinicians conducting a number of trials to find the best administration schedule that would maximise the activity while controlling the toxicity. Pre-clinical testing in mice had shown that toxicities could be reduced when the drug was given with circadian periodicity (17). By appropriate scheduling of administration in patients (chronotherapy) it was found that toxicities, such as neutropenia and paraesthesia, were less frequent and improved responses were seen in colon cancer when used together with 5-fluorouracil (18). The drug was then licensed to Sanofi, France, for marketing worldwide with the major indications being adjuvant and metastatic colorectal cancers.

Third Generation – Satraplatin

Following the success of their collaboration on carboplatin, Johnson Matthey, ICR and Bristol-Myers Squibb (following their merger) reviewed their options for further developments in this field. Two targets were identified; firstly, to adapt the platinum agents to provide an orally administered drug as an alternative to the intravenously injectable cisplatin and carboplatin and, secondly, to achieve activity in tumours which were resistant, or had acquired resistance, to cisplatin. Significant progress on the first target came when Giandomenico described versatile routes for converting platinum(IV) hydroxido complexes to their carboxylate counterparts (19). Selecting a compound for clinical trials required careful judgement on balancing the antitumour activity with emetic potential. The compound selected was *cis*-ammine(cyclohexylamine)-*cis*-dichlorido-*trans*(diacetato)platinum(IV), satraplatin (JM-216, **Figure 4**) (20). After some years of clinical trials on hormone resistant prostate cancer, it was determined that the compound did not result in significant life

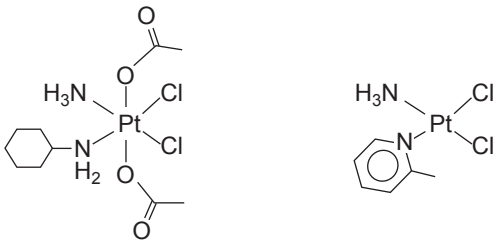

Fig. 4. Third generation platinum compounds

extension for patients and the development was abandoned (21).

Third Generation – Picoplatin

The compound chosen for clinical trials to study the question of activity in cisplatin resistant tumours was *cis*-ammine(2-methylpyridine)dichloridoplatinum(II), picoplatin (**Figure 4**) (22). The 2-methylpyridine ligand reduces the interaction of the complex with strongly binding ligands in an associative ligand substitution pathway. This is important in reducing the likelihood of interaction of the complex with sulfur donors, such as glutathione, which might deactivate the compound (23). Licenses for developing this compound were granted to a number of companies after Bristol-Myers Squibb withdrew from the programme, but none of the trials revealed sufficient activity to warrant marketing approval (21).

'Unconventional' Platinum Compounds

Other options for identifying useful activity were also explored by several groups, in particular through searching for activity outside the spectrum displayed by cisplatin compounds defined by the early structure-activity rules established by Cleare (7). These empirically determined 'rules' identified neutral complexes with *cis* configuration, two am(m)ine or one bidentate chelating diamine carrier ligands and two ligands that could be replaced for subsequent binding to DNA as showing much greater anticancer activity than related complexes. However, with careful choice of compounds it has been shown that most of these 'rules' can be overcome to produce potent compounds. For example, although *trans*-$PtCl_2(NH_3)_2$ is inactive compared with cisplatin, other *trans* compounds such as JM-335 (24–27) or those containing planar organic ligands (28) (see **Figure 5**) do show significant

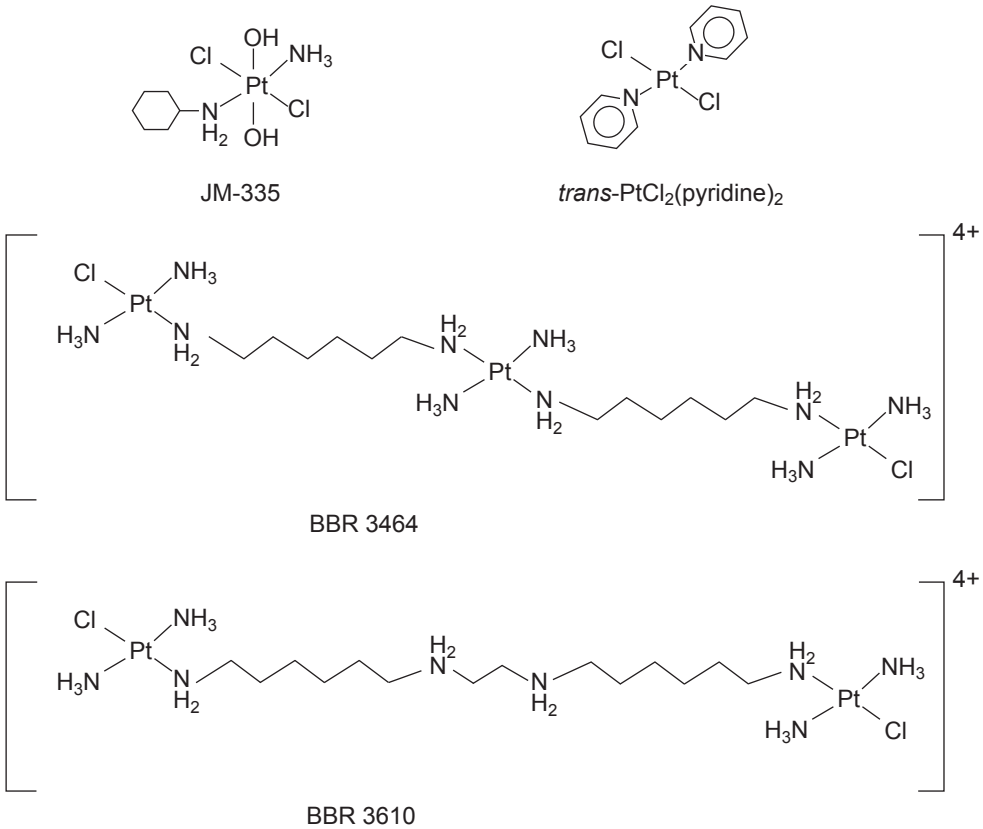

Fig. 5. 'Unconventional' platinum anticancer compounds

activity. However, results from testing cisplatin-resistant xenograft tumours were not sufficiently encouraging for these compounds to be taken forward to clinical study. Dinuclear or oligonuclear complexes of platinum can form different lesions on DNA compared to monomeric cisplatin and this is another area that has been investigated (29). Of particular interest in this regard is the ionic trinuclear complex BBR3464 (**Figure 5**) (30). This compound was developed for clinical trials by Boehringer Mannheim Italia, Italy, but again the level of activity was not sufficient to justify large scale phase III trials (31, 32).

Ruthenium Compounds

As it became increasingly apparent that an immense effort would be required to identify a platinum compound with improved therapeutic properties over cisplatin, carboplatin and oxaliplatin, so many researchers turned to other metals to open up new avenues to identifying compounds which might offer activity where cisplatin was ineffective. Ruthenium complexes were among the first suggested for detailed study (33) and a number of different compounds have been followed up. Early studies of a wide range of metal complexes identified ruthenium dimethylsulfoxide (DMSO) complexes, both *cis*- and *trans*-[$RuCl_4(DMSO)_2$], as being of interest (34). Ruthenium oxidation states II, III and IV are stable in water in various complexes. Ruthenium(III) complexes are relatively inert to substitution compared with ruthenium(II) and this suggested the potential of ruthenium(III) compounds to act as prodrugs for ruthenium(II) species which might be formed by reduction in the body (33). This theory became known as 'activation by reduction' and relied on the fact that tumour masses grow without the associated development of vascularisation systems typical of normal tissue and so offer a less oxygen rich and hence more reducing environment of lower pH than normal tissues. Thus the action of the complexes might be enhanced relative to normal tissue.

Ruthenium(III) Complexes

This theory was evaluated during the development of Na[$RuCl_4$(DMSO)(Im)] (NAMI, Im = imidazole) (34). Results from testing against lung and mammary tumours in mice were encouraging, but NAMI lacked many of the ideal physical characteristics for pharmaceutical development. In particular, the compound is hygroscopic and crystallises with two DMSO molecules of crystallisation resulting in variability in elemental composition and poor stability. Many of these problems were resolved by switching to the imidiazolium salt [ImH][$RuCl_4$(DMSO)(Im)] (NAMI-A, **Figure 6**) (35). This has no molecules of crystallisation resulting in good stability and has good solubility in water. In addition, its synthesis from ruthenium trichloride is a simple and high yielding process. Solution studies showed that the complex is likely to undergo chloride hydrolysis in

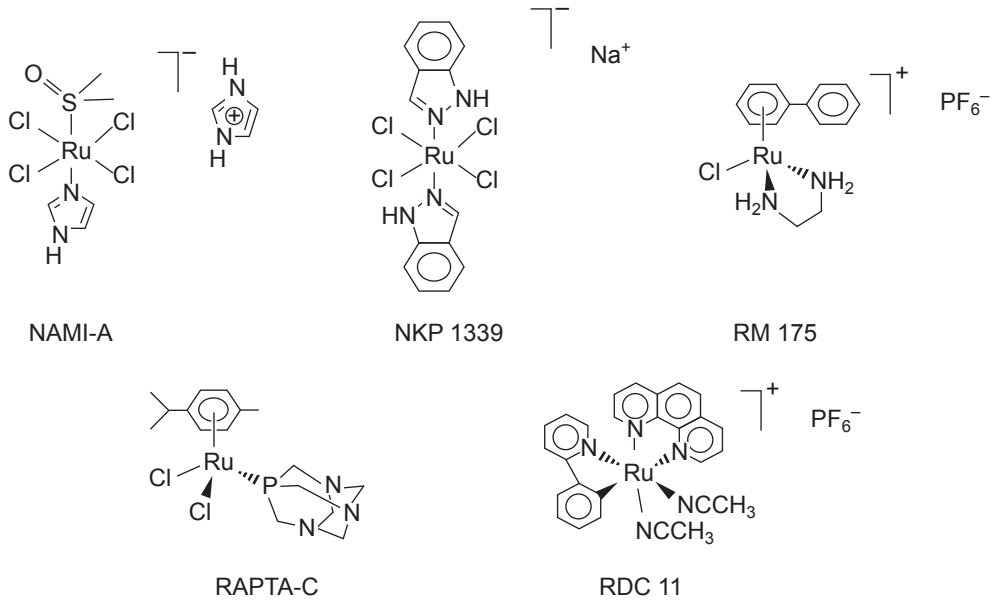

Fig. 6. Ruthenium anticancer compounds

aqueous media either before or after reduction which occurs rapidly in the presence of biological reductants such as ascorbic acid or cysteine. Studies of interaction with DNA suggested a lower and less selective reactivity than cisplatin, but still the potential to interfere with DNA replication. The complex shows significant interaction with plasma proteins albumin and transferrin which might assist its delivery to the tumour. Further research into the mechanism of action has suggested that these complexes do not act primarily by reaction with DNA but provide antimetastatic activity through influencing cell adhesion, motility and invasiveness.

These properties were sufficiently encouraging to initiate single-agent phase 1 clinical trials of NAMI-A in 1999. Twenty-four patients with a variety of tumours were treated and a maximum tolerated dose of 300 mg m^{-2} day^{-1} was determined. Clinical progress since that time has been limited, however, with further phase 1 studies devoted to drug combinations, but no target applications have been identified (35).

Over a similar period the group led by Keppler explored the activity of the related complexes [IndH][$RuCl_4(Ind)_2$] and Na[$RuCl_4(Ind)_2$] (KP1019 and NKP1339, Ind = indazole, **Figure 6**) (36). The initial pre-clinical studies were carried out with the former compound, but a phase 1 study identified the need for a more soluble compound to allow for higher doses and so the second derivative was adopted. As for NAMI-A, rapid binding to plasma proteins is thought to play an important role in tumour targeting. Efforts have been made to demonstrate whether reduction to Ru(II) occurs *in vivo*, but these have not been conclusive. Again, as for NAMI-A, there is evidence that the anticancer activity of these compounds does not arise primarily through direct DNA damage and so they should not be considered as analogues of cisplatin. KP1019 and NKP1339 are believed to induce apoptosis *via* the mitochondrial pathway (37).

Phase 1 trials with KP1019 achieved a dose of 600 mg m^{-2} day^{-1} twice weekly over three weeks. At this level there were limited side effects and the change to NKP1339 for increased solubility was required to take the dose higher. Doses up to 780 mg m^{-2} day^{-1} were administered by infusion on days 1, 8 and 15 of a 28 day cycle. Nausea was dose limiting at this level (36).

Ruthenium(II) Complexes

The ‘activation by reduction’ theory is clearly not applicable if ruthenium(II) complexes are used directly. Ruthenium(II) is the common oxidation state for a variety of organometallic complexes and, although in some cases these have very little aqueous solubility, it is in this area where groups led by Sadler and Dyson have concentrated their efforts. So-called ‘piano stool’ complexes containing arene ligands have a number of useful features for the design of suitable complexes (38). Firstly, the arene group provides the opportunity for variation in hydrophobicity and steric requirements which allow for varying levels of interaction with DNA by intercalation. Of the other three positions (the ‘legs’ of the stool) one position for a monodentate anion provides a site for substitution by biological ligands such as guanine, while the remaining two sites provide the opportunity to tune the kinetics of this substitution. Sadler chose to investigate complexes with one bidentate ligand, such as RM175 containing a neutral 1,2-diaminoethane ligand (see **Figure 6**) (39). After hydrolysis of the chloride ligand, the bidentate ligand is also influential in determining the pK_a of the aqua ligand and preventing the formation of large amounts of hydroxido-complex (as occurs in the cellular hydrolysis of cisplatin). Numerous studies of the interaction of these compounds with nucleobases, oligonucleotides and DNA, in addition to reactions with amino acids and proteins indicate a likelihood of interaction with DNA but suggest that the mechanism(s) of action of these complexes are significantly different from those of cisplatin, offering hope that they can be employed in different treatments in cancer therapy from cisplatin.

The group of Dyson studied ruthenium(II) arene complexes containing 1,3,5-triaza-7-phosphatricyclo-[3.3.1.1] decane (pta) using the acronym RAPTA for this class (40). One example, RAPTA-C, is shown in **Figure 6**. The exchange of the chlorides for a bidentate dicarboxylate ligand gives improved solubility and reduced hydrolysis, as it does in the case of the platinum drugs. Interestingly, through the synthesis of a complex containing 1,4,7-trithiacyclononane $RuCl_2$(P-pta)([9]aneS_3) Alessio was able to show that aromaticity is not required for the face-capping ligand (41, 42). Studies of the intracellular targets for these compounds have suggested that these are predominantly proteins, that they interact only weakly with DNA and that the mechanism of action may be more similar to that proposed for NAMI-A than for the platinum agents (43).

Work is continuing in these groups with the aim of modifying the basic structure to achieve greater

selectivity of action or applications to other treatment methods (44).

Another group of organometallic derivatives with only a single Ru-C linkage has been reported by Pfeffer and coworkers (45). The complex RDC11 (see **Figure 6**) contains a chelating phenylpyridine ligand. As with other ruthenium compounds there is evidence that direct interaction with DNA is less important for the action of this compound than for cisplatin and this opens the way for extending the application of metal-based drugs to additional tumours, creating new possibilities for combination therapies.

Conclusions

It is notable that each of these last investigations is being undertaken in academic groups without the sponsorship of a major pharmaceutical company. With our increasing understanding of genomics in recent years the focus for the pharmaceutical industry is moving towards identifying treatments that play a more direct role in controlling cancer development than can be provided by small molecule chemotherapy. Nevertheless, experience tells us that the opening up of new fields such as this will take longer than anticipated and time still remains for new small molecule drugs to find a place in cancer therapy.

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