Pure Appl. Chem., Vol. 83, No. 9, pp. 1709–1719, 2011.
doi:10.1351/PAC-CON-10-11-03

Increased understanding of platinum anticancer chemistry*,**

Jan Reedijk[1,2]

[1]Leiden Institute of Chemistry, Leiden University, P.O. Box 9502, 2300 RA, Leiden, The Netherlands; [2]Department of Chemistry, King Saud University, P.O. Box 2455, Riyadh 11451, Saudi Arabia

Abstract: The development of a few worldwide routinely used Pt(II) coordination compounds is described from a mechanistic point of view and related to the molecular aspects of Pt-DNA binding. Mechanistic knowledge developed from these studies is applied nowadays for the design and synthesis of new bifunctional and trifunctional compounds, aimed for use as improved anticancer drugs.

Keywords: antitumor; carboplatin; cisplatin; copper; mechanism; oxaliplatin; ruthenium.

INTRODUCTION

When Peyrone, over 165 years ago [1], described the compound nowadays known as *cis*-diamminedichloridoplatinum(II) and nicknamed "cisplatin", he in fact also reported one of the first studies discussing and recognizing isomerism in Pt coordination chemistry; however, only in his second, corrected paper [2] did he describe and accept the phenomenon of "isomers" as such in detail, as elegantly described by Kaufmann [3].

The development lasted until the mid-1960s until Rosenberg did his often reviewed experiments with *E. coli* bacteria and an electric field, using Pt electrodes in ammonium chloride as an electrolyte. These experiments started to show and recognize the medicinal power of cisplatin [4,5]. Nowadays, cisplatin and some of its derivatives are used worldwide in almost any hospital that treats cancer patients [6–8].

This short review will deal with a brief summary of this discovery and its uses, with a focus on the mechanism of action, and the strategies followed worldwide toward the design of newer derivatives with improved properties. After I wrote the first review for this journal [9], a number of other reviews have been written for a selection of journals with a varying focus, i.e., on the kinetics of ligand exchange [10,11], the hydrogen bonding [12], the competition with S-donor ligands in the cells [13], the transport in and out of the cell [14], and the DNA distortion after Pt binding [15]. The biochemical aspects have also been reviewed over the years, but largely by others [7,16–24]. I refer to those reviews for the early studies, including the discovery story [25], and after a brief introduction I will focus in this overview on recent data from us and others, mainly from 2009 and 2010, which have not yet been reviewed in detail.

From the early experiments of Rosenberg [5] it already became clear that DNA might be the major target of the drug, whereby a crucial question was the discrimination between tumor cells and healthy cells. Nowadays, it is generally accepted that cisplatin and related Pt compounds can enter many

*Paper based on a presentation made at the 11th Eurasia Conference on Chemical Sciences, The Dead Sea, Jordan, 6–10 October 2010. Other presentations are published in this issue, pp. 1643–1799.

**Dedicated to the memories of Barnett Rosenberg, 1926–2009, and Yoshinori Kidani, 1923–2010, discoverers of cisplatin and oxaliplatin, respectively.

cells, both healthy and tumor cells; however, most healthy cells and a number of tumor cells can revert the damage, and remove the Pt from the cells [14].

THE DRUGS AND THEIR INTRODUCTION IN THE CLINIC

In the memorial issue of *Cancer Research*, B. A. Chabner wrote: "It would be frightening to imagine the current status of cancer treatment without this essential drug" [26]. Indeed, since the routine introduction in the clinic at the end of the 1970s, the life-saving effects of cisplatin and newer derivatives have been impressive [7] .

Rather early in the research on cisplatin, many activities developed worldwide in a search for derivatives with improved activities or better administration. Structure–activity relationships were soon found [27], followed by many other studies later, all agreeing on the basic requirements for active Pt drugs, which can be easily summarized as: Pt(II) compounds, with two N-donor ligands in a *cis* position, with one of the donor nitrogens carrying a N–H group. So, all compounds meeting these criteria are predicted to be active against cancer cell lines. More recently, rule-breaker compounds were found, like *trans*-bis(amine)Pt compounds, monofunctional compounds, dinuclear compounds, trinuclear compounds, and Pt(IV) compounds. Nevertheless, the use in the clinic is worldwide still restricted to only 3 compounds, with a few more in China, Japan, and South Korea, representing 3 generations of Pt compounds. In the second generation, the leaving groups have changed, whereas in the third generation also the amines have changed. The amount of drug administered per patient varies from 100–200 mg/day for about 5 days in the case of cisplatin, up to a 5-times higher dose for carboplatin. The total amount of Pt, used worldwide in drugs, is estimated to be about 3000 kg with carboplatin taking about 2/3 of it [28]. A summary of a selection of the drugs in use [7,29] and their schematic development is presented in Fig. 1. The Pt(IV) compound Satraplatin and other Pt(IV) amine compounds are known to be operating after in vivo reduction [30,31].

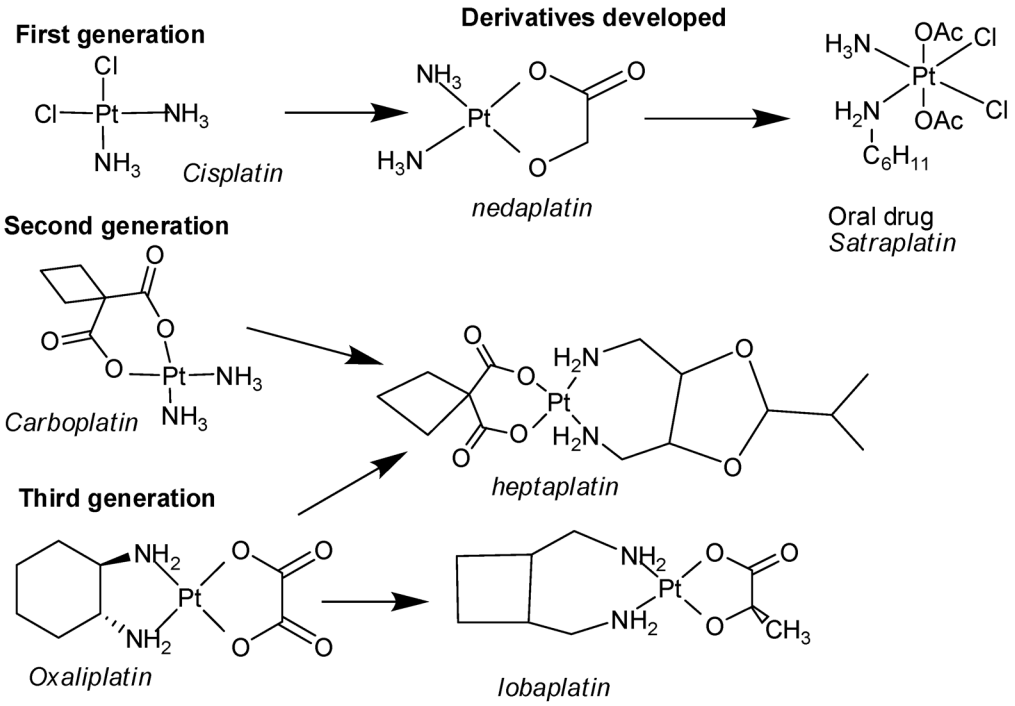

Fig. 1 Selection of drugs in current use and in advanced development or tests.

Details about the administration protocol and the use of protective agents and rescue agents have been addressed in my recent review on these aspects [14]. Despite the limited number of routinely used drugs so far, many activities in academic and industrial research laboratories are devoted to better drugs (solubility, side effect reductions, tumor targeting, avoidance of resistance, and specific tumors). Some of these attempts will be discussed later in this review.

THE MECHANISM OF ACTION AT THE MOLECULAR LEVEL

The stability and limited hydrolysis of cisplatin in blood, the cellular uptake, and the eventual binding to cellular DNA have been extensively reviewed and will not be repeated here. The recent finding of activated cell-wall transport, using the site CTR1, which is used by nature to allow Cu to enter the cell, should be mentioned, however [32,33].

After realizing that DNA was a major molecular target, in vitro studies toward competitive base binding were performed, showing a strong preference for guanines at the N7 site and chelation by two nearby guanines, such as GG and GCG, as we and others have studied quite early using simple nucleosides and oligonucleotides [34–36]. Subsequently, in vivo studies also showed the strong preference for GG [37] with, in addition, significant binding to 5'-AG (but not to 5'-GA [38]) and GCG. Even though some 70 % of the Pt was found coordinated at GG sites, irrespective of the used DNA source, it cannot be a priori concluded that this binding site is also the major lesion leading to cancer cell killing. In Fig. 2, a schematic DNA kink (bending of some 35–45º) and distortion is presented, based on several studies with NMR [12,22,39–42] and X-ray diffraction (XRD) [43,44]. For more details, the reader is referred to the original literature and reviews.

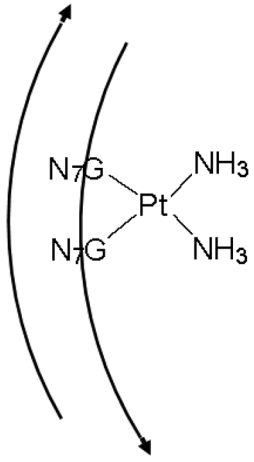

Fig. 2 Schematic representation of a kink in the DNA upon chelation of $Pt(NH_3)_2^{2+}$ to two neighboring guanine bases.

Obstacles of Pt compounds on their way to reach the DNA are numerous. To be mentioned are [14,45,46]:

a) reagents (i.e., ligands) in the blood plasma: proteins, protective agents;
b) receptors at cell wall and reagents in the cellular membrane;
c) reagents inside the cell, such as glutathione, S-donor peptides; and
d) reagents in the nuclear membrane.

In general, studies of the molecular mechanism of action of Pt antitumor compounds deal with (a) reactions with DNA (fragments) and (b) reactions with other cell (wall) components. Use can be made of advanced techniques, such as using fluorescing labels (in real time) to follow the kinetic pathways. All this information can then be applied in the design of and to make new Pt compounds, based on the mechanistic knowledge, as will be discussed below. The likely competition in cells to other ligands, like S-donors such as methionine and glutathione, apparently can be overcome, so that eventually sufficient Pt species can reach the nuclear DNA [14].

THE MECHANISM OF ACTION AT THE CELLULAR AND ORGANISM LEVEL

Knowing now significant details about the molecular aspects of the binding of Pt species to DNA, the key question can be addressed, namely, "what are the consequences on the level of tumor cells in living organisms". In a very brief, simplified summary the mechanism can be described as follows:

- Cisplatin binds at DNA on a very specific site, i.e., the N7 positions of two neighboring guanine bases.
- The resulting distortion of the DNA is relatively small (a kink; see Fig. 2); replication of platinated DNA in cells is blocked due to this kink; as replication enzymes detect the anomaly in the DNA and stop functioning.
- The distortion is not recognized in certain (tumor) cells (and DNA is NOT repaired); so these cells will die.
- In other (healthy, resistant) cells, the damage is recognized (and repaired by repair enzymes).

Indeed, it has been known for a long time that some cells are killed by cisplatin and similar compounds, while other cells survive. These are the healthy cells, and of course these cells should recover upon cisplatin treatment, and also a number of tumors that are insensitive to this treatment. Moreover, it is known that in some patients resistance is developed against cisplatin, likely due to the fact that those (few) tumor cells that are not killed by cisplatin can still grow and develop. Knowing that most, *but not all*, cells (healthy and non-healthy cells) will take up cisplatin, a first origin of resistance could be due to a reduced uptake. Other possible factors are: increased deactivation in S-donor ligand-rich cells, increased DNA repair, or decreased apoptosis. A schematic representation of cisplatin resistance has been depicted in a simplified model, as given in Fig. 3.

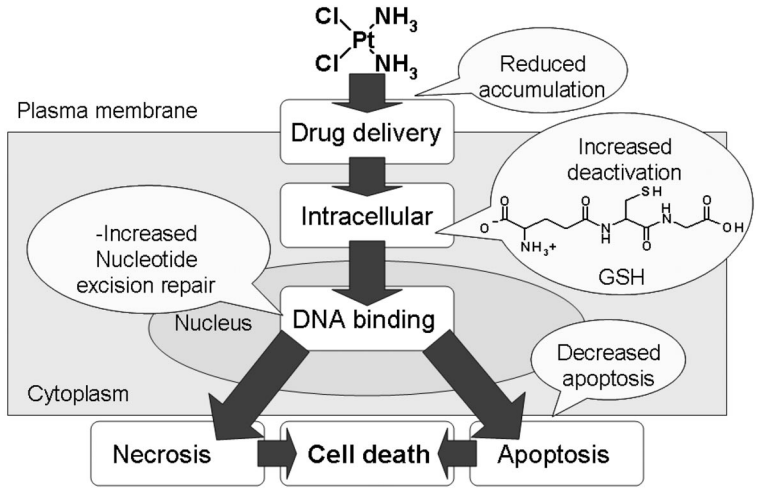

Fig. 3 Schematic picture of possible origins of resistance when cisplatin enters a cell.

After the Pt species have done the job, they must leave the body. We have shown earlier, using fluorescently labeled Pt compounds, that the Pt in the cells is likely to use the Golgi apparatus to leave the cells [47]. From earlier work it was known already that 50 % of the administered cisplatin left the body through the kidneys; the other 50 % may require some 2 months before 100 % excretion occurs though the bile [48].

DESIGN OF NEW DRUGS BASED ON MECHANISTIC KNOWLEDGE: GENERAL

Given the side effects, the resistance development, and the restricted number of sensitive tumors, a continuous interest in the development of new compounds has been ongoing since the early 1980s. Several approaches have been, and are being, followed, and only a brief summary of these can be presented here. In fact, all routes toward new drugs are based on current mechanistic knowledge. In Fig. 4, I have schematized this process.

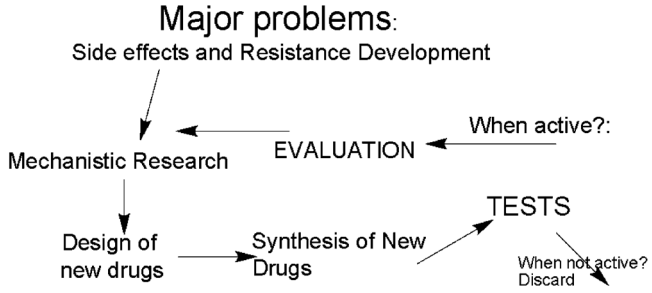

Fig. 4 Strategy in mechanistic drug design, as followed in many laboratories.

To develop drugs that can overcome resistance, of course, detailed knowledge of its mechanism is required on all possible stages, as indicated in Fig. 3. The recent work of several groups appears to be dedicated to this resistance and repair process and better understanding of the repair processes [46,49], and this might well lead to improved drugs [50] and binding at different target, like in mitochondria [51,52]. In general, the search for new metal-based anticancer drugs can be classified in the following approaches. Specific references are provided below to read more on the details; structural examples I have given before [14].

- Monofunctional guanosine-binding Pt drugs; here the renaissance of pyriplatin, *cis*-[$Pt(NH_3)_2$(pyridine)Cl]Cl should be mentioned, and its interesting recent mechanistic findings as well as dinuclear analogs [53,54]. Also, a very interesting, very recent finding where hormone is attached to deliver and activate the drug should be mentioned [55].
- Variations of cisplatin with bulky ligands, like in the picoplatin derivatives [56,57].
- Bifunctional *trans*-Pt compounds of formula *trans*-Pt(N-donor1)(N-donor2)Cl_2; several groups have been and still are active in this field [58–60].
- Prodrugs that need to be activated, usually Pt(IV) compounds that need to be reduced, like by photoactivation [61–63].
- Drugs attached on a carrier, for slow release; this appears to be an industrially highly relevant topic [64].
- Targeted drugs, in combination with controlled slow release and activation, at a specific part in the body [65–68].
- Pt compounds with a second (or even a third) functionality, like an intercalator attached, a second (or third) Pt, a link with a second, different metal (non-Pt) [54,69–71].

- Non-Pt compounds, specifically Ru coordination compounds [72–75] and organometallic Ru compounds [76–83]. The RAPTA-C Ru compound is a special case already in clinical trials [84,85]. In addition to Ru, Ir might also be promising [86], as well as other metals that have different DNA-binding modes [21] or bind at other targets.

I shall complete this review with a brief discussion of our own recent approach, namely, mixed-metal bifunctional Pt–Cu and Pt–Ru compounds, and metal compounds with an attached intercalator. Of course, I need to stress that others have recently reviewed and discussed several of these new approaches [18,67,87–89].

DESIGN OF NEW DRUGS BASED ON MECHANISTIC KNOWLEDGE: BIFUNCTIONAL DRUGS

In our recent work, the design of new metal-based anticancer drugs has been based on:

- Their expected DNA binding, i.e., at guanines or at other places, such as by intercalation.
- The control of kinetics of the reactions (in blood, cell-wall transport, and competition with other ligands).
- The control of hydrogen bonds and other supramolecular interactions (such as groove binding).

Knowing that cisplatin and similar compounds bind at two neighboring guanines, in the major groove of the DNA, causing a kink in the DNA chain, and also knowing that other reagents can bind differently to DNA, such as by intercalation, or by binding and/or reacting in the minor groove, we have recently designed and synthesized a number of such compounds and studied their anticancer activity and DNA-cutting properties.

A schematic overview of a selection of the so-obtained compounds is presented in Fig. 5. In the case of the Ru–Pt compounds [90], a 3D structure could be determined in the solid and in solution, but no significant anticancer activity was found for X = O. Compounds with X = NH are expected to also

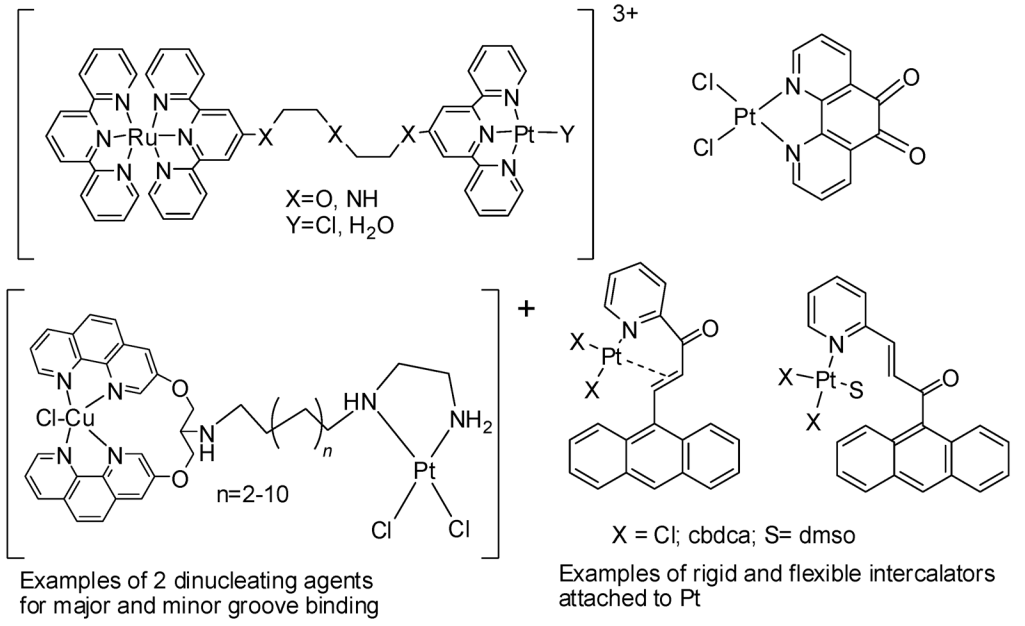

Fig. 5 Structures of some Pt compounds with another DNA-interacting group.

bind to the phosphate backbone and, therefore, are likely to be stronger bound, leading perhaps to improved anticancer activity. This approach has in fact been successfully introduced recently by Damian et al. [91] for a chimera peptide, building on a combinatorial project by Robillard [92].

In the case of the Cu–Pt compounds, surprisingly high anticancer activities and also DNA cutting, even with double-strand breaks, were found [93–95]. Regretfully, a correlation between the chain length and the activity and the DNA cutting activity was not found [94,96]. Changing to the Ru–Cu compounds, again interesting anticancer and DNA-cleavage activities were found, but these are requiring further studies [97] to obtain a quantitative view and a possible structure–activity correlation.

When Pt is used connected with either flexible or nonflexible interactions (see Fig. 5), again both active and inactive compounds have been obtained [98–100]. The compound with 5,6-phendione in addition shows highly promising antimicrobial activity and may open the road to a new class of antimicrobial compounds [98].

OUTLOOK FOR THE FIELD

In an evaluation and reviewing process of anticancer drugs, it is legitimate and relevant to ask: Do we really still need new compounds, given the currently extremely high costs of drug development and the relatively successful available drugs? My answer is wholeheartedly: Yes!

Indeed, to improve effectiveness and to develop drug targeting, and especially to find new leads to treat cisplatin-resistant or insensitive cells, design and synthesis of new drugs is expected to remain a strong field for the next few years. It appears that several of my colleagues have a quite similar opinion [14,18,57,67,87–89,101–103]. Despite the fact that some drugs, like satraplatin and picoplatin, are currently in a status of little activity, also due to financial problems [28], research activities continue, both in academia and in industry. So in the next few years one can expect exciting developments in metal-based drug design for potential use in anticancer drugs

CONCLUDING REMARKS

Much of the chemistry of Pt anticancer drugs is based on coordination chemistry, i.e., with metals attached to ligands of intermediate binding strengths. The consequence of this is that the kinetics of the M–L binding is often more important than the thermodynamic binding. Pt and Ru are so-called "slow metals", where the ligands exchange on the same time scale as cell division processes [11,14]. This might well explain their success in anticancer chemistry.

Also, another structural effect should be mentioned in a generalization of the discussion of why metals are so important in DNA reactions, be it cell division or anticancer chemistry. This deals with the role of additional H-bonding interactions, both in the kinetics of the process and in the stabilization of the adduct structure. The reason is that just 3 to 4 hydrogen bonds have about the same thermodynamic strength as a metal-coordination bond, and therefore the two contributions should always be considered together.

I should address finally another item, dealing with the environment. Organic drugs, even if they are very toxic, can usually be degraded to water, ammonia, and carbon dioxide. Inorganic (metal-containing) drugs, however, may remain a risk for much longer periods. One can, therefore, ask the question: Could ground water or surface water suffer from too much heavy metals originating from drugs? And: Is collection of "drug metals" for that reason needed in hospitals? Metal ions as such are nonbiodegradable and will always remain in the environment, even though the toxicity also depends on the ligands bound to the metal. Indeed, realizing that in a country of the size of the Netherlands, the amount of Pt administered to all patients is about 5–10 kg per year, recovery of heavy metals, from urine of Pt-treated patients, should be seriously considered!

ACKNOWLEDGMENTS

The author thankfully acknowledges his former M.Sc., Ph.D., and postdoctoral students, who have contributed to many of the results reviewed above. Their names appear in the list of references and in previous review articles. Support concerted by COST Actions D1, D8, D20 and D39 to allow short-term scientific mission of students and travel for several years, is gratefully acknowledged. Support from the Netherlands Research Organisation (NWO) and its Chemical Council (CW) is also gratefully acknowledged, most recently for the TOP grant with number 700.53.310 and the CERC3 grant 700.52.706. The author finally wishes to thank Johnson & Matthey (Reading, UK) for their generous loan schemes over the years of K_2PtCl_4 and $RuCl_3{\cdot}3H_2O$.

REFERENCES

1. M. Peyrone. *Ann. Chem. Pharm.* **51**, 1 (1844).
2. M. Peyrone. *Ann. Chem. Pharm.* **55**, 205 (1845).
3. G. B. Kauffman, R. Pentimalli, S. Doldi, M. D. Hall. *Plat. Metals Rev.* **54**, 250 (2010).
4. B. Rosenberg, L. Van Camp, T. Krigas. *Nature* **205**, 698 (1965).
5. B. Rosenberg, L. Van Camp, J. E. Trosko, V. H. Mansour. *Nature* **222**, 385 (1969).
6. B. Lippert. *Cisplatin, Chemistry and Biochemistry of a Leading Anticancer Drug*, Wiley-VCH, Weinheim (1999).
7. L. R. Kelland. *Nat. Rev. Cancer* **7**, 573 (2007).
8. D. Wang, S. J. Lippard. *Nat. Rev. Drug Discov.* **4**, 307 (2005).
9. J. Reedijk. *Pure Appl. Chem.* **59**, 181 (1987).
10. J. Reedijk. *Proc. Natl. Acad. Sc. USA* **100**, 3611 (2003).
11. J. Reedijk. *Plat. Metals Rev.* **52**, 2 (2008).
12. J. Reedijk. *Inorg. Chim. Acta* **198–200**, 873 (1992).
13. J. Reedijk. *Chem. Rev.* **99**, 2499 (1999).
14. J. Reedijk. *Eur. J. Inorg. Chem.* 1303 (2009).
15. J. Reedijk. *Chem. Commun.* 801 (1996).
16. F. Arnesano, G. Natile. *Coord. Chem. Rev.* **253**, 2070 (2009).
17. V. Brabec. In *Progress in Nucleic Acid Research and Molecular Biology*, Vol. 71, pp. 1–68, Elsevier (2002).
18. P. C. A. Bruijnincx, P. J. Sadler. *Curr. Opin. Chem. Biol.* **12**, 197 (2008).
19. P. C. A. Bruijnincx, P. J. Sadler. In *Advances in Inorganic Chemistry, Vol 61: Metal Ion Controlled Reactivity*, pp. 1–62, Elsevier Academic Press, San Diego (2009).
20. T. W. Hambley. *Coord. Chem. Rev.* **166**, 181 (1997).
21. M. A. Jakupec, M. Galanski, V. B. Arion, C. G. Hartinger, B. K. Keppler. *Dalton Trans.* 183 (2008).
22. E. R. Jamieson, S. J. Lippard. *Chem. Rev.* **99**, 2467 (1999).
23. Y. W. Jung, S. J. Lippard. *Chem. Rev.* **107**, 1387 (2007).
24. E. Wong, C. M. Giandomenico. *Chem. Rev.* **99**, 2451 (1999).
25. R. A. Alderden, M. D. Hall, T. W. Hambley. *J. Chem. Educ.* **83**, 728 (2006).
26. B. A. Chabner. *Cancer Res.* **70**, 428 (2010).
27. M. J. Cleare, J. D. Hoeschele. *Bioinorg. Chem.* **2**, 187 (1973).
28. E. M. Thayer. *C&EN News*, issue 26, June 28, **88**, 24 (2010).
29. N. J. Wheate, S. Walker, G. E. Craig, R. Oun. *Dalton Trans.* **39**, 8113 (2010).
30. S. H. Choi, R. B. Cooley, A. S. Hakemian, Y. C. Larrabee, R. C. Bunt, S. D. Maupas, J. G. Muller, C. J. Burrows. *J. Am. Chem. Soc.* **126**, 591 (2004).

31. M. D. Hall, R. C. Dolman, T. W. Hambley. In *Metal Ions in Biolgical Systems, Vol 42: Metal Complexes in Tumor Diagnosis and as Anticancer Agents*, pp. 297–322, Marcel Dekker, New York (2004).
32. R. Safaei, S. B. Howell. *Crit. Rev. Oncol./Hematol.* **53**, 13 (2005).
33. F. Arnesano, S. Scintilla, G. Natile. *Angew. Chem., Int. Ed.* **46**, 9062 (2007).
34. J. H. J. den Hartog, C. Altona, J. C. Chottard, J. P. Girault, J. Y. Lallemand, F. A. A. M. de Leeuw, A. T. M. Marcelis, J. Reedijk. *Nucleic Acids Res.* **10**, 4715 (1982).
35. A. T. M. Marcelis, J. H. J. Denhartog, J. Reedijk. *J. Am. Chem. Soc.* **104**, 2664 (1982).
36. A. T. M. Marcelis, C. Erkelens, J. Reedijk. *Inorg. Chim. Acta* **91**, 129 (1984).
37. A. M. J. Fichtinger-Schepman, J. L. van der Veer, J. H. J. den Hartog, P. H. M. Lohman, J. Reedijk. *Biochemistry* **24**, 707 (1985).
38. B. Van Hemelryck, J. P. Girault, G. Chottard, P. Valadon, A. Laoui, J. C. Chottard. *Inorg. Chem.* **26**, 787 (1987).
39. D. Yang, S. S. G. E. van Boom, J. Reedijk, J. H. van Boom, A. H.-J. Wang. *Biochemistry* **34**, 12912 (1995).
40. F. Reeder, Z. J. Guo, P. D. Murdoch, A. Corazza, T. W. Hambley, S. J. Berners-Price, J. C. Chottard, P. J. Sadler. *Eur. J. Biochem.* **249**, 370 (1997).
41. S. U. Dunham, C. J. Turner, S. J. Lippard. *J. Am. Chem. Soc.* **120**, 5395 (1998).
42. J. M. Teuben, C. Bauer, A. H.-J. Wang, J. Reedijk. *Biochemistry* **38**, 12305 (1999).
43. B. Spingler, D. A. Whittington, S. J. Lippard. *Inorg. Chem.* **40**, 5596 (2001).
44. P. M. Takahara, C. A. Frederick, S. J. Lippard. *J. Am. Chem. Soc.* **118**, 12309 (1996).
45. A. R. Timerbaev, C. G. Hartinger, S. S. Aleksenko, B. K. Keppler. *Chem. Rev.* **106**, 2224 (2006).
46. S. Ahmad. *Chem. Biodivers.* **7**, 543 (2010).
47. C. Molenaar, J.-M. Teuben, R. J. Heetebrij, H. J. Tanke, J. Reedijk. *J. Biol. Inorg. Chem.* **5**, 655 (2000).
48. L. R. Kelland, S. Y. Sharp, C. F. O'Neill, F. I. Raynaud, P. J. Beale, I. R. Judson. *J. Inorg. Biochem.* **77**, 111 (1999).
49. L. Martelli, E. Ragazzi, F. Di Mario, M. Basato, M. Martelli. *Anticancer Res.* **29**, 3931 (2009).
50. G. Y. Zhu, P. Chang, S. J. Lippard. *Biochemistry* **49**, 6177 (2010).
51. L. A. Onambele, D. Koth, J. A. Czaplewska, U. S. Schubert, H. Görls, S. Yano, M. Obata, M. Gottschaldt, R. Prokop. *Chem.—Eur. J.* (2010). In press.
52. S. B. Prasad, G. Rosangkima, A. Kharbangar. *Mitochondrion* **10**, 38 (2010).
53. D. Wang, G. Y. Zhu, X. H. Huang, S. J. Lippard. *Proc. Natl. Acad. Sci. USA* **107**, 9584 (2010).
54. L. Gatti, P. Perego, R. Leone, P. Apostoli, N. Carenini, E. Corna, C. Allievi, U. Bastrup, S. De Munari, S. Di Giovine, P. Nicoli, M. Grugni, M. Natangelo, G. Pardi, G. Pezzoni, J. W. Singer, F. Zunino. *Mol. Pharm.* **7**, 207 (2010).
55. C. Sanchez-Cano, M. Huxley, C. Ducani, A. E. Hamad, M. J. Browning, C. Navarro-Ranninger, A. G. Quiroga, A. Rodger, M. J. Hannon. *Dalton Trans.* **39**, 11365 (2010).
56. A. C. G. Hotze, Y. Chen, T. W. Hambley, S. Parsons, N. A. Kratochwil, J. A. Parkinson, V. P. Munk, P. J. Sadler. *Eur. J. Inorg. Chem.* 1035 (2002).
57. P. J. S. Miguel, M. Roitzsch, L. Yin, P. M. Lax, L. Holland, O. Krizanovic, M. Lutterbeck, M. Schurmann, E. C. Fusch, B. Lippert. *Dalton Trans.* 10774 (2009).
58. S. M. Aris, N. P. Farrell. *Eur. J. Inorg. Chem.* 1293 (2009).
59. C. Li, Z. Y. Li, E. Sletten, F. Arnesano, M. Losacco, G. Natile, Y. Z. Liu. *Angew. Chem., Int. Ed.* **48**, 8497 (2009).
60. U. Kalinowska-Lis, J. Ochocki, K. Matlawska-Wasowska. *Coord. Chem. Rev.* **252**, 1328 (2008).
61. L. Cubo, A. M. Pizarro, A. G. Quiroga, L. Salassa, C. Navarro-Ranninger, P. J. Sadler. *J. Inorg. Biochem.* **104**, 909 (2010).
62. N. J. Farrer, J. A. Woods, V. P. Munk, F. S. Mackay, P. J. Sadler. *Chem. Res. Toxicol.* **23**, 413 (2010).

63. F. S. Mackay, J. A. Woods, P. Heringova, J. Kasparkova, A. M. Pizarro, S. A. Moggach, S. Parsons, V. Brabec, P. J. Sadler. *Proc. Natl. Acad. Sci. USA* **104**, 20743 (2007).
64. E. Gabano, M. Ravera, D. Osella. *Curr. Med. Chem.* **16**, 4544 (2009).
65. J. R. Rice, J. L. Gerberich, D. P. Nowotnik, S. B. Howell. *Clin. Cancer Res.* **12**, 2248 (2006).
66. S. van Zutphen, J. Reedijk. *Coord. Chem. Rev.* **249**, 2845 (2005).
67. K. S. Lovejoy, S. J. Lippard. *Dalton Trans.* 10651 (2009).
68. N. Margiotta, N. Denora, R. Ostuni, V. Laquintana, A. Anderson, S. W. Johnson, G. Trapani, G. Natile. *J. Med. Chem.* **53**, 5144 (2010).
69. E. I. Montero, J. Y. Zhang, J. J. Moniodis, S. J. Berners-Price, N. P. Farrell. *Chem.—Eur. J.* **16**, 9175 (2010).
70. J. B. Mangrum, N. P. Farrell. *Chem. Commun.* **46**, 6640 (2010).
71. Y. Qu, M. C. Tran, N. P. Farrell. *J. Biol. Inorg. Chem.* **14**, 969 (2009).
72. T. Gianferrara, A. Bergamo, I. Bratsos, B. Milani, C. Spagnul, G. Sava, E. Alessio. *J. Med. Chem.* **53**, 4678 (2010).
73. T. Gianferrara, I. Bratsos, E. Iengo, B. Milani, A. Ostric, C. Spagnul, E. Zangrando, E. Alessio. *Dalton Trans.* 10742 (2009).
74. T. Gianferrara, I. Bratsos, E. Alessio. *Dalton Trans.* 7588 (2009).
75. I. Bratsos, S. Jedner, T. Gianferra, E. Alessio. *Chimia* **61**, 692 (2007).
76. A. D. Phillips, O. Zava, R. Scopelitti, A. A. Nazarov, P. J. Dyson. *Organometallics* **29**, 417 (2010).
77. A. Casini, C. G. Hartinger, A. A. Nazaroy, P. J. Dyson. In *Medicinal Organometallic Chemistry*, Vol. 32, pp. 57–80, Springer-Verlag, Berlin (2010).
78. P. Govender, N. C. Antonels, J. Mattsson, A. K. Renfrew, P. J. Dyson, J. R. Moss, B. Therrien, G. S. Smith. *J. Organomet. Chem.* **694**, 3470 (2009).
79. P. J. Dyson, G. Sava. *Dalton Trans.* 1929 (2006).
80. T. Ruiu, C. Garino, L. Salassa, A. M. Pizarro, C. Nervi, R. Gobetto, P. J. Sadler. *Eur. J. Inorg. Chem.* 1186 (2010).
81. H. K. Liu, J. A. Parkinson, J. Bella, F. Y. Wang, P. J. Sadler. *Chem. Sci.* **1**, 258 (2010).
82. L. Salassa, C. Garino, G. Salassa, C. Nervi, R. Gobetto, C. Lamberti, D. Gianolio, R. Bizzarri, P. J. Sadler. *Inorg. Chem.* **48**, 1469 (2009).
83. I. Bratsos, S. Jedner, A. Bergamo, G. Sava, T. Gianferra, E. Zangrando, E. Alessio. *J. Inorg. Biochem.* **102**, 1120 (2008).
84. A. Ratanaphan, P. Temboot, P. J. Dyson. *Chem. Biodivers.* **7**, 1290 (2010).
85. G. Suss-Fink. *Dalton Trans.* **39**, 1673 (2010).
86. A. M. Pizarro, P. J. Sadler. *Biochimie* **91**, 1198 (2009).
87. S. H. van Rijt, P. J. Sadler. *Drug Discov. Today* **14**, 1089 (2009).
88. C. G. Hartinger, P. J. Dyson. *Chem. Soc. Rev.* **38**, 391 (2009).
89. B. W. Harper, A. M. Krause-Heuer, M. P. Grant, M. Manohar, K. B. Garbutcheon-Singh, J. R. Aldrich-Wright. *Chem.—Eur. J.* **16**, 7064 (2010).
90. K. van der Schilden, F. Garcia, H. Kooijman, A. L. Spek, J. G. Haasnoot, J. Reedijk. *Angew. Chem., Int. Ed.* **43**, 5668 (2004).
91. M. S. Damian, H. K. Hedman, S. K. C. Elmroth, U. Diederichsen. *Eur. J. Org. Chem.* 6161 (2010).
92. M. S. Robillard, A. P. M. Valentijn, N. J. Meeuwenoord, G. A. van der Marel, J. H. van Boom, J. Reedijk. *Angew. Chem., Int. Ed.* **39**, 3096 (2000).
93. S. Özalp-Yaman, P. de Hoog, G. Amadei, M. Pitie, P. Gamez, J. Dewelle, T. Mijatovic, B. Meunier, R. Kiss, J. Reedijk. *Chem.—Eur. J.* **14**, 3418 (2008).
94. P. de Hoog, M. Pitié, G. Amadei, P. Gamez, B. Meunier, R. Kiss, J. Reedijk. *J. Biol. Inorg. Chem.* **13**, 575 (2008).

95. P. de Hoog, C. Boldron, P. Gamez, K. Sliedregt-Bol, I. Roland, M. Pitié, R. Kiss, B. Meunier, J. Reedijk. *J. Med. Chem.* **50**, 3148 (2007).
96. P. de Hoog, M. J. Louwerse, P. Gamez, M. Pitié, E. J. Baerends, B. Meunier, J. Reedijk. *Eur. J. Inorg. Chem.* 612 (2008).
97. S. van der Steen, P. de Hoog, K. van der Schilden, P. Gamez, M. Pitie, R. Kiss, J. Reedijk. *Chem. Commun.* **46**, 3568 (2010).
98. S. Roy, K. D. Hagen, P. U. Maheswari, M. Lutz, A. L. Spek, J. Reedijk, G. P. van Wezel. *ChemMedChem* **3**, 14274 (2008).
99. P. Marques-Gallego, G. V. Kalayda, U. Jaehde, H. den Dulk, J. Brouwer, J. Reedijk. *J. Inorg. Biochem.* **103**, 791 (2009).
100. P. Marques-Gallego, M. A. Gamiz-Gonzalez, F. R. Fortea-Perez, M. Lutz, A. L. Spek, A. Pevec, B. Kozlevcar, J. Reedijk. *Dalton Trans.* **39**, 5152 (2010).
101. R. C. Todd, S. J. Lippard. *Metallomics* **1**, 280 (2009).
102. J. Mattson, P. Govindaswamy, A. K. Renfrew, P. J. Dyson, P. Stepnicka, G. Suss-Fink, B. Therrien. *Organometallics* **28**, 4350 (2009).
103. A. M. Montana, C. Batalla. *Curr. Med. Chem.* **16**, 2235 (2009).

