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Anticancer Activity of Metal Complexes: Involvement of Redox Processes

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Abstract

Cells require tight regulation of the intracellular redox balance and consequently of reactive oxygen species for proper redox signaling and maintenance of metal (e.g., of iron and copper) homeostasis. In several diseases, including cancer, this balance is disturbed. Therefore, anticancer drugs targeting the redox systems, for example, glutathione and thioredoxin, have entered focus of interest. Anticancer metal complexes (platinum, gold, arsenic, ruthenium, rhodium, copper, vanadium, cobalt, manganese, gadolinium, and molybdenum) have been shown to strongly interact with or even disturb cellular redox homeostasis. In this context, especially the hypothesis of “activation by reduction” as well as the “hard and soft acids and bases” theory with respect to coordination of metal ions to cellular ligands represent important concepts to understand the molecular modes of action of anticancer metal drugs. The aim of this review is to highlight specific interactions of metal-based anticancer drugs with the cellular redox homeostasis and to explain this behavior by considering chemical properties of the respective anticancer metal complexes currently either in (pre)clinical development or in daily clinical routine in oncology.

I. Introduction

Since ancient times, metal compounds have been successfully used for the treatment of a variety of diseases. Already the ancient Egyptians knew about the therapeutic potential of gold salts (272). In traditional Chinese medicine, arsenic drugs, like arsenic trioxide (ATO), were used as antiseptic agents or in the treatment of rheumatoid diseases, syphilis, and psoriasis (93, 370). Indeed, ATO was one of the first compounds that was suggested for anticancer therapy, and during the 18th and 19th century ATO represented the main treatment for leukemia. The modern era of metal-based anticancer drugs began with the discovery of the platinum(II) complex cisplatin by Barnett Rosenberg in the 1960s (323). Nowadays, cisplatin and its successors carboplatin and oxaliplatin are among the most important chemotherapeutics used against a wide variety of different cancers (189, 323). Stimulated by the success of cisplatin, also other coordination compounds based on ruthenium, gold, titanium, copper, rhodium, vanadium, and cobalt were tested for their

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anticancer activity and several promising candidates are currently in (pre)clinical evaluation (79, 100, 106, 149, 188, 202, 203, 285, 343).

One of the characteristics of metals is their potential to undergo redox processes, as determined by their redox potentials. Especially, transition metal ions are usually able to switch between several oxidation states. However, not all oxidation states are observed under physiological conditions in the living organism. Due to the redox activity of metals and, therefore, a possible disturbance of the sensitive cellular redox homeostasis, a tight regulation of the metal and redox balance is crucial for health and survival (15, 17, 19, 127, 134, 158).

Cancer cells are known to differ distinctly in their redox metabolism from healthy tissues (134, 381). Thus, enhanced levels of intracellular reactive oxygen species (ROS) are often observed in tumor cells and the specific milieu of the solid tumor is characterized by high metabolic activity, hypoxia, and, in general, reductive conditions. Consequently, interference with the cellular redox homeostasis of cancer cells seems an attractive and promising approach for cancer therapy (a general overview on the role of ROS in the activity of metal anticancer drugs is summarized in Fig. 1). Indeed, many of the currently used chemotherapeutic drugs have been shown to exert some interaction with the cellular redox balance and there are several attempts to specifically target the altered redox conditions in cancer cells (9, 74, 77, 134, 138, 149). Due to their redox properties, especially metal compounds often directly interact with and disturb the cellular redox homeostasis. This review aims to evaluate and summarize the current knowledge on the role of redox processes in the modes of action of metal compounds used in anticancer therapy or being in (pre)clinical development.

II. Redox Processes in Living Organisms

A. Mammalian redox metabolism

To understand the intracellular behavior of redox-(inter) active anticancer metal compounds, it is useful to consider the mechanisms responsible for the physiological cellular redox balance. Generation of ROS in general is a normal physiological process with several important functions for the living organism in metabolism, signal transduction, regulation of cellular functions, as well as in host defense (388). The most important ROS with physiological relevance are superoxide ($O_2^{\bullet\,-}$), hydrogen peroxide (H_2O_2), as well as the hydroxyl radical ($OH^{\bullet}$) (detailed characteristics are given in Table 1). These species have been shown to be directly involved in the regulation of diverse signal transduction pathways important for cell proliferation, differentiation, and cell death (127, 388).

The redox environment within a cell strongly differs in diverse intracellular compartments (127). The most redox-active parts of the cell are the mitochondria, which consequently are also the major intracellular generators of ROS (221). In contrast, the cytoplasm is characterized by low levels of ROS and a less redox-active milieu. Thus, it might be hypothesized that the cytoplasm on the one hand functions as redox buffer zone between the cellular organelles and on the other hand allows specific ROS signaling (127). The high reactivity of ROS makes their tight regulation necessary for cell survival. This is also indicated by the wide range of redox-associated diseases, which include, besides diverse neurodegenerative disorders such as Alzheimer’s and Parkinson’s diseases, also several types of cancer (134). Consequently, the living organism constantly maintains a complex oxidant–antioxidant homeostasis system with diverse ROS generating and degrading systems in different compartments of the cell. There are several regulatory levels for maintenance of redox balance in the cell involving enzymatic (such as superoxide dismutases, catalase, thioredoxin reductases [TrxR], glutathione reductases [GR], and glutathione peroxidases [GPx]) as well as nonenzymatic antioxidants (such as glutathione [GSH], thioredoxin [Trx], and several vitamins) (Fig. 2).

Superoxide dismutases (SOD) catalyze the dismutation of $O_2^{\bullet -}$ to O_2 and to the less reactive but very diffusible H_2O_2. In humans, there are three kinds of SOD: the cytosolic Cu/Zn-SOD, the mitochondrial Mn-SOD, and the extracellular SOD (again containing a Cu/Zn core) (248). Although these forms of SOD exert similar functions, they distinctly differ —besides their metal centers—also in chromosomal localization, genomic sequence, and protein structure. Basically, the Mn-SOD does not share any substantial homology with the Cu/Zn-SODs. Nevertheless, regulatory elements for several redox-responsive transcription factors, including Nrf2, NF-κB, AP-1, AP-2, and Sp1, have been described in the promoter regions of most if not all SOD genes (248).

The peroxisome-located catalase very effectively promotes the conversion of H_2O_2 to H_2O and O_2. Notably, this enzyme has one of the highest turn over rates known, as one protein is able to convert ~6 million molecules H_2O_2 per minute.

GPx is the general name for a family of multiple isozymes. So far, five GPx have been identified in humans (all containing selenium) that catalyze the reduction of H_2O_2 or organic hydroperoxides to water (or corresponding alcohols) using reduced GSH as an electron donor (48).

With regard to nonenzymatic antioxidants ascorbate (the monodeprotonated form of ascorbic acid), GSH, and Trx seem to be the most important molecules inside cells (Fig. 3). Especially in case of ascorbate and GSH, intracellular levels in the millimolar range have been reported (22, 81). However, in contrast to GSH which is produced by the human body, ascorbate is an essential nutrient, which has to be ingested *via* food. Ascorbate is a very good reducing agent (50). Consequently, oxidizing free radicals, including $OH^{\bullet}$, $RO^{\bullet}$, $ROO^{\bullet}$, or $GS^{\bullet}$, have higher reduction potentials and can be scavenged by ascorbate. Such, potentially very damaging radicals are replaced by the less reactive ascorbate radical (50), which is also the reason why ascorbate is termed as “antioxidant.” However, ascorbate also reduces several redox-active metals such as iron and especially copper (50, 222, 234), thereby inducing redox cycling and ROS generation of these metals *via* Fenton chemistry (compare Section II.*C*.). Nevertheless, as most transition metals exist in inactive, protein-bound form *in vivo* (Compare Section III.), the relevance of reaction with ascorbate under normal physiological conditions has been questioned. Moreover, it is widely unexplored whether the intracellular ascorbate levels impact the anticancer therapy with metal compounds in the *in vivo* situation.

Besides its direct radical scavenging properties, ascorbic acid serves as crucial cofactor in several enzymatic reactions, including various hydroxylation reactions (234). Consequently, ascorbate was found to be essential for the biosynthesis of collagen as well as L-carnitine, and the conversion of dopamine to norepinephrine (217, 316).

The second important low-molecular-weight antioxidant inside the cell is the tripeptide GSH (113, 388). GSH is synthesized in the cytosol in a two-step process catalyzed by the glutamate cysteine synthetase followed by GSH ligase. Its degradation occurs exclusively in the extracellular space (22). Similar to ascorbate, GSH is highly abundant in most intra-cellular compartments with concentrations in the mM range, whereas in blood plasma only μM concentrations were detected (22). Notably, GSH is not only used in several processes directly involved in the cellular redox balance but has also diverse additional functions. Thus, GSH was found to play an important role in cell death regulation and depletion of GSH seems to be crucial for the execution of apoptosis (115). Moreover, GSH contains several potential coordination sites for diverse metal ions, including arsenic, copper, zinc, as well as cadmium. Elevated cellular GSH levels have been frequently associated with resistance of cells to metal compounds treatment (155). Additionally, GSH is an essential component of the phase II detoxification system, where it conjugates or is conjugated by glutathione-*S*-transferases (GSTs) to diverse endo- and xenobiotics to enhance their hydrophilicity and to facilitate their elimination. In general, GSH-conjugates are excellent substrates for diverse ATP-driven efflux pumps (especially of the multi-drug resistance [MRP, ABCC] protein family) (22), which are responsible for the final extrusion of GSH-metabolites out of the cell. For most metal-containing compounds interaction with GSH has been described, but with different results. For example enhanced GSH pools are associated with detoxification of and resistance to Pt^{II} or As^{III} drugs (155). In contrast, there are several metal compounds such as Pt^{IV},Co^{III}, and Ru^{III} where GSH-mediated reduction is believed to be crucial for activation of their anticancer potential.

With respect to its role in redox balance, GSH has several functions (388): (i) scavenging of hydroxyl and superoxide radicals, (ii) cofactor for several detoxifying enzyme reactions (concerning, e.g., GPx, peroxiredoxins, and glutaredoxins), and (iii) involvement in the regeneration of other important antioxidants such as vitamins C and E. In course of these reactions, two GSH molecules are oxidized to GSSG, which then accumulates inside the cell (388). As GSSG is able to react with protein thiol groups forming protein adducts, cells physiologically contain high levels of GR, which maintains most of the GSH in its reduced form.

In addition to GSH and ascorbate, the Trx system represents the third major antioxidant defense system in human cells (37). Trx are small polypeptides with a size of 12 kDa harboring in close vicinity two cysteine residues in the active sites. In the transfer of electrons to respective substrates (e.g., proteins containing a so-called Trx fold), Trx undergo reversible oxidation of the two cysteine residues by formation of disulfide bonds leading to the oxidized Trx-S_2. The reduction back to the dithiol form [Trx-(SH_2)] is catalyzed by the selenium-containing TrxR and for this reaction NADPH serves as electron donor (15):

$$\mathrm{Trx}-\mathrm{S}_2+\mathrm{NADPH}+\mathrm{H}^+ \xrightarrow{\mathrm{TrxR}} \mathrm{Trx}-(\mathrm{SH})_2+\mathrm{NADP}^+ \quad 1$$

$$\mathrm{Trx}-(\mathrm{SH})_2+\mathrm{Protein}-\mathrm{S}_2 \rightleftharpoons \mathrm{Trx}-\mathrm{S}_2+\mathrm{Protein}-(\mathrm{SH})_2 \quad 2$$

In humans, three different TrxR isoenzymes have been identified. Besides the cytoplasmic Trx1 and TrxR1 couple, mitochondria harbor a separate Trx mechanism executed by Trx2 and TrxR2. A third system was predominantly found in the testis (TrxR3). This reductase is capable of reducing GSH in addition to Trx and was consequently termed thioredoxin glutathione reductase (TGR).

Interestingly, knock-out mice for all Trx/TrxR genes are lethal during embryogenesis (240, 275), indicating the widespread and essential regulatory functions of the Trx/TrxR system in mammalian cells and tissues. Comparable to GSH, in addition to mere protection against oxidative stress, this cellular redox system regulates several other biological processes. Such Trx, together with the glutaredoxin system, is delivering electrons for the substrate turn-over cycle of the ribonucleotide reductase (compare Section III.*A*.2.). Additionally, the Trx system has been shown (in analogy to the GSH system) to protect cells from apoptosis induction (37). Several antioxidant defense systems are directly affected by and/or depending on reduction by Trx/TrxR: (i) Peroxiredoxins are a family of thiol-containing peroxidases that are oxidized by peroxides and reduced back to the reactive state by Trx.

Peroxiredoxins are very abundant (up to 1% of soluble proteins) in the cytoplasm and diverse cell organelles and are key players in resistance against oxidative stress and regulation of H_2O_2-mediated signal cascades (82, 269, 270). (ii) Also, the antioxidant heme oxygenase-1 (HO-1), which catalyzes the conversion of the pro-oxidant molecule heme into the products biliverdin, iron ions, and CO, is regulated by the Trx/TrxR system. HO-1 is expressed ubiquitously in many cell types, and transcription is activated by numerous prooxidant molecules like heme, metal ions, proinflammatory cytokines, and ROS (287). Cell-type dependently both a positive and negative effect of TrxR activity on HO-1 expression was reported (102, 259, 383). (iii) Trx is also involved in the reduction of methionine sulfoxide formed during radical scavenging by oxidation of methionine residues of proteins (226). The reduction of methionine sulfoxide by Trx allows repeated scavenging of potentially damaging oxygen and nitrogen species (403). (iv) Additionally, to these important protein regulators of oxidative stress, diverse low-molecular-weight antioxidant systems, including ascorbate and flavonoids are regulated by the Trx/TrxR system (378).

Notably, both GSH as well as Trx1 are important in the redox-dependent regulation of several proteins, including important transcription factors as well as receptor and sensor proteins. There is, for example, increasing evidence for redox-sensing switches in protein structure based on two so-called critical cysteine residues (263). Oxidizing conditions induce the formation of a disulfide bond between these cysteine residues resulting in a conformational change of the protein structure. Subsequently, these alterations in the secondary protein structure lead to changed protein function. As an example, the DNA binding of redox-sensitive transcription factors AP-1, NF-κB, Nrf2, and p53 is only possible under reducing conditions when the critical cysteines are free (127). In general, cleavage of the disulfide bond is mainly performed by cellular reductants including Trx1/2 and GSH (263). Another mechanism of redox-dependent protein modifications is based on *S*-glutathionylation (88, 249). In the cell notable amounts of GSH are reversibly bound to −SH groups of diverse cysteinyl residues generating *S*-glutathionylated proteins. Interstingly, GSTs have been recently shown to catalyze the forward reaction of *S*-glutathionylation extending the protective role of this enzyme family toward drugs that are not substrates for phase II detoxification (380). This results in altered protein conformation and consequently —depending on the targeted protein—either in activation or inactivation. In mammalians a large panel of proteins targeted by *S*-glutathionylation has been identified by redox proteomics (88). This list includes diverse protein classes/families such as several mitochondrial and glycolytic enzymes, heat shock proteins, as well as many transcription factors (88).

When generally considering the interaction of metals with the cellular redox homeostasis, it has to be kept in mind that the cell harbors an extended and very complex arsenal of control mechanisms to ensure tight regulation of its redox balance. Consequently, it is not surprising that also the impact of anticancer metal compounds upon the cellular redox balance will be complex and not always easy to predict.

B. Cellular response to oxidative stress and resistance to metal compounds

Disturbance of the oxidant–antioxidant balance favoring oxidizing environment is called oxidative stress. Elevated levels of oxidative stress are known to induce cell damage and cell death by interference with multiple important cellular molecules. ROS can be produced by extracellular stress, such as irradiation, air pollutants, and exposure to toxic agents. Additionally, some intracellular metabolic and/or signaling pathways generate ROS as byproducts of oxygen-dependent enzymatic reactions. Examples for these processes are the mitochondrial respiratory chain, glucose oxidation, the cytochrome P450 family, and protein folding in the endoplasmic reticulum (ER). Most important ROS-induced damages include (i) DNA single-strand breaks, (ii) disruption of the mitochondrial inner membrane causing mitochondrial dys-function, (iii) lipid peroxidation leading to disturbed cell membranes, and (iv) oxidation of cysteine residues to sulfenic (SOH), sulfinic (SO_2H), or sulfonic acid (SO_3H) resulting in changes in the secondary protein structure (388) (Fig. 1). However, these oxidative stress-induced damages do not necessarily always result in cell death, but the induced DNA damage can also lead to genomic instability and hence tumor initiation and/or progression (134). Moreover, low levels of oxidative stress were shown to promote cell proliferation and induce diverse protection and survival pathways.

Surviving oxidative stress is only possible by activation of a coordinated effort to get rid of the stressors and to avoid destructive damages (Fig. 2). Consequently, transcription factors are central to oxidative stress response allowing simultaneous activation of an array of diverse genes involved in metabolism, detoxification, export of xenobiotics, as well as in the repair of the induced cellular damages. As anticancer metal drugs are redox-active substances interfering with the cellular redox status and supporting ROS generation by different mechanism, such protective response mechanisms are almost generally activated as a consequence of cell exposure. While in the nonmalignant tissues these responses are important for reducing unwanted adverse effects, they might counteract the cancer cell-damaging effect of drugs such causing therapy failure (155).

Within the respective transcription factors several are known for their redox-sensitive regulation often based on critical cysteins (compare Section II.*A.*) and the presence of antioxidant responsive elements in the promoter regions. This list includes AP-1, NF-*κ*B, p53, and Nrf2. The AP-1 transcription factor is important in regulating genes involved in cell cycle progression, inflammation, and apoptosis. With regard to its protein structure, AP-1 exists either in the form of homo- or heterodimers consisting of Jun (c-Jun, Jun B, and Jun D) and Fos (c-Fos, FosB, Fra-1, and Fra-2) family members, which interact *via* their basic leucine-zipper domains (249, 262). Oxidative stress is known to activate the MAP kinase pathway, which in turn leads to increased transcription of c-fos and c-jun (127, 249). However, AP-1 is also negatively regulated by oxidative conditions. The critical cystein residues essential for the inhibition of AP-1-mediated transcription are found in the DNA-binding domain (Cys269) as well as close to the leucine-zipper domain (Cys320) (262). It is believed that upon changes in the GSH/GSSG ratio, *S*-glutathionylation of the Cys269 residue occurs, which sterically blocks binding of AP-1 to DNA (249, 262). Thus, redox regulation of AP-1 seems to be dependent on several opposing mechanisms.

Many forms of cellular stress induced by different stimuli, including ROS but also inflammatory cytokines (TNF-*α*, IL-6), bacterial toxins, and radiation are known to activate NF-*κ*B (394). Thus, it is not surprising that regulation of this stress-responsive transcription factor is rather complex involving opposing mechanisms at multiple levels of the NF-*κ*B signaling pathway. In a nutshell, there are five known members of the NF-*κ*B family (p50, RelA (p65), c-Rel, p52, and RelB), which form homo- and heterodimers. In unstressed cells, these dimers are inactivated by binding to I*κ*B proteins (249, 262, 394). Upon oxidative stimulation, these I*κ*B proteins are rapidly phosphorylated (at Ser32 and Ser 36) by I*κ*B kinase α (IKKα) and β (IKKβ) and degraded *via* the ubiquitin-proteasome pathway. The resulting free NF-*κ*B dimers translocate to the nucleus and activate transcription of diverse genes involved in stress response, inflammation, and apoptosis (249, 262, 394).

The Nrf2-Keap1-ARE system plays a central role in the protection of cells and tissues against oxidative stress as recently reviewed by Singh *et al.* (355) and Hayes *et al.* (151). It consists of the transcription factor Nrf2 (nuclear factor erythroid 2-related factor), which is tightly bound to the actin-binding protein Keap1 (kelch-like ECH-associated protein) in unstressed cells (170). This protein fixes, on the one hand, Nrf2 in the cytosol and, on the other hand, is an adaptor for an E3 ligase-mediating ubiquitination and in turn proteosomal degradation of Nrf2. Consequently, Nrf2 has a short half-life in unstressed cell. This situation is dramatically changed by the impact of ROS interacting with multiple reactive cysteines in the Keap1 molecule leading to loss of Nrf2 binding and/or Nrf2 degradation. Consequently, enhanced amounts of Nrf2 are imported into the nucleus where it binds to so-called ARE or EpRE (antioxidant or electrophilic response elements) present in the promoter or enhancer regions of multiple genes involved in oxidative and electrophilic stress response (151). The efficiency of target gene activation might thereby be modulated by dimerization of Nrf2 with other early response gene products like AP-1 family members and MAF proteins. Surprisingly, strong evidence suggests that constitutive activation of Nrf2 based on mutations in Keap1 or Nrf2 is frequent in several cancer types and contributes to chemoresistance (390). Interestingly, the list of genes with ARE promoter elements contains mainly those proteins that are also involved in the resistance of tumor cells against anticancer metal compounds (151, 355). First, several protection mechanisms regulating cellular redox balance are upregulated by Nrf2, including GSH, Trx, and peroxiredoxins (compare Section II.*A*.). In case of GSH, enzymes involved in synthesis (glutamate-cysteine ligase and glutathione synthetase), in redox recycling (GPx and GR), and in conjugation (several GSTs) are activated in response to Nrf2. In case of Trx, both the gene coding for Trx and the one for TrxR contain ARE sequences. As outlined in this review, multiple metal drugs cause oxidative stress by Fenton-like reactions and interaction with the cellular iron homeostasis. Interestingly, also several genes involved in iron metabolism are responsive to Nrf2 like ferritin H and HO-1 (compare Section III.*A*.).

While Nrf2 is a general alert and protection system for all forms of oxidative and electophilic stress, also more specific transcription factor responses to disturbance of metal homeostasis (compare Section III.) exist. Thus, the metal-responsive transcription factor (MTF-1), a zinc finger protein, and its cognate DNA binding site, the metal-response element (MRE), regulate cellular responses to heavy metals, ionizing radiation, and oxidative stress and control expression of components involved in metal homeostasis, such as zinc (ZnT-1) and copper (CTR1) transporters (351).

Additionally, both Nrf2 and MTF-1 bind to the promoter regions and activate several members of the important cellular metal-binding metallothioneines (MT). Mammalian MTs are small cysteine-rich proteins of 6–7 kDa, which are able to bind monovalent as well as divalent metal ions (70, 295). All cysteines in these molecules occur in reduced form and are coordinated to the metal ions to form metal-thiolate clusters with bridging sulfur groups. Although this allows binding of a range of metals (under cell-free conditions), mammalian MTs contain mostly zinc under physiological conditions (295). Moreover, MT genes have been shown to be highly inducible by metals such as Zn, Cu, or Cd and induction of MT and ZnT-1 expression *via* MTF-1 was shown to protect cells against zinc and cadmium toxicity (70, 288). Consequently, it is generally accepted that MTs are necessary, on the one hand, for detoxification of potentially toxic metal ions and, on the other hand, are involved in the regulation of metabolically essential trace elements (especially Zn) (70, 295). However, the involvement of this signaling pathway in regulation of the effects of metals (besides Zn, Cu, and Cd) is widely unknown. Recently, microarray studies revealed that gallium nitrate-resistant lymphoma cells displayed a marked increase in MTF-1, MT-2A, and ZnT-1 (415). Consequently, it has been suggested that under specific conditions MT might be involved in acquired resistance against metallodrugs.

In addition to the transcription factor-mediated protection from oxidative stress, also several other important signaling pathways exist to cope with ROS-induced cellular damages. Thus, ROS also induce ER stress and in turn the unfolded protein response (UPR) (Fig. 2). Under unstressed conditions, protein folding in the ER is catalyzed by the protein disulfide isomerase (PDI) and the ER oxidase 1 (ERO1). During this process ROS are produced, which are normally detoxified by, for example, the GSH system. Metal compounds can disturb this protein folding pathway, for example, by inhibition of chaperons like heat-shock proteins or by inhibition of ROS detoxification pathways, consequently rising the number of misfolded proteins, which leads to ER stress. Moreover, ROS-induced protein oxidation by metal complexes plays a major role in the accumulation of misfolded proteins and consequently ER stress and UPR. ER stress is recognized by three main sensors (PERK, IRE1a, and ATF6), which mediate signals to induce expression of specific UPR or ER-associated degradation (ERAD) proteins, such as chaperons and heat-shock proteins. In a nutshell, PERK signaling leads to a specific stop of mRNA translation, thereby attenuating the accumulation of newly synthesized proteins. IRE1a has an endonuclease site that activates X-box binding protein 1 (XBP1), a transcription factor for UPR and ERAD-related genes, by alternative splicing. Finally, ATF6 acts in its cleaved form as transcription factor similar to XBP1. In general, it is believed that these pathways are an adaptive response to cope with oxidative stress and to preserve cell function and survival. However, continuous stress and protein misfolding can lead to the activation of CHOP, a central transcription factor in ER stress, which induces proapoptotic proteins, such as Bim, and inhibits antiapoptotic ones such as bcl-2. Consequently, prolonged ER stress can induce not only survival pathways but also apoptosis [detailed reviews on protein folding and ER stress (129, 194, 232, 352)].

With regard to systemic cancer therapy, it has to be kept in mind that all the cellular responses to disturbance of the redox balance and oxidative stress described above significantly impact on the anticancer activity of, for example, metal compounds. Most of the concerted protection mechanisms activated by, for example, Nrf2 or UPR significantly reduce the sensitivity of malignant cells toward oxidative stress-inducing compounds, including anticancer metal drugs. This can result in (i) reduced drug uptake; (ii) enhanced efflux of drugs or conjugates *via* ABC transporters; (iii) enhanced drug metabolization; (iv) drug binding by MTs; (v) protection from oxidative stress by, for example, the above-mentioned anti-oxidative molecules (compare section II.*A*.); (vi) enhanced repair of metal drug-mediated damages, for example, of DNA or proteins; and (vii) activation of antiapoptotic programs involving, for example, bcl-2 and IAP family members. These chemotherapy resistance mechanisms against anticancer metal compounds have been reviewed recently by others and our group (155, 390) and are, thus, not in focus of this article.

Overall, it has to be kept in mind that, in general, cancer cells are characterized by an imbalance in redox homeostasis, leading to enhanced intracellular ROS generation (134, 381). The mechanisms underlying these redox alterations in tumor cells are diverse and very complex. For example, increased metabolic activity, mitochondrial malfunction and changes in virtually all antioxidant molecules are typically observed in cancer cells (134). Consequently, the interference with the cellular redox homeostasis of cancer cells seems an attractive and promising target for cancer therapy (9, 74, 77, 134, 138, 149). Indeed, many of the currently used chemotherapeutic drugs interact with the cellular redox balance und there are several attempts to specifically target the altered redox conditions in cancer cells. Thus, it is not surprising that—due to their redox properties—especially metal-containing compounds or drugs interfering with the cellular metal homeostasis by metal chelation (134) are in the focus of interest.

C. Fenton chemistry in biological context

In 1876, Henry John Horstman Fenton discovered the strong oxidative effects of Fe^{II} and H_2O_2 on some organic substrates (109), and later the occurrence of $OH^{\bullet}$ in this reaction was suggested by Haber and Weiss (136). The “Fenton reaction” is defined as:

$$Fe^{II}+H_2O_2 \rightarrow Fe^{III}+OH^{\bullet}+OH^{-} \quad 3$$

Thus, the reaction of Fe^{II} and H_2O_2 can produce the highly reactive $OH^{\bullet}$ which is able to damage biological molecules like nucleic acids, lipid membranes, and proteins. The generated Fe^{III} can then be reduced back to Fe^{II} by the superoxide radical $O_2^{\bullet\,-}$

$$O_2^{\bullet-}+Fe^{III} \rightarrow O_2+Fe^{II} \quad 4$$

Together with the Fenton reaction this leads to an iron-catalyzed production of $OH^{\bullet}$, the so-called Haber-Weiss reaction, where iron cycles between its ferrous Fe^{II} and ferric Fe^{III} form (Fig. 4) (396). In addition to the superoxide radical, also biological reductants like ascorbate and several thiols (e.g., GSH) are able to reduce Fe^{III} to Fe^{II} (220). Consequently, not only $OH^{\bullet}$, but also reactive organic species such as peroxyl ($ROO^{\bullet}$), alkoxyl ($RO^{\bullet}$), and thiyl ($RS^{\bullet}$) radicals are formed *via* the Haber-Weiss reaction (289). Following the stepwise one-electron reduction cascade of molecular oxygen:

$$O_2 \rightarrow O_2^{\bullet-} \rightarrow H_2O_2 \rightarrow OH^{\bullet} \rightarrow H_2O \quad 5$$

both the superoxide radical and H_2O_2 are constantly produced under physiological conditions in healthy cells (compare Section II.*A*.). The responsible mitochondrial and microsomal biomolecules include several oxidases, fumarate reductase, flavins, tetrahydropterins, and catecholamines (220). In some reactions, like that of glucose oxidase and urate oxidase, O_2 is directly reduced to H_2O_2. However, in most cases O_2 is first reduced to $O_2^{\bullet\,-}$ and subsequently dismutated by SOD to H_2O_2 and O_2. The generated H_2O_2 is further processed by catalases, peroxidases, or peroxiredoxins (319). In general, the concept of ROS generation by reaction of a metal ion with H_2O_2 is not limited to Fe^{II}. Thus, the term “Fenton-like reactions” is also used in context with other metal ions like copper, cobalt, and vanadium that can substitute iron.

III. Homeostasis of Redox-Active Metals in Mammalians

A. Iron homeostasis

A crucial feature of the biological activity of iron is the possibility to readily switch in a one-electron oxidation– reduction reaction between the ferrous form, Fe^{II}, and the ferric form, Fe^{III}. Under aerobic conditions, Fe^{II} is readily oxidized in solution to Fe^{III}, which is virtually insoluble at physiological pH (289). Consequently, the bioavailability of iron is generally limited. To maintain iron in a soluble form and perform iron uptake, utilization, and storage diverse proteins binding Fe with high affinity (e.g., transferrin and ferritin) have evolved in biological systems.

1. Iron transport—In the blood stream iron is bound in its ferric state to the serum proteins transferrin and albumin. Human transferrin (Tf) is a large nonheme monomeric glycoprotein with a molecular mass of ~80 kDa and in blood plasma the concentration is 2–3.6 mg/ml (~35 μM) (8). At the slightly alkaline pH of 7.4, Tf can bind one or two ferric ions with an overall blood iron load of 30% (69). The cellular uptake of iron *via* the transferrin-dependent pathway is well investigated and has been extensively reviewed (214, 215, 304) (Fig. 5A). In a nutshell, two iron-loaded Tf molecules bind to one dimeric Tf-receptor (TfR1), whereas the binding constant of iron-free Tf to the receptor is distinctly lower. This Tf-TfR1 complex is then endocytosed into the cell. The acidic pH of the endosomal lumen induces a conformational change in Tf leading to release of the bound iron from its carrier. The Tf molecule itself remains tightly bound to the TfR1 under these conditions. The complex is then relocated to the cell surface, where the extracellular pH leads to dissociation of the apo-Tf molecules from the receptor. After reduction by a ferrireductase, Fe^{II} is transferred into the cytosol by the divalent metal transporter (DMT1) (277, 278).

Once in the cytosol, iron becomes part of the labile iron pool (LIP). This low-molecular-weight pool of weakly chelated iron rapidly passes through the cell. Under physiological conditions, the LIP represents only a minor fraction of the total cellular iron (3%–5%), but it is the crucial linkage between iron uptake and the permanent intracellular chelation by iron-dependent proteins (205). Thus, it has to be expected that all dietary iron should pass the LIP stage. The LIP harbors both Fe^{II} and Fe^{III} associated with a variety of low-molecular-weight ligands with low affinity to iron ions, including citrate, phosphates, carbohydrates, carboxylates, and polypeptides. However, the actual nature of the LIP is still widely unexplored (183).

Cell damage associated with iron overload is attributed to increased levels of the LIP, which promotes the production of ROS *via* Fenton-like chemistry (compare Section II.*C*.) (126). Additionally, due to the only weak chelation of iron in the LIP, it is also the major coordination site for many therapeutic iron chelators (303). Chelation of the LIP-bound iron results—due to iron deprivation—also in prevention of iron redox-cycling and reduced ROS formation (46). With regard to metal compounds, it seems likely that interaction with the LIP also contributes to metal-induced intracellular ROS production.

2. Intracellular iron proteins—Iron is utilized as cofactor in several proteins, including aconitases, cytochromes, ribonucleotide reductase (RR), as well as heme complexes (214). With regard to anticancer therapy, the RR (199), as enzyme that provides dNTPs essential for proliferation and DNA repair, has been considered an ideal target for cancer therapy. This led to the (pre)clinical development of several RR inhibitors, including gemcitabine, hydroxyurea, the thiosemicarbazone Triapine, or the lanthanum compound KP772 (156, 341). Another important intracellular iron-binding protein is ferritin where excessive iron is stored (227, 372). Ferritin is a ubiquitous and highly conserved multimeric protein and consists in vertebrates of an apoprotein shell of 24 light and heavy subunits around a core of up to 4500 iron atoms (158, 416). As new iron is packed into the ferrihydrite mineral core, it is converted from Fe^{II} to Fe^{III} by the inherent ferroxidase activity of the heavy ferritin subunits (416). Due to its iron-storage function ferritin prevents excess iron of the LIP from taking part in the Fenton reaction, which makes it crucial for the protection of the cell from ROS (227, 280).

B. Copper homeostasis

Copper is another redox-active metal, which is important in the biochemistry of every living organism. In biological systems copper exists mainly in two oxidation states: cuprous Cu^{I} and cupric Cu^{II}. Copper is used as cofactor in several redox reactions of enzymes with fundamental biological functions in growth and survival of cells such as the cytochrome c oxidase of the mitochondrial electron chain, the lysyl oxidase important for connective tissue formation, as well as the Cu/Zn-SODs (compare Section II.*A*.). However, due to its redox properties, copper (comparable to iron) has to be tightly regulated in the living organism to prevent formation of ROS. Thus, copper is constantly protein-bound and, for its distribution, always transferred directly from one protein to the other (Fig. 5B). The central structural requirement in Cu-binding proteins, which is necessary for these intimate protein–protein trans-chelation reactions, is the presence of unique cysteine, methionine, or histidine-rich domains, which bind Cu^{I} *via* metal–sulfur or metal–nitrogen bonds (166).

Overall, there is virtually no free copper in the healthy organism. In the blood plasma, most copper is bound to ceruloplasmin (152), a cuprous oxidase, which is important in the body iron homeostasis by oxidizing Fe^{II} in the plasma, allowing iron binding to transferrin. However, the importance of ceruloplasmin in copper transport and homeostasis has been questioned (152). The remaining plasma copper (about 350 ng/ml) is bound to proteins of the exchangeable copper pool (258). This pool is composed primarily of albumin and α_2-macroglobulin (transcuprein). In contrast to the extensively investigated and well-understood iron uptake using the transferrin receptor pathway, little is known how copper exactly enters mammalian cells. The main Cu uptake transporter in mammalian (liver) cells seems to be the copper transporter 1 (CTR1) (193). In addition, other metal transporters, including CTR2 and the divalent metal transporter 1 (DMT1), contribute to copper uptake of mammalian cells. In the cytoplasm, a highly specialized chaperone system assures the distribution of copper to the target proteins. There are three major functional groups of copper chaperones (17, 19): (i) ATOX1, which delivers copper to the P-type ATPases (ATP7A and B) of the secretory transgolgi network, (ii) CCS, which brings copper to the Cu/Zn-SOD in the cytoplasm, and (iii) cyclooxygenase 17 (Cox17), which transports copper to the inner mitochondrial membrane proteins Cox11 and Sco1 from which it is subsequently incorporated into cytochrome c oxidase.

Unlike iron, physiological storage of copper seems unnecessary as copper body levels are maintained primarily by balancing dietary absorption, distribution, and utilization (17). However, excess of copper (and other metals) stimulates the expression of metallothioneins, a protein family that is characterized by its outstanding metal binding capacity and is crucial in the protection of the body from toxic heavy metals (70, 295) (compare Section II.*B.*).

IV. From Electrochemistry to Cellular Redox Reactions and Anticancer Therapy

A. Oxidation and reduction: the principles of redox processes

In contrast to most organic cancer therapeutics being redox-inactive in the cellular environment, many metal-containing drugs can undergo redox processes. These changes significantly influence and alter the physicochemical properties of such complexes including geometry, charge, and reactivity. Consequently, the knowledge of the redox potential can be crucial for the understanding of the mode of action underlying the anticancer activity of metal compounds.

For each redox couple of metal ions $M^{n+}/M^{(n-1)+}$ with adjacent oxidation states and for a variety of redox reactions standard electrode potentials (E^o) are available in literature (24, 162, 218). This potential is given for standard conditions of 298.15 K, 1 bar pressure, at pH 0, and at 1 M concentration of the reduced and oxidized forms. The E^o potentials are always referenced to the normal hydrogen electrode (NHE), which consists of hydrogen gas bubbled with 1 bar around a platinum electrode in an aqueous solution with pH 0. The potential of the NHE, according to the reaction

$$2H^+ + 2e^- \leftrightarrow H_2 \quad 6$$

has been arbitrarily set to 0.00 V. Considering two different redox reactions, for example $Fe^{III} + e^- \leftrightarrow Fe^{II}$ with a standard redox potential $E^o = +0.77$ V versus NHE and GSSG + $2H^+ + 2e^-$ 2GSH with $E^o = +0.18$ V versus NHE (162, 336), it is directly possible to predict that under standard conditions Fe^{III} will be reduced to Fe^{II} and GSH will be oxidized to GSSG. This is based on the thermodynamic principle that the redox couple with the more positive standard redox potential is always reduced and the one with the more negative potential is oxidized. However, apart from thermodynamics, which gives information, if a reaction is possible or not, also the kinetics have to be considered, which give information about the reaction rate. Thus, in principle a reaction that is possible from the thermodynamical point of view may not occur because of too slow kinetics.

However, when using redox potentials in a biological context, a range of additional factors have to be considered:

(i) the pH dependency—the majority of redox reactions, including all involving H^+ ions, exhibit pH-dependent potentials. For example the potential of the redox reaction

$$O_2+4H^++4e^- \leftrightarrow 2H_2O \quad 7$$

is + 1.23 V versus NHE at pH 0, + 0.815 V at pH 7, and + 0.40 V at pH 14. Thus, for the physiologically relevant situation of pH 7 a separate denotation $E^{o'}$ has been defined. Depending on the number of electrons and protons involved in the redox reaction, the redox potential shifts when the cellular pH changes. For example, the potential of GSH (with a two electron/two proton couple) changes with a slope of −0.061 V/pH at 37°C (162, 336).

(ii) the proportion dependency of oxidized and reduced form—the standard redox potential $E^{o'}$ for the reaction

$$O_2+e^- \leftrightarrow O_2^{\bullet-} \quad 8$$

at −0.16 V versus NHE implies equal concentrations of O_2 and $O_2^{\bullet-}$ (336). However, in the cellular environment a more realistic concentration of O_2 is ~10^{-5} M and of $O_2^{\bullet-}$ it is 10^{-10} *M*. These differences in concentration result in a profound change of the redox potential of this reaction. The reason is a term in the Nernst equation (the underlying mathematical expression for estimation of redox potentials), which contains the proportion of oxidized to reduced species (e.g., O_2 to $O_2^{\bullet-}$). Thus, a change in the proportion strongly impacts on the redox potentials resulting in $E^{o'}$ ~ + 0.14 V versus NHE for O_2/O_2 in the cellular environment (336). This dependency on the concentrations is extremely important due to the lack of equilibrium conditions in biological systems.

(iii) the reference electrode—as the setup of the NHE is rather difficult to implement in routine measurements, in most cases other reference electrodes are used and the reported values are referred to them or converted to the NHE by addition of a constant value. In aqueous solution the most important references are the saturated silver/silver chloride electrode (+ 0.197 vs. NHE) and the saturated calomel electrode (+ 0.241 vs. NHE) (23). For nonaqueous solutions, ferrocenium/ferrocene is frequently used as internal reference with a conversion value that depends on the solvent (25, 293).

(iv) the biologically accessible redox potential window—in biological systems the accessible redox potential window ranges only from around −0.4 to +0.8 V versus NHE (197). The strongest reducing agent of the major redox active components in cells is the nicotinamide adenine dinucleotide phosphate couple ($NADP^+ + 2e^- + H^+ \leftrightarrow NADPH$) with approximately −0.38 V versus NHE (336). On the other side, the strongest oxidizing agent is oxygen itself according to $O_2 + 4H^+ + 4e^- \leftrightarrow 2H_2O$ at +0.815 V at pH 7.0. However, oxygen is kinetically inert and, thus, *in vivo* reactions involving molecular oxygen have to be catalyzed by enzymes (e. g. the above 4-electron reaction is catalyzed by cytochrome c oxidase). Usually, all redox reactions with higher or lower potentials than the biological window cannot occur in the cellular environment. However, it has to be mentioned that besides common biological reducing and oxidizing agents, also ROS like $OH^\bullet$, $O_2^{\bullet-}$, and H_2O_2 (see also Table 1) as well as organic radicals such as $RO^\bullet$, $ROO^\bullet$, and $RS^\bullet$ are present in cells. Especially, radicals are often characterized by very high $E^{o'}$ redox potentials (e.g., $OH^{\bullet}$ [+ 2.31 V], $RO^{\bullet}$ [+1.60 V], $ROO^{\bullet}$ [~1.00 V], and $RS^{\bullet}$ [e.g., cysteine + 0.92 V]) (140) and are able to oxidize far more compounds than the common cellular redox systems. Furthermore, oxidizing radicals like $GS^{\bullet}$ can react with GS^{-} to form strongly reducing $GSSG^{\bullet -}$ radicals with redox potentials of −1.50 V (49). However, it has to be considered that in the cellular environment common redox agents like GSH are available in up to mM concentrations, whereas intracellular concentrations of radical species are generally very low and these highly reactive species often immediately react at their place of origin.

B. The impact of metal and ligand on redox potentials

Usually, the standard redox potentials of metal ion redox couples $M^{n+}/M^{(n-1)+}$ are determined in aqueous solution without additional coordinating ligands. However, in biological systems as well as in synthetic metal complexes, coordinating ligands are frequently present, which often induce dramatic changes in the redox potential of a metal ion. One example is a series of investigational Ru^{III} anticancer complexes (Table 2) (318). Starting with $[Ru^{III}Cl_6]^{3-}$ at a redox potential of −1.36 V versus NHE the stepwise exchange of one chlorido ligand by indazole results in increasing redox potentials, ending up with *trans*-$[Ru^{III}Cl_2(Hind)_4]+$ at + 0.59 V versus NHE, nearly 2.0 V more positive then $[Ru^{III}Cl_6]^{3-}$ Thus, the knowledge of the exact coordination sphere of a metal ion in the biological environment is necessary to draw conclusions about its redox properties. Moreover, the use of different ligands enables tuning of the redox potential of a selected metal ion, yielding in metal complexes with the desired redox properties.

Next to the ligands, the nature of the metal ion itself influences the redox properties of coordination compounds (see Fig. 6 for metal ions with an identical ligand set).

As example, the electrochemical response of the metal complexes $[M(Dp44mT)_2]$, with M = manganese, iron, cobalt, nickel, copper, and Dp44mT = di-2-pyridylketone 4,4-dimethylthiosemicarbazone is shown in Figure 6 (33). Although for each metal ion the $M^{III/II}$ redox couple was investigated (for M = $Cu^{II/I}$), the complexes exhibit very different potentials. For example, $[Ni(Dp44mT)_2]^{+}$ with a redox potential of + 0.52 V versus NHE was found to be much easier to reduce than its cobalt analog $[Co(Dp44mT)_2]^{+}$ at −0.62 V.

C. Anticancer metal compounds and redox processes: overview

The interaction of transition metal complexes with the cellular redox balance is well investigated (140). For example, depletion of the GSH pools has been frequently described for many metal-containing anticancer drugs (253, 291, 414). However, the underlying modes of action strongly depend on the chemical/physical properties of the metal ion. Especially the hardness/softness of a metal ion seems to have a crucial impact on the intracellular reaction behavior of the complexes. Transition metals (“acids”) as well as the donor atoms of the potential ligands (“bases”) can be classified into soft (low charge/large ionic radius), intermediate, and hard (high charge/small ionic radius) according to the “hard and soft acids and bases” (HSAB) concept (294). Based on this concept, soft acids react faster and form stronger bonds with soft bases, whereas hard acids react faster and form stronger bonds with hard bases. Thus, the soft acids Pt^{II}, As^{III}, or Au^{I} easily react with soft bases like sulfur-containing GSH and other cysteine-rich molecules, such as TrxR and metallothioneins (compare Section II.*A*.). This leads to redox-independent formation of GSH conjugates and, consequently, cellular GSH pool depletion and sensibilization to ROS (34, 73, 239, 253, 358). In contrast, in case of intermediate to hard metal ions (such as V^{V}, Co^{III}, Cu^{II}, or Ru^{III}) with lower affinity for soft donor systems such as the thiol moiety in GSH (Compare Section II.*A*.), GSH pool depletion is caused by ROS generation *via* Fenton-like reactions, which leads in parallel to reduction of the metal and to oxidation of GSH to GSSG.

An important part of the mode of action of several metal-based drugs related to redox processes is widely known as the "activation by reduction" hypothesis (compare Section V.*A*.2., V.*D*., V.*E*., and V.*H*.). This concept is based on the idea to apply a less cytotoxic prodrug, which is then activated by intratumoral reduction. Especially, in case of Pt^{IV},Ru^{III},Co^{III}, and Cu^{II} drugs activation by reduction is believed to be important in their modes of action (9, 74, 77, 134, 138, 149). Reduction results in increased reactivity of the metal center together with labilization/dissociation of the ligand. However, activation by reduction does not necessarily increase the intracellular activity of the metal drug *per se*, but may also contribute to selective transport and release of cytotoxic ligands within the tumor tissue as observed for several cobalt complexes.

V. Metal-Based Anticancer Drugs and Their Redox-Related Modes of Action

Anticancer metal complexes have been shown to strongly interact with or even disturb cellular redox homeostasis resulting in enhanced levels of oxidative stress (Fig. 2). In the following sections we summarize the current knowledge on Pt, Au, As, Ru, Rh, Cu, V, Co, Mn, Gd, and Mo complexes regarding the involvement of redox processes in their anti-cancer activity.

A. Platinum

Platinum (Pt) is used for many purposes in modern life. For example, it is applied as catalyst, used in electronics, and for jewelry. Further, it plays a decisive role in anticancer agents, such as cisplatin and oxaliplatin. The most common oxidation states of platinum are + 2 (d^8) and + 4 (d^6). According to the HSAB concept Pt^{II} is a "soft acid" and therefore readily reacts with "soft bases" like sulfur. In contrast, Pt^{IV} is a hard acid and prefers oxygen containing ligands. The oxidation states + 1 and + 3 are less common.

1. Platinum(II)—The era of metal-based anticancer drugs began with the discovery of the anticancer properties of the square-planar Pt^{II} cisplatin (*cis*-$[PtCl_2(NH_3)_2]$) (Fig. 7) by Barnett Rosenberg in the 1960s (323). Nowadays, cisplatin is one of the most important chemotherapeutics used clinically against a wide variety of different solid tumors, including testicular, bladder, ovarian, as well as head and neck cancer (189). In general, it is accepted that the anticancer activity of cisplatin is based on the formation of platinum-DNA adducts. This coordination leads to a significant distortion of the helical DNA structure resulting in inhibition of DNA replication and transcription. Further, several signaling pathways are activated which—as a final consequence—lead to cell cycle arrest and/or apoptosis (189, 301).

Due to the Pt center of cisplatin, it is reasonable that the drug reacts not only with DNA but also with donor atom-containing proteins (compare Section II.*A*. and IV.*C*.), with particularly high affinity to sulfur and seleno amino acids. This is supported by the fact that less than 1% of intravenously administered cisplatin reaches DNA. Therefore, several other cellular targets have been suggested (130, 154, 315). Such DNA damage-independent mechanisms might involve, for example, alteration of cell membrane fluidity by inhibition of the Na^+ / H^+ membrane exchanger NHE1 and, consequently, activation of FAS-mediated apoptosis (314). Cisplatin detoxification is at least partially based on formation of cisplatin-GSH conjugates (100), which leads to intracellular GSH pool depletion (253), disturbance of the cellular redox homeostasis, and, consequently, increased levels of intracellular ROS (34, 73, 239, 358). Moreover, cisplatin treatment was found to deplete cellular NADPH pools (98, 238) resulting in altered mitochondrial redox status, which then causes hydroxyl radical generation. Further, recent studies suggest the ER as cytosolic target of cisplatin and induction of apoptosis also *via* ER stress (233). All these processes can lead to lipid peroxidation and oxidative protein damage, which contribute to the disruption of the mitochondrial membrane structures (146, 238) and consequently lead to apoptosis induction (compare Section II.*B*.).

Further, cisplatin directly reacts with TrxR, which has a redox-active disulfide/dithiol moiety in its active site and a reactive seleno-cysteine residue at the C-terminus (333). Cisplatin has been shown to irreversibly inhibit the activity of human TrxR in cell-free setting and in cell models in a dose- and time-dependent manner (16). Interestingly, in a cell-free system cisplatin inhibited the TrxR activity only in the presence of NADPH. It is therefore claimed that cisplatin interacts only with the reduced form of TrxR, which is generated by NADPH (16, 333) (compare Section II.*A*.). Notably, human GSH reductase, which has a strong homology to human TrxR and contains a similar redox-active disulfide/dithiol moiety but no seleno-cysteine residue, is not inhibited by cisplatin (16, 251, 404, 405). Therefore, the highly reactive seleno-cysteine residue at the C-terminal domain was suggested to be the TrxR target of cisplatin (405). These data were supported by a study investigating the ability of different modified forms of the cytosolic TrxR1 protein to induce apoptosis. As expected, the unmodified full-length TrxR1 with an intact selenocysteine residue did not promote cell death. In contrast, both a truncated selenocysteine-deficient TrxR1 form as well as a TrxR1, which was derivatized at the selenocysteine residue with cisplatin, were able to induce cell death in A549 lung cancer cells (11). Arnér *et al*. (16) showed that in addition to cisplatin, also different GSH-cisplatin conjugates inhibited the activity of TrxR. Interestingly, these GSH-adducts, in contrast to cisplatin alone, were able to reduce the activity of the GSH reductase system (16). Further, cisplatin resistance can be accompanied by overexpression of metallothioneins and GSTs (compare Section II.*A*.) (363). The latter enzymes catalyze the conjugation of GSH to the platinum complexes, which then can be excreted from the cells, for example, *via* the drug-conjugate efflux pump ABCC2 (67, 73). Several clinical studies showed that augmented expression and gene amplification of GSTs were unfavorable prognostic factors in ovarian cancer patients and could be associated with cisplatin resistance in head and neck squamous cell carcinoma (84, 366).

Thus, it can be summarized that the intracellular redox homeostasis is severely affected by cisplatin due to the disruption of the TrxR and GSH reductase systems. Therefore, it is not surprising that different studies have shown a correlation between Trx, TrxR, GSH, GSTs, and GR expression with cisplatin resistance (155, 363, 406). It has to be mentioned that cisplatin-induced oxidative stress participates not only in its cytotoxic effects against tumor cells, but is also responsible for unwanted effects such as nephrotoxicity (73) and hepatotoxicity (85, 146). Several studies demonstrated that the cisplatin-induced renal tubular injuries involve multiple signaling pathways, including ROS-mediated p53 signaling (179). Interestingly, it has been shown that γ-glutamyl-transpeptidase (γ-GT) expression plays a crucial role in cisplatin nephrotoxicity. While in the tumor tissue γ-GT expression was connected with resistance, kidney γ-GT expression rendered the cells sensitive to cisplatin toxicity, suggesting different mechanisms of apoptosis induction in tumor cells and proximal tubular cells. The authors further suggest that in the kidney excreted Pt-GSH conjugates are metabolized by γ-GT, reabsorbed, and further metabolized to reactive thiols, which primarily target mitochondria and thereby induce apoptosis and necrosis in the kidney tissue (144). Cisplatin-induced oxidative liver and renal damage and its possible protection by the hydroxyl radical scavenger dimethylthiourea (DMTU) were further studied *in vivo* in Wistar rats (98, 330). DMTU protected against decreased hepatic ATP levels, lipid peroxidation, cardiolipin oxidation, sulfhydryl protein oxidation, mitochondrial membrane rigidification, GSH oxidation, NADPH oxidation, and apoptosis (98).

In clinical use these severe side effects together with intrinsic and acquired resistance limit the application of cisplatin (155). To overcome these limitations, diverse novel metal-based anticancer drugs have been designed and around 30 compounds have so far been evaluated in clinical studies (65). From a plethora of newly synthesized square-planar four-coordinate cisplatin analogs (120) only two further Pt^{II} complexes have gained world-wide clinical approval, namely, the second- and third-generation derivatives carboplatin and oxaliplatin (Fig. 7). In addition, three other Pt^{II}-based drugs, namely, nedaplatin, lobaplatin, and heptaplatin (Fig. 7), have gained limited regional approval (172). These Pt^{II} drugs are believed to target DNA in analogy to cisplatin. Carboplatin is less toxic than cisplatin. This can be explained by the increased stability of carboplatin due to its dianionic biscarboxylato leaving group instead of the two chlorido ligands in the case of cisplatin, leading to a slower rate of aquation. After dissociation of the leaving group, carboplatin forms identical DNA adducts as cisplatin (198). Consequently, this drug is active in a comparable spectrum of tumors and cross-resistance to cisplatin is frequently observed (155). In contrast, oxaliplatin has been shown to be active against cisplatin-resistant tumor cell lines. However, in the clinical situation some cross-resistance between cisplatin and oxaliplatin has been observed (364). Differences in the activities of oxaliplatin and cisplatin can be explained by lower DNA adduct formation by oxaliplatin (408) and the more hydrophobic and bulkier (*1R,2R*)-cyclohexanediamine (Dach) ligand, which induces DNA bending different to cisplatin. Further, cisplatin and oxaliplatin adducts are recognized differently by mismatch repair proteins, DNA polymerases, and damage-recognition proteins (60).

For both oxaliplatin and carboplatin, only a few reports on the effects on cellular redox homeostasis are currently available. Laurent *et al.* investigated the impact of endogenous ROS production on tumor growth and the consequence of ROS modulation on oxaliplatin cytotoxicity (208). In this study, a dose-dependent increase of ROS production associated with a decrease in proliferation was detected after oxaliplatin treatment in a murine colon cancer model *in vitro* and *in vivo* (208). Moreover, addition of exogenous GSH or *N*-acetylcysteine (NAC) reduced oxaliplatin cytotoxicity, whereas depletion of GSH with buthionine sulfoximine (BSO) or cotreatment with SOD mimics (compare Section V.*I.*) increased the sensitivity toward oxaliplatin (7, 208). In accordance, in a cell-free system the levels of oxaliplatin-induced DNA damages were increased by the addition of SOD mimetics whereas NAC reduced them. The same effects were observed in combination studies *in vivo* (208).

Comparable to cisplatin, the Trx system is also influenced by oxaliplatin. This platinum drug inhibited the activity of TrxR in a cell-free system similar to cisplatin (405), whereas in a cellular environment TrxR was inhibited significantly stronger by cisplatin than oxaliplatin (157). In contrast, carboplatin had no effect on TrxR activity in cell-free systems (405), a rather unexpected result considering the similarities of carboplatin and cisplatin. However, the TrxR inhibitory activity of carboplatin has never been tested in live cells *in vitro* or *in vivo*. Therefore, two alternative hypotheses have been proposed. On the one hand, an intracellular activation might yield a more reactive carboplatin derivative that inhibits the TrxR similar to cisplatin. On the other hand, the lack of TrxR inhibition might be an explanation for the lower cytotoxicity of carboplatin compared to cisplatin (405).

Beside cisplatin, carboplatin, and oxaliplatin, only a few Pt^{II} drugs were investigated with respect to their impact on redox homeostasis of cancer cells. For example (2,2′:6,2″terpyridine)platinum(II) complexes (Fig. 8) exhibit their cytotoxic activity against different tumor cell lines (30, 224) not only by intercalating into DNA (176, 243) but also by inhibiting the human TrxR in a dose-dependent manner. TrxR activity was blocked with IC_{50} values in the low nM range, whereas the GSH reductase inhibitory concentrations were > 1000-fold higher (30). These results are again in accordance with the inhibition of TrxR and GSH reductase by cisplatin (16, 251, 404, 405). Two of the (2,2′:6,2″-terpyridine)platinum(II) complexes were further investigated in an orthotopic rat glioblastoma model. Both compounds had no effect on the blood redox parameters but reduced TrxR and GSH peroxidase activities significantly in the tumor tissue (3). For another set of terpyridine-platinum(II) complexes it has been shown by X-ray crystallography and MALDI mass spectroscopy that the complexes inhibit the TrxR activity by blocking the selenocysteines at the C-terminal active-site of the protein (223).

2. Platinum(IV)—The anticancer activity of Pt^{IV} complexes was discovered together with cisplatin in the 1960s (323), but these platinum drugs have been studied and developed less extensively than Pt^{II} compounds. The octahedrally coordinated Pt^{IV} compounds have a higher coordination number (six *vs* four) than the square-planar Pt^{II} complexes and therefore the possibility to introduce additional axial ligands. These ligands have a strong impact on diverse pharmacological properties of the compounds, such as lipophilicity, stability, and reduction potential (compare Section IV.*B*.). Furthermore, the ligands can be designed for targeting specific tumor sites or as additional bioactive components. Pt^{IV} complexes are kinetically more inert than their Pt^{II} counterparts and have a lower reactivity with biomolecules. These characteristics are the reason for reduced unwanted side effects, lower toxicities, as well as the possibility of oral administration (120, 139).

The first Pt^{IV} drugs in clinical trials were *cis,trans, cis*-$[PtCl_2(OH)_2(isopropylamine)_2]$ (JM9, iproplatin) and $[PtCl_4$(D,L-cyclohexane-1,2-diamine)] (tetraplatin, ormaplatin; Fig. 9). The clinical development was abandoned due to the low activity in the case of iproplatin (382) and the severe neurotoxicity caused by tetraplatin (276, 337). Recently, another Pt^{IV} complex, namely, *cis,trans*-$[PtCl_2(OAc)_2(NH_3)(cyclohexylamine)]$ (JM-216, satraplatin) (Fig. 9), has been considered for approval by the FDA for the treatment of hormone-refractory prostate cancer in a combination regimen with prednisone, a synthetic corticosteroid. However, a phase III study did not achieve the anticipated endpoint of overall survival improvement (Agennix, http://agennix.com, ref. accessed 2010-09-15). Further clinical trials with satraplatin in a combination regime are ongoing (155).

Comparable to Ru^{III} and Co^{III} drugs (compare Sections IV.*C*., V.D., and V.*H*.), Pt^{IV} complexes are considered as pro-drugs, which undergo reduction in the intracellular milieu. During this process the axial ligands are released and the corresponding anticancer active square-planar Pt^{II} analogs are formed. Therefore, the reduction potential of the Pt^{IV} complexes as well as the redox status of the tumor environment have strong impacts on the activity of Pt^{IV} anticancer drugs (124, 138). Several studies show that the reduction potential is influenced by the nature of the axial ligands and to a lesser extent by the equatorial ligands (compare Section IV.*B*.). For Pt^{IV} complexes with a given equatorial coordination pattern, reduction most easily occurs when chlorido ligands are in the axial position. Carboxylato ligands lead to an intermediate reduction potential, whereas hydroxido ligands possess strong electron donating properties resulting in low reduction potentials and therefore complexes that are difficult to be reduced (105, 120, 137, 141). In addition, Choi *et al*. showed that the reduction rates depend not only on the electron-withdrawing power of the axial ligands but also on the bulkiness of these ligands (74).

Several groups have investigated the correlation between the cytotoxicity and the reduction potential of Pt^{IV} compounds. It can be summarized that on the one side the cytotoxicity is mainly dependent on the activity of the resulting Pt^{II} complexes. On the other side, it depends on where and how readily the Pt^{IV} compounds are reduced. The clinical results of iproplatin and tetraplatin can be directly linked to their reduction properties. For iproplatin (axial hydroxido ligands, low redox potential) it was found that *in vivo* large amounts are not reduced, resulting in low toxicity but equally low activity (296). In contrast, tetraplatin (axial chlorido ligands, high redox potential) was very rapidly reduced and all detected biotransformation products were Pt^{II} analogs explaining the very high toxicity (62). The reduction of satraplatin (axial acetato ligands) is rapid but slowed down *in vivo*, resulting in at least six metabolites of which *cis*-amminedichlorido-(cyclohexylamine)platinum(II) (JM118) (Fig. 9) is the most abundant one. A comparatively mild toxicity was detected after satraplatin treatment (120, 312).

Even though there is a correlation between the activity of Pt^{IV} compounds and their reduction potential, it is difficult to predict their *in vivo* anticancer activity. One explanation of this disparity could be the early reduction of Pt^{IV} complexes in the blood stream, which can lead to lower lipophilicity and drug uptake (138).

One of the major questions regarding Pt^{IV} compounds concerns the *in vivo* kinetics and the mechanisms of reduction. Several cell-free and *in vitro* experiments investigated this problem, but still the reactions are not fully understood and *in vivo* analyses are incomplete. A large amount of molecules that are involved in the redox homeostasis of cells can reduce Pt^{IV} complexes, such as GSH, methionine, cysteine, ascorbate, and others. These reductants were mainly investigated with model compounds such as *trans*-$[PtCl_2(CN)_4]^{2-}$, tetrachloridoam(m)ine platinum(IV) compounds and *cis*,-*trans*,*cis*-$[PtCl_2(OCOCH_3)_2(NH_3)_2]$ (68, 210, 345, 346).

As described previously (155), GSH possesses the ability to detoxify Pt^{II} drugs and enhanced GSH levels are associated with resistance (compare Section II.*A*.). With regard to Pt^{IV} complexes, GSH is believed to have an important role in activation (eq. 9). Eastman *et al*. showed that tetraplatin binds only very slowly to DNA whereas the addition of two stoichiometric equivalents of GSH markedly increased this reaction.

$$Pt^{IV}+2GSH \rightarrow Pt^{II}+GSSG+2H^{+} \quad 9$$

At higher GSH concentrations the DNA binding of tetraplatin decreased, indicating that the Pt^{II} analog of tetraplatin can be detoxified by reaction with GSH comparable to cisplatin (101). These data were confirmed by Kido *et al*. in a cell-free setting using salmon sperm DNA (191). Notably, levels of DNA platination after incubation of tetraplatin with GSH were similar to those of its reduction product $[Pt^{II}Cl_2(Dach)]$ (61).

A sensitive leukemic L1210 cell model and two cisplatin- and oxaliplatin-resistant cell lines are sensitized toward tetraplatin by addition of GSH (191). A relationship between intracellular GSH levels, drug resistance, and cytotoxicity was shown for tetraplatin and iproplatin in several cell models (245, 297). However, in another study GSH cotreatment with tetraplatin of intraperitoneally inoculated cisplatin-sensitive and -resistant L1210 tumor cells in mice did not enhance the activity and reduced the platinum concentration in the plasma compared to tetraplatin alone (192).

One possible reduction mechanism (Fig. 10) of tetraplatin and other Pt^{IV} complexes with axial halogenido ligands by GSH is a halogenido-bridged electron transfer. Therefore, the thiol of GSH reacts with the highly polarized chlorido ligand of the platinum complex. From the resulting GS-Cl-Pt^{IV} transition state GSCl is eliminated, which can further react with GSH to GSSG and HCl. Expulsion of the *trans* ligand yields the square-planar platinum(II) complex (138).

In addition to tetraplatin, also for iproplatin a relationship between intracellular GSH levels, drug resistance, and cytotoxicity was shown in several cell models (245, 297). Recently, Volckova *et al*. suggested a new mechanism for the reduction of iproplatin in which one

GSH is coordinated to the metal center in equatorial position before the reduction of Pt^{IV} to Pt^{II} by additional equivalents of GSH. This reaction yields in chloridobis(isopropylamine)(glutathionato)platinum(II) and not the commonly believed *cis*-dichloridoplatinum(II) complex (392). Controversial data have been presented, whether GSH can reduce or detoxify satraplatin. In contrast to iproplatin, satraplatin was stable *in vitro* in GSH-containing solutions with and without NADH (55). On the one hand, GSH has been proposed as major deactivation pathway for satraplatin (112, 313). On the other hand, Mellish *et al.* found no correlation between GSH and satraplatin-induced cytotoxicity (246) and no increased GSH levels were found in JM118-resistant cells (327).

Beside the cysteine of GSH, also a range of other proteins/biomolecules possessing cysteine (containing a thiol moiety) or methionine (containing a thioether moiety) are able to interact with platinum complexes. The Cys thiol and the Met thioether are oxidized to disulfide-bridged cystine (compare Section II.*A*.) and methionine *S*-oxide, respectively. The cysteine/cystine system has a major structural function in biomolecules and the redox balance of cells. In general, thiols are stronger reductants and more pH-dependent than thioethers.

The model substance *trans*-$[PtCl_2(CN)_4]^{2-}$ is reduced by both cysteine and methionine at 2:1 and 1:1 molar ratios (amino acid: Pt complex), respectively (345, 346). There are only limited data available whether iproplatin or tetraplatin can be reduced by these amino acids. Pendyala *et al.* hypothesized that iproplatin can be reduced intracellularly by cysteine (296), but no mechanism of reduction has been suggested. In the case of tetraplatin *in vivo* biotransformation products are, next to $Pt^{II}(Dach)Cl_2$, also Dach-Pt-methionine and Dach-Pt-cysteine species (374).

Next to GSH, also ascorbic acid (vitamin C) is considered to be a major low-molecular-weight antioxidant/reductant in the body (compare Section II.*A*.). A number of papers investigated the possible reduction of Pt^{IV} complexes by ascorbate. However, the investigations disagree in key aspects (42, 74, 211, 212, 402). Further, ascorbic acid has two pK_a values with 3.95 and 11.24 ($H_2A \leftrightarrow HA^- \leftrightarrow A^{2-}$). Thus, at physiological pH nearly all the ascorbic acid (H_2A) is present as the singly deprotonated ascorbate anion (HA^-) (138), which is therefore the major reductive species in the cellular environment.

Concerning the interaction of ascorbate with Pt^{IV}, Bose *et al.* suggested a complex mechanism for the reaction of iproplatin with ascorbate at pH 7 (42, 402). Therefore, the overall reactions are the expected two one-electron oxidations of ascorbate yielding dehydroascorbic acid and simultaneous reduction of Pt^{IV} to Pt^{II}. However, the direct reaction of iproplatin and ascorbate is very slow. Thus, a Pt^{II} catalyzed reduction of a Pt^{IV}-ascorbate complex by a second ascorbate molecule, with intermediate ascorbate radicals, is believed to take place. Choi *et al.* analyzed the reduction of Pt^{IV} complexes at pH 7 and confirmed the expected correlation between the reduction rate and the reduction potential (74). The investigations showed again that iproplatin is very slowly reduced by ascorbate and Choi supports the occurrence of an ascorbate radical. In contrast, Lemma *et al.* suggested for some model compounds like *cis*-$[PtCl_4(NH_3)_2]$ that not ascorbate or a Pt^{II}-catalyzed reaction is responsible for the Pt^{IV} reduction but the doubly deprotonated form of ascorbic acid A^{2-} (211, 212), even though it represents less than 1% of ascorbic acid at pH 7. The authors assume that the electron transfer from ascorbate to the Pt^{IV} center involves a reductive attack by A^{2-} /HA^- on one of the halido ligands forming an activated halido-bridged complex with subsequent elimination of two *trans* ligands and formation of Pt^{II} (211). In a further study of this group, the reduction of satraplatin by ascorbate to JM118 was investigated (Fig. 9). It was found that only A^{2-} and not HA^- was able to reduce satraplatin at pH 7 with a suggested outer-sphere mechanism as described above (212). Recently, Gibson *et al.* analyzed the reduction of a doubly labeled *cis*,*trans*,*cis*-

$[Pt^{IV}Cl_2(OCO^{13}CH_3)_2(^{15}NH_3)(n\text{-butylamine})]$ complex by ascorbate at pH 7 with $[^1H,^{15}N]$ and $[^1H,^{13}C]$ HSQC NMR spectroscopy. Interestingly, the NMR pattern revealed that the elimination by ascorbate did not only lead to the expected product $[Pt^{II}Cl_2(^{15}NH_3)(n\text{-butylamine})]$ without the two axial acetato ligands, but also to complexes that have lost one axial acetato and one equatorial chlorido ligand, or two equatorial ligands, suggesting the existence of multiple reduction mechanisms (124, 268). These findings confirm that the reduction of Pt^{IV} by ascorbate might depend on several factors and that diverse reduction pathways can take place.

As discussed above, it is thought that sulfhydryl groups are major players in the reduction of Pt^{IV} compounds. However, in the case of satraplatin, there is so far no evidence for reduction by GSH, methionine, or cysteine. Recently, a new possible mechanism was suggested by Carr and colleagues (55). They investigated the reduction of satraplatin by heme-containing metalloproteins, such as cytochrome c and hemoglobin, and the role of their iron atoms. Satraplatin was stable in solutions containing hemoglobin or NADH alone. However, when hemoglobin and NADH were combined, satraplatin was reduced mainly to JM118. As this reaction could be inhibited with carbon monoxide, which inhibits heme-containing proteins by binding to the heme-iron, involvement of the heme ferrous iron was suggested. Similar results were obtained with cytochrome c. In contrast, reduction of satraplatin by cysteins in hemoglobin was, comparable to GSH, not observed, as shown by incubation with a sulfhydryl blocking agent (55). The role of redox-active proteins in the reduction of platinum(IV) complexes in the cellular environment is supported by differing reduction rates of *cis,trans,cis*-$[Pt^{IV}Cl_2(OCO^{13}CH_3)_2(NH_3)_2]$ in aqueous extracts measured for several cancer cell lines. Interestingly, kinetics found for the high-molecular-weight fraction (>3 kDa) of the extracts was very similar compared to the whole cell extracts, whereas the low-molecular-weight fraction (<3 kDa), including GSH, was nearly ineffective in reducing Pt^{IV} (267). However, biological data from several studies demonstrated an impact of GSH and other intracellular reductants on the activity of Pt^{IV} complexes. Nevertheless, it has to be considered that there are still major missing links to understand the intracellular mechanisms of these reactions. Also, the impact of intracellular enzymatic reduction by, for example, one-electron reductases is relatively unexplored (89, 90).

Consequently, “what do we really know about it?” asked Gibson critically in a recent review about the mechanism of action of platinum agents (124). He addressed the problem that most of the information on the mechanism of action of platinum compounds comes from cell-free analyses of biologically relevant molecules—for example, nucleosides—in aqueous solutions coincubated with platinum drugs using chemical methods, which lack the sensitivity and specificity necessary to characterize the platinum species in biological solutions. On the other hand, biochemical analyses of biological fluids, cells, or animals treated with the drugs have insufficient resolution to characterize platinum adducts at the molecular level (124).

B. Gold

The medical use of gold (Au) has a long history. Already the ancient Egyptians used gold compounds as therapeutic agents and alchemists made elixirs of “drinkable gold,” as it was believed that gold has immortalizing properties. The rational use of gold compounds in medicine started with the application of gold cyanide against tuberculosis in the 1920s. However, due to severe toxicities the treatment was changed to less toxic gold(I)thiolate complexes, namely, aurothiomalate and aurothioglucose (Fig. 11). These complexes were also applied against rheumatoid arthritis, an autoimmune inflammatory disease, which was thought to be a disease related to tuberculosis (250). In 1985, auranofin, [tetra-O-acetyl-β-D-(glucopyranosyl)thio](triethylphosphine) gold(I) (Fig. 11), was approved as orally available drug against rheumatoid arthritis, which was less toxic but also less efficient. However, auranofin still causes enormous side effects and only a subgroup of patients responds to the treatment. Due to this, only severe cases of rheumatoid arthritis are currently treated with Au^{I} drugs (250, 272). The success of cisplatin in cancer therapy and a prospective long-term study which showed that rheumatoid patients treated with Au^{I} compounds had a lower rate of malignancies than those treated with other drugs (117), led to a comprehensive search for Au^{I} and Au^{III} complexes against cancer. However, beside auranofin no further gold compound was so far approved for the treatment of any disease. Currently, aurothiomalate is investigated in a phase I study against advanced nonsmall cell lung cancer (clinicaltrials.gov identifier: NCT00575393).

1. Gold(I)—Gold in its elemental form is stable in a wide range of conditions. The oxidation states of gold range from −1 to + 5, out of which 0 ($d^{10}s^{1}$), + 1 (d^{10}), and + 3 (d^{8}) are the most important ones. The coordination geometry of the gold(I) complexes is usually linear (two ligands), even though there can also be a trigonal three-coordinate or a tetragonal four-coordinate sphere surrounding the gold center (343). Like Pt^{II}, Au^{I} is regarded as a soft acid in the HSAB concept and prefers soft ligands (bases), as, for example, thiolates, cyanides, phosphines, and soft halides. Main representatives of Au^{I} complexes with anticancer activity are aurothiomalate, aurothioglucose, auro(bis)thiosulfate, and auranofin (Figs. 11 and 12). With exception of the latter, these complexes form polymers with Au^{I} connected *via* thiolate sulfur bridges (343). In general, Au^{I} complexes are thought to be pro-drugs because they rapidly exchange their ligands and several gold-containing metabolites are formed. In the blood, for example, one of the major anchoring sites is the deprotonated cysteine-34 of serum albumin. In the case of auranofin, the binding leads to a release of the triethylphosphine ligand and consequently to oxidation to Au^{III} (76). For the cellular Au^{I} uptake it has been postulated that the albumin-bound Au^{I} and other metabolites can be transported into and out of cells *via* a thiol-shuttle (357).

Important metabolites of Au^{I} complexes are dicyanoaurate(I) ($[Au^{I}(CN)_2]^-$), metallothionein—and glutathione—Au^{I} complexes (104, 207, 284). In general, it is believed that, due to their thermodynamical stability, Au^{I} drugs do not change their oxidation state *in vivo*. However, there is evidence for the generation of Au^{III} species by powerful oxidants such as hypochlorite, an immunological oxidant at inflammation sites. Hypochlorite is involved in the generation of the metabolite $[Au^{I}(CN)_2]^-$, which can be found in the blood and urine of gold-treated patients. During an oxidative burst in granulocytes and macrophages cyanide is generated from thiocyanate and hypochlorite, which can further react *in vivo* with Au^{I} drugs to form $[Au^{I}(CN)_2]^-$. Further, it has been shown that $[Au^{I}(CN)_2]^-$ can be oxidized by hypochlorite to Au^{III} species, such as tetracyanidoaurate ($[Au^{III}(CN)_4]^-$) (53). As shown by electrospray ionization-mass spectrometry, GSH can then reduce the generated Au^{III} species through the two intermediates $[Au(CN)_3(GS)-H]^{2-}$ and $[Au(CN)_2(GS)_2]^{3-}$ back to $[Au^{I}(CN)_2]^-$ (417). In general, formation of $[Au^{I}(CN)_2]^-$ species leads to an enhanced gold uptake into red blood cells and has been connected to enhanced side effects. Therefore, a better understanding of the $Au^{I/III}$ redox cycling is of great interest for the clinical use of gold compounds (53, 343).

In several studies, a number of Au^{I} complexes showed *in vitro* and *in vivo* anticancer activity. Most of the initially developed Au^{I} compounds, including auranofin, are active in animal models against leukemia but not against solid tumors. The greatest activity was achieved when Au^{I} was coordinated to phosphine- and thiosugar-ligands. Based on this knowledge, a series of Au^{I}-phosphine complexes was synthesized. On the one hand, neutral two-coordinate complexes, such as auranofin and [chlorido(triethylphosphine)gold(I)] (Fig. 12) exist on the other hand, a group of cationic, tetrahedral Au^{I} complexes with two chelating bis(diphenylphosphine)ethane (DPPE) or bis(di-2-pyridylphosphino)propane (D2PYPP) ligands (Fig. 12) have been developed.

Initially, it has been thought that Au^I compounds target DNA similar to cisplatin. However, later it has been shown that DNA is not the primary target (202). In addition to the above described redox cycling of Au^I compounds, an interaction with cellular redox processes by targeting mitochondria has been demonstrated (160, 161, 307). One of the earliest observed effects after $[Au(DPPE)_2]^+$ treatment in cisplatin-sensitive or -resistant murine P388 leukemia cells as well as in rat hepatocytes was the decrease of ATP concentration and stimulation of mitochondrial respiration. It has been suggested that $[Au(DPPE)_2]^+$ caused an uncoupling of oxidative phosphorylation, and thus inhibition of oxidative ADP phosphorylation (159, 356). One of the major impacts of Au^I substances on redox homeostasis of cancer cells is the inhibition of the cytosolic and mitochondrial Trx system (compare Section II.*A*.) (122, 378, 389). Due to the high affinity of Au^I to soft ligands (122), it is not surprising that Au^I complexes might bind to the selenium atom of TrxR and thereby inhibit the activity of both cytosolic and mitochondrial TrxRs. In combination, TrxR inhibition and disturbance of mitochondrial respiration lead to increased ROS, mitochondrial swelling, a decrease in mitochondrial membrane potential, and subsequently to apoptosis. Additionally, it has been shown that auranofin inhibits the TrxR1 in a p53-independent manner (153). Similar to cisplatin (compare Section V.*A*.1.), Au^I complexes effect the GR and Gpx system only at higher concentrations. Explanations for this are either the structure of the active site or the lability of the gold–ligand bonds (122, 209). Further, it has been shown that the generation of H_2O_2 by Au^I complexes did not cause significant lipid peroxidation. Therefore, it was concluded that there is no generalized oxidative stress responsible for Au^I-induced cell death. Additionally, no enhanced nitric oxide production and no alterations in GSH levels or its redox status were observed (320). Next to alterations of the GSH- and Trx-system, auranofin potently induces HO-1 expression by activating Keap1/Nrf2 signaling *via* Rac1/iNOS induction and MAPK activation (196) (Compare Section II.*B*.). Further, it has been shown that auranofin can inhibit the activation of STAT3, NF-κB, and the homodimerization of toll-like receptor 4 (177, 195, 420).

2. Gold(III)—Au^{III} is isoelectronic and isostructural with Pt^{II} and forms therefore also square-planar four-coordinate complexes. However, due to the high reactivity of Au^{III} complexes and reduction to Au^I or Au^0 under physiological conditions, it has been questioned whether they might be useful drugs. Nonetheless, there is a growing interest in Au^{III} complexes, as novel substances with improved stability are available (Fig. 13). Au^{III} complexes can be divided in four subgroups, namely, (i) classical square-planar mononuclear gold(III) complexes, most often with nitrogen or halide ligands, (ii) gold(III) porphyrins, (iii) organometallic gold(III) compounds with carbon-gold bonds, and (iv) oxo-bridged dinuclear gold(III) complexes (272). In contrast to Au^I complexes, there is a greater affinity of Au^{III} for DNA and the binding can be both electrostatic and covalent. However, several studies suggest that the formed Au^{III}-DNA adducts are less stable than that formed by cisplatin (236, 322) presumably because of lower hydrolytic stability (57, 322).

Similar to Au^I complexes (and platinum(II) drugs), Au^{III} compounds are known to strongly target sulfur-containing amino acids (preferably cysteins), imidazole (His), and selenol groups (selenocysteine) of proteins. Therefore, it is not surprising that for a great number of Au^{III} complexes inhibition of the TrxR and disruption of the mitochondrial functions have been proposed as major modes of action (272). The GSH reductase system is only inhibited at higher concentrations of Au^{III} drugs, comparable to Au^I compounds (321).

Two proteomic studies support the general idea that Au^{III} disturbs the cellular redox balance (229, 395). Next to the Au^I complex auranofin, $[Au_2(6,6'\text{-dimethyl-}2,2'\text{-bipyridine})(l\text{-}O)_2]PF_6$ (Auoxo6) (Fig. 13), an oxo-bridged dinuclear Au^{III} complex, and Au^{III} porphyrin 1a (Fig. 13), alter proteins involved in the cellular redox homeostasis, including Trx and peroxiredoxin 1 and 3 (395). Based on these data, it has been proposed that Auoxo6 has a mode of action comparable to auranofin. The observations strongly suggest that Auoxo6 is reduced to a Au^{I} species in the biological milieu (229). This hypothesis is supported by a previous study with a series of dinuclear Au^{III} complexes, including Auoxo6. In cell-free systems, ascorbic acid, and GSH, added at a slight excess, caused a relatively fast and complete reduction of the Au^{III} centers. Further, interactions with human serum albumin, horse heart cytochrome c, and bovine ubiquitin were analyzed spectrophotometrically. The spectral patterns suggested a progressive reduction of Au^{III} centers and a concomitant appearance of the respective free ligands. The authors concluded that all tested compounds retain significant oxidizing properties and, thus, may undergo important redox-driven transformations within a reducing biological environment (57).

Next to the inhibition of TrxR, a variety of mechanisms of action were proposed for Au^{III} complexes, such as the modulation of kinases and proteasome inhibition (272). Interestingly, inhibition of ROS production by NAC reversed the inhibition of the proteasome by a Au^{III}-dicarbamato complex (AUL12) (Fig. 13). Even though analyses with the Au^{I} analog AUL15 resulted in a similar outcome, this substance did not induce the production of ROS. Therefore, the authors suggest that different redox-dependent and -independent mechanisms are responsible for the overall different effects of Au^{I} and Au^{III} complexes (428).

C. Arsenic

Arsenic (As) has two biologically important oxidation states, As^{III} and As^{V}. As^{III}, as a soft metal ion (comparable to Pt^{II} and Au^{I}), preferentially reacts with sulfur- and nitrogen-containing residues of proteins, such as thiols in cysteines and imidazole nitrogens in histidine residues (compare Section IV.*C*., V.*A*.1., and V.*B*.1.). The interaction with thiols can generate stable cyclic dithioarsinite complexes in which both sulfur atoms are bound to arsenic. These reactions can cause loss of function of the involved proteins and might be a key factor of arsenic cytotoxicity (93). As^{III} compounds are known to interfere with and disturb the oxidation/reduction equilibrium through complex redox reactions involving the cellular oxidant/antioxidant systems, including GSH and TrxR (225) (compare Section II.*A*.). In contrast, As^{V} compounds, whose biological activity is mainly based on substitution for phosphate in molecules like ATP, are significantly less cytotoxic as compared to As^{III} (271, 298).

Arsenic compounds have been used by humans in many respects since ancient times for example in various alloys, and as pesticides, herbicides, insecticides, and also for medical purposes [for review see (271)]. Thus, some of the oldest remedies known include arsenic. These compounds were empirically discovered as treatment for diverse diseases and in variable preparations, including external pastes, oral preparations, and injections. Also, in traditional Chinese medicine, arsenic acid and arsenic trioxide (ATO) (Fig. 14) were used as antiseptic agents or in the treatment of rheumatoid diseases, syphilis, and psoriasis. In the Western world the potassium bicarbonate-based Fowler's solution of ATO for oral use developed in 1788 was frequently applied against aczema, asthma, and psoriasis but also against malignant diseases including leukemias like CML and Hodgkin's disease. In fact, already Celsus in the first century AC had suggested activity of arsenic against solid tumors (271). During the 18th and 19th century ATO represented the main treatment for leukemia and its importance remained until the development of modern radio- and chemotherapy during the 20th century. Then ATO was replaced by novel chemotherapeutic regimens and in part was abandoned based on chronic toxicity in treated patients. Surprisingly, during the 1990ies a Chinese group reported an exceptionally high rate of complete, long-lasting remissions after ATO treatment in a small cohort of patient with acute promyelocytic leukemia (APL), a specific subtype of acute myeloid leukemia (AML) (66, 344, 431). These promising initial data were proofed in larger patient cohorts and international randomized studies (359, 360), leading to the approval of ATO for the treatment of APL in 2000.

Concerns remained about arsenic poisoning and secondary malignancies known to result from long-term environmental exposure to inorganic arsenic mainly due to drinking water contamination (339). However, long-term observations (mean 70 months since treatment) in China did not indicate a higher risk for secondary malignancies in 85 alltrans retinoic acid/ ATO-treated APL patients and urine arsenic levels had returned to levels far below the safety limit 24 months after the last treatment (167).

Based on the persistent environmental exposure, sophisticated metabolic pathways have developed during evolution allowing efficient detoxification of arsenic-containing compounds, which now also impact on ATO as clinically applied drug. The redox-driven metabolism has been studied extensively concerning environmental intake and toxicity, whereas specific studies on ATO as cancer therapeutic are comparably sparse. Immediately after dissolution of ATO in water, it forms arsenous acid (H_3AsO_3), the trivalent hydrolysis product of ATO (367), which is thought to be the pharmacologically active form of ATO. Arsenic is progressively methylated during its metabolism/detoxification involving a series of oxidation and reduction steps (Fig. 15). *S*-Adenosylmethionine represents the major methyl donor for these reactions. In general, only arsenic(III) species (e.g., inorganic arsenic(III) compounds or monomethyl arsenous acid) can be methylated by the arsenite methyltransferase to the respective arsenic(V) metabolites (monomethyl arsonic acid or dimethylarsinic acid). Thus, continual reduction steps are necessary to allow progressive methylation reactions. Several enzymes have been suggested to drive these reductions including most importantly glutathione-*S*-transferase omega (GSTO)—involving GSH as a reductant—(422, 423) and recently also a glyceraldehyde-3-phosphate dehydrogenase (132). As GSTO (−/−) mice are still able to reduce As^V (75), it was also suggested that arsenite methyltransferase might itself harbor the respective reductive activity, whereas Trx and NADPH are used as electron donors (339). Consequently, this enzyme would be sufficient for sustaining the whole methylation pathway which was experimentally confirmed at least in cell-free systems (216, 401).

In addition to this well-described oxidative methylation pathway, recently a reductive methylation pathway was discovered (150), circumventing the need for subsequent oxidation/reduction steps and involving the formation of an arsenic triglutathione complex (Fig. 15). This complex is a direct substrate of arsenite methyltransferase catalyzing the formation of methylarsenic diglutathione and dimethylarsenic glutathione, which are hydrolyzed at low GSH concentrations followed by H_2O_2-mediated oxidation to monomethylarsonic and dimethylarsinic acids (13, 271). Little is known to what extent these methylation pathways are important during treatment of APL patients with ATO.

With regard to its anticancer activity, the mechanisms underlying the mode of action of ATO are complex and cell type-dependent (107). However, it has to be stated that in general DNA damage, which is frequently suggested for metal-containing anticancer agents, is not involved in the activity of ATO. Besides direct interaction with the APL-specific PML-RARα fusion protein (429), a multitude of studies in diverse cell types have indicated that ATO-induced cytotoxicity is at least in part based on the enhanced production of ROS including H_2O_2, superoxide anion, and hydroxyl radical in a Fenton-like reaction (compare Section IV.*A*.) and consequently in radical-mediated signals/damages (43, 180).

Paul *et al*. suggested that ROS production was mainly mediated *via* an electron transfer inhibition of complex I of the electron transport chain of the mitochondria, whereas no significant effects on complex II and III were detected (292). This is in good agreement with the fact that ATO-induced apoptosis is mainly characterized by progressive mitochondrial membrane depolarization, and enhanced radical stress. Accordingly, bcl-2 family members exerting their apoptosis-regulatory mechanisms mainly at the outer mitochondrial membrane have major impact on ATO-induced cytotoxicity. Additionally, mitochondrial protein translation by thiostrepton-sensitized melanoma cells against ATO (44). Moreover, ATO has been characterized as an "oxidative stress-sensitive drug," meaning that cells under enhanced ROS-mediated stress are hypersensitive against ATO (419). Thus, the anticancer activity of ATO and the exerted side effects are strongly influenced by the cellular redox status and the functionality of radical-scavenging protection systems like the GSH and Trx systems (compare Section II.*A*.). Nevertheless, it has to be mentioned that several recent studies challenged the role of ROS in ATO-mediated apoptosis induction. Morales *et al.* demonstrated that the strong ATO-mediated antioxidant response, mainly mediated by the antioxidant-induced transcription factor Nrf2 (compare Section II.*B*.), is not required for ATO-induced apoptosis in four myeloma cell models (255). Neither Nrf2 down-modulation by siRNA nor ROS inhibition by butylated hydroxyanisole (BHA) protected cells from ATO. Surprisingly, ROS generation was even dispensable from Nrf2 activation. Interestingly, also the ATO-chelating cysteine-rich MTs (Compare Section II.*B*.), well-known to mediate protection against environmental metals, were inefficient to block ATO-mediated apoptosis.

In contrast to ROS, the role of GSH in the regulation of ATO cytotoxicity is beyond dispute. An inverse correlation between the cellular GSH content and the activity of ATO has been demonstrated in multiple cancer models (107). Stimulating the activity of GSH peroxidases by pretreatment with selenite-mediated ATO resistance in APL cells (180). Upregulation of GSH levels by, for example, *N*-acetylcysteine (NAC) or lipoic acid protected leukemic and solid tumor cells against ATO (87). Accordingly, GSH depletion by BSO (87, 107, 410, 414) or ascorbic acid (87, 125, 131) distinctly enhanced ATO cytotoxic activity against multiple cancer cell types. Moreover, treatment with ATO itself reduced the cellular GSH content (142). Consequently, ATO exerts synergistic activity with several other agents disturbing the cellular redox/ROS status, including, for example, substances of natural origin like isoflavones (329), the α-tocopherol (vitamin E) analog trolox (92), and cisplatin (427). Assuming a role of ROS in ATO-mediated cytotoxicity, GSH might exert its protective function mainly as a radical scavenging agent. Indeed, GSH binds arsenic to form a transient $As(GS)_3$ complex (see above), thus preventing the inhibition of cellular redox-regulatory enzymes. Moreover, reduction of pentavalent to trivalent arsenic can occur nonenzymatically with GSH as electron donor, or *via* GSTO again involving GSH as a reductant. Additionally, as arsenic is believed to involve electrophilic attacks of cysteine residues in cellular proteins, GSH might function as a substrate sequestering arsenic from critical cysteine-containing cellular proteins (370, 386).

A second important cellular redox stabilization system influenced by ATO is Trx together with its reducing enzyme TrxR (compare Section II.*A*.). Also, overexpression of Trx-1 protected cancer cells against ATO-mediated mitochondrial apoptosis induction (375). When TrxR was inhibited by dinitrochlorobenzene (DNCB) or natural compounds (e.g., isoflavonoids), cells were sensitized toward ATO, again indicating that reduced Trx can counteract ATO-mediated cytotoxicity (178, 375). Consequently, it was shown that ATO itself is capable of inhibiting TrxR by interaction with the enzyme's active site (225). Additionally, arsenites and the trivalent metabolite monomethylarsonic acid were identified as potent inhibitors of TrxR (219). Moreover, besides GPx, TrxR belongs to the most important cellular selenocysteine residue-containing proteins (compare Section II.*A*.) and arsenic is well known to interfere with the selenium metabolism in a redox-dependent manner. Accordingly, as an additional interaction between ATO and the cellular redox system, significant impacts of ATO and/or its metabolites on the expression of GSH and Trx have been reported (123, 369). Further, ATO was suggested to induce ER stress-mediated apoptosis in human neutrophils (38), again suggesting proteins as direct targets of ATO-mediated cytotoxicity.

In general, research on arsenic-containing anticancer drugs focused so far mainly on ATO. However, some other compounds were investigated with regard to their anticancer activities. Hence, darinaparsin (ZIO-101; Fig. 14)—a dimethylated arsenite compound linked to GSH —seems to be active against a wide variety of hematologic and solid tumors and to exert less severe side effects (387). Comparable to ATO, darinaparsin induces apoptosis *via* the mitochondrial pathway. However, it does not impact on bcl-2 and the oncogenic APL fusion protein. Moreover, this compound exerts even stronger ROS production as compared to ATO. In contrast to ATO, the cytotoxicity of darinaparsin is not dependent on intracellular GSH levels and it exerts activity against ATO-resistant tumors (235, 241). In general, mode of action data for this compound are very limited so far. Nevertheless, this novel arsenic compound has been evaluated in several phase I/II studies, whereby one phase II study with intravenous application of darinaparsin in hepatoma failed to show clinical benefit and consequently was terminated after the first stage of efficacy analysis (409). In contrast, a phase I study at a different schedule demonstrated promising activity in several therapy-refractory solid tumor types (387). Another example for an organic arsenic compound, *S*-dimethylarsinothiosuccinic acid (MER1, Fig. 14), demonstrated PML-RAR-independent, ROS-mediated cytotoxic activity against cancer cells *in vitro* and limited toxicity *in vivo* (128). However, clinical evaluation of this compound has not been reported so far. 4-(*N*-(*S*-glutathionylacetyl)amino)phenylarsonous acid (GSAO, Fig. 14) is a small, synthetic mitochondrial poison containing trivalent arsenic that targets angiogenic endothelial cells (92) and is currently being tested in a phase I clinical trial (NCT01147029) (97) and first antivascular activities were reported from that study at ASCO 2010 (J Clin Oncol 28:15s, 2010; suppl; abstr TPS167). GSAO is believed to exert its antiangiogenic activity by interacting with two cysteines of the adenine nucleotide translocator (ANT) at the inner mitochondrial membrane. Inactivation of ANT by GSAO causes increase in superoxide levels based on mitochondrial damage, proliferation arrest, ATP depletion, mitochondrial depolarization, and apoptosis in endothelial cells. GSAO is processed at the cell surface and in the cytosol especially by γ-GT before reacting with mitochondria (94). Whether redox mechanisms are involved in the anticancer/antiangiogenic activities is widely unknown.

D. Ruthenium

Ruthenium (Ru) is a relatively rare element, which has, to current knowledge, no biological functions. Ru compounds occupy a wide variety of oxidation states (−2, 0, + 2, + 3, + 4, + 6 and + 8), of which Ru^{II} and Ru^{III} are most relevant in biological environment, and different coordination geometries are known, that are, tetrahedral, square-pyramidal, and octahedral (162, 164).

Ruthenium complexes are among the best studied non-platinum metal complexes with anticancer activity, and two candidates, KP1019 and NAMI-A (Fig. 16), have recently been tested in clinical phase I trials. KP1019 was developed for solid tumors, whereas NAMI-A was developed as a purely antimetastatic drug. Both compounds proved to be tolerable with only minor side effects, especially in case of KP1019, whereas formation of blisters was considered as dose-limiting toxicity in case of NAMI-A (95, 149, 308). Additionally, 5/6 and 1/24 patients with solid tumors obtained a stable disease after treatment with KP1019 and NAMI-A, respectively (149, 308). Next to Ru^{III} compounds, there are currently several promising organometallic Ru^{II} complexes with arene ligands (Fig. 16) in preclinical evaluation (45, 413).

With regard to their modes of action, ruthenium complexes have been assumed to target DNA comparable to platinum drugs and the DNA-binding properties of ruthenium compounds have been studied extensively mainly under cell-free conditions. However, although Ru has been detected in nuclei and bound to extracted DNA of cells after drug treatment, there is increasing evidence that the anticancer activity of some ruthenium compounds, like KP1019 and NAMI-A (77, 79, 154), but also of some Ru^{II}(arene) complexes (57), is not based on direct DNA damage. Ru^{III} compounds are characterized by a high affinity to (serum) proteins, which has been suggested to be crucial for drug accumulation into the tumor tissue and to be responsible for the minor adverse effects observed in clinical trials with KP1019 (365, 377).

Ruthenium complexes can be divided into two major classes, namely, octahedral Ru^{III} complexes and piano-stool Ru^{II} compounds. The classical octahedral Ru^{III} coordination compounds, like KP1019 or NAMI-A, feature a ruthenium center, which is usually able to be reduced and reoxidized in the cellular environment. The ability of the cellular redox systems to reduce/oxidize the ruthenium complex strongly depends on the exact coordination sphere. For example, in an extensive study on the role of the number and nature of the azole ligands on the antiproliferative activity and their redox potentials, a significant correlation for these parameters was found for a series of mono-, bis-, tris-, and tetrakis indazole/imidazole complexes (14, 173, 317). Thus, for the bis(indazole) complex KP1339 (redox potential ~0.03 V vs. NHE) an IC$_{50}$ of ~120 μM was observed, whereas for the bis(imidazole) complex KP418 (redox potential −0.24 V vs. NHE) even 300 μM did not induce 50% growth inhibition in SW480 cells (186). In contrast to the Ru^{III} compounds, Ru^{II}(arene) "piano-stool" complexes are normally unable to change their +2 oxidation state due to stabilization by the -bonded arene ligand.

Comparable to Pt^{IV} and some Co^{III} compounds (compare Section V.*A*.2. and V.H.), the principle of "activation by reduction" is a central hypothesis in the mode of action of many Ru^{III} drugs. However, there are some major differences between Pt^{IV} and Ru^{III} complexes: reduction of the Pt^{IV} center to Pt^{II} induces profound changes in their coordination geometry (from octahedral to square-planar) and leads to ligand release, whereas the coordination geometry of Ru compounds remains widely unchanged upon reduction (318). However, for both Ru^{III} and Pt^{IV} complexes reduction causes labilization and subsequent ligand exchange reactions, such as Cl to aqua in case of KP1019 (318, 338). Consequently, reduction facilitates and often increases reactivity with biomolecules and, in some cases, even determines the structure of the formed adducts. For example, in case of ethylenediaminetetraacetato (EDTA) Ru complexes, binding to the N3 and N7 atoms of GMP was found to be dependent of the Ru oxidation state (63).

The reduction of Ru^{III} compounds by GSH and other biological reductants such as ascorbic acid has been extensively investigated, however, mainly in cell-free settings. Notably, due to the tight binding of Ru drugs to serum proteins the extracellular reduction of the Ru center seems improbable (300, 376). Consequently, it is assumed that reduction of ruthenium compounds takes place inside the cell after release of the Ru moiety from its biological carrier, which makes the Ru complex accessible for reduction (291). As DNA has been in the focus as major intracellular target for a long time, many experiments have been performed using DNA as reaction target (77, 80, 116, 334). Such studies show, for example, that the selectivity of $[Ru(NH_3)_5Cl]^{2+}$ (Fig. 16) for DNA bases is influenced by GSH. The reaction with adenine and cytosine and the cleavage of such adducts is less affected by GSH, whereas the binding to guanine is significantly altered (116). Moreover, agarose gel electrophoresis studies with plasmid DNA and $[Ru^{III}(NH_3)_5]$ complexes revealed in presence of a reducing agent and O$_2$ moderate DNA cleavage ability, potentially *via* a hydroxyl radical mechanism, whereas coordination of a $[Ru^{III}(NH_3)_5]$ to DNA did not cause DNA cleavage (78).

Several studies indicate that reduction of ruthenium facilitates reaction with biomolecules only at low GSH concentrations (116, 338). At higher GSH concentrations often decreased reactivity (149, 338) probably due to coordination of GSH to the reduced species and reoxidation to Ru^{III} was observed. Interestingly, also in case of some Ru^{II}(arene) complexes (99, 393) redox reactions with GSH were reported in cell-free settings, although the Ru^{II} center itself is usually unable to participate in redox reactions (148). Notably, the kind of interactions with GSH differ between the diverse Ru^{II}(arene) complexes. For example, GSH conjugation to the Ru center by substitution of the chlorido ligand was reported in case of 1,2-ethylenediamine (en) complexes (393). In the case of phenylazopyridine Ru^{II} complexes the ligand is reduced causing catalytic oxidation of GSH to GSSG, in contrast to the metal-free ligand alone which is redox inactive (99). Also, for a Ru(arene)(en) complex bearing thiolato ligands such as isopropyl- and phenylthiolates, oxidation of the ligand as well as of GSH was observed in the presence of oxygen, which is reduced to ROS (299). Together, this indicates that already in cell-free systems the reaction pathways of ruthenium complexes are very complex and difficult to predict. As only a few studies have been performed on living cells, the *in vivo* situation is even less understood. Some of these experiments support the hypothesis of activation by GSH-mediated reduction also *in vivo*. Thus, enhanced activity of several Ru^{III} compounds (including KP1019 and analogs) has been reported against the cisplatin-resistant cell model O-342/DPP, which is characterized by enhanced GSH levels (118, 426). In case of Ru^{II}(arene) drugs the activity against GSH-overproducing cisplatin-resistant A2780cis cells differed throughout the tested compound panel (6). However, there are also reports on the protective effects of intracellular GSH levels against Ru^{III} drugs. For example, depletion of the intracellular GSH pools by pretreatment with BSO led to increased sensitivity of cancer cells to $[Ru(NH_3)_5Cl]^{2+}$ (116) or KP1019 (155), and pretreatment with the radical scavenger and GSH precursor NAC protected human colon carcinoma cells against KP1019-induced ROS (185). Consequently, a comprehensive, detailed analysis of the *in vivo* interaction of intracellular GSH pools with ruthenium compounds and its impact on their activity seems urgently needed for better understanding of the mode of action of this class of compounds.

Besides GSH, there are also some recent reports on TrxR inhibition (compare Section II.*A*.) by Ru^{III} as well as Ru^{II}(arene), in particular, RAPTA compounds (Fig. 16) (58, 261). In contrast to sodium arsenite which targets TrxR1 and TrxR2, the tested ruthenium compounds mainly inhibited the cytosolic TrxR1 in cell-free experiments. As both Ru^{III} and Ru^{II} compounds display this inhibitory potential, it seems unlikely that redox interactions of the Ru core are responsible for the TrxR1 inhibition.

Interestingly, several Ru^{III} compounds (including NAMI-A and KP1339, the sodium salt of KP1019) have been identified as direct nitric oxide (NO) scavengers by Moribelli *et al.* (256). Comparable to $O_2^{\bullet -}$, the highly reactive NO$^{\bullet}$ is known as intracellular and intercellular messenger for diverse physiological processes especially in vascular homeostasis and neurotransmission as well as inflammatory/immune response and tumor progression (31). Under serum-free conditions, Ru^{III} drugs react with NO$^{\bullet}$, which lead to reduction of Ru and formation of a Ru-NO moiety (256). This NO$^{\bullet}$ scavenging was shown to inhibit endothelial cell migration and angiogenesis especially in case of NAMI-A. Consequently, it seems likely that the antiangiogenic activity of NAMI-A might be related to this NO-scavenging activity.

In summary, although the exact modes of action of ruthenium compounds are still not fully understood, there is ample evidence that redox reactions and interference with the cellular redox balance play an important regulatory role in the anticancer activity of many ruthenium compounds.

E. Copper

Copper (Cu) is one of the most important transition metals in human physiology and, consequently, its uptake and distribution are tightly regulated (compare Section III.*B*.).

Moreover, there is growing evidence that elevated copper levels are associated with cancer (134). There are currently several approaches to target cancer cells by diverse copper chelating agents, which include besides D-penicillamine, clioquinol, and trientine also the molybdenum-containing tetrathiomolybdate (compare Section V.*I*.). However, despite some rather early reports regarding the activity of copper complexes *in vivo* (331), the development of copper-containing compounds as anticancer agents remained in most cases at a very early stage of preclinical development and clinical studies are so far missing.

With regard to redox properties, the current knowledge on Cu compounds is primarily based on investigations using Cu complexes of α-*N*-heterocyclic carboxaldehyde thiosemicarbazonates (Cu-TSC) (52), 2,2′-bipyridyl-6-carbothioamide (Cu-BPYTA) (273, 274), and of 1,10-phenanthroline (Cu-phen) (Fig. 17). As BPYTA shares several structural and functional characteristics with thiosemicarbazones, it is not surprising that their modes of action seem to be widely similar. Both are well-known tridentate chelators and have been used for the synthesis of a wide range of metal complexes, including besides Cu also Fe, Co, Zn, Ni, or Ga (204, 274, 328, 331, 421). With regard to their modes of action, metal-free BPYTA (274) as well as thiosemicarbazones like triapine (342, 421) are known for their ribonucleotide reductase (RR) inhibitory potential (compare Section III.*A*.2.). The RR inhibition is based on the disruption of the R2-localized tyrosyl radical and is believed to be executed by an intracellularily formed redox-active Fe complex of BPYTA or TSC, able to generate ROS by redox cycling between $Fe^{III/II}$. Comparably, also the copper complexes Cu-BPYTA (273) and Cu-TSC (264) were shown to inhibit the R2 tyrosyl radical, although it is widely unclear whether the underlying mechanisms are similar to their Fe complexes. Interestingly, addition of Cu to triapine significantly increased its RR inhibitory potential (111). It is not known whether 1,10-phenanthroline complexes are also able to inhibit the RR. However, we have recently revealed RR inhibition by the lanthanum 1,10-phenanthroline complex KP772, which was accompanied by the intracellular formation of an Fe-phen complex (156). In the light of these results interference with the RR tyrosyl radical by Cu-phen does not seem unlikely.

Cu complexes are well known for their redox activity, which seems to be at least involved if not responsible for most of their described biological activities (51, 242, 384). The redox cycling of Cu complexes is based on the reduction of Cu^{II} to Cu^{I} by intracellular thiols such as GSH under oxygen-containing conditions (compare Section II.*A*.) (12, 52, 72, 264, 332, 353). Schematically, the underlying reaction pathway for Cu-TSC is given in equations 10–12 (additional ligands like OH^- or H_2O are omitted for clarity; TSC = thiosemicarbazonato). Briefly, most Cu^{II} complexes rapidly form adducts with GSH (26, 230, 332), leading to Cu^{I} complexes and $GS^{\bullet}$. In the presence of oxygen, this Cu^{I} complex is able to generate a superoxide anion, which can induce ROS *via* a Fenton-like reaction (51, 52, 222, 384) (compare Section II.*C*.).

$$\left[\mathrm{Cu^{II}}\,(\mathrm{TSC})\right]^{+}+\mathrm{GSH}\rightarrow\left[(\mathrm{GS})\,\mathrm{Cu^{II}}\,(\mathrm{TSC})\right]+\mathrm{H^{+}}\quad 10$$

$$\left[(\mathrm{GS})\,\mathrm{Cu^{II}}\,(\mathrm{TSC})\right]\rightarrow\mathrm{GS^{\bullet}}+\left[\mathrm{Cu^{I}}\,(\mathrm{TSC})\right]\quad 11$$

$$\left[\mathrm{Cu^{I}}\,(\mathrm{TSC})\right]+\mathrm{O_2}\rightarrow\mathrm{O_2}^{\bullet-}+\left[\mathrm{Cu^{II}}\,(\mathrm{TSC})\right]^{-}\quad 12$$

For dianionic thiosemicarbazonato ligands (52) it was shown that the resulting Cu^{I} complexes are also able to form GSSG *via* the following reaction:

$$\left[\mathrm{Cu^{I}\,(TSC)}\right]+\mathrm{GSH}\rightarrow\left[\mathrm{Cu^{I}\,(GS)}\right]+\mathrm{TSC}+\mathrm{H^{+}} \quad 13$$

$$\left[\mathrm{Cu^{I}\,(GS)}\right]+\mathrm{GS^{\bullet}}\rightarrow\mathrm{GSSG}+\mathrm{Cu^{II}} \quad 14$$

These reactions lead to (transient) depletion of intracellular GSH pools, which has been frequently observed in cells after treatment with diverse Cu compounds (12, 190, 231, 242, 264). Elevated intracellular GSH levels and enhanced drug export by GSH-dependent multidrug-resistance transporters, such as MRP1 (ABCC1), are frequent handicaps for successful chemotherapy (compare Section II.*A*.) (155). Thus, the transient GSH depletion by Cu compounds came recently into focus of interest for overcoming of GSH-dependent drug resistance. Thus, an *N*-(2-hydroxyacetophenone)glycinato copper(II) complex CuNG (Fig. 17) was developed with the aim to reduce resistance of the MRP1-overexpressing and highly drug-resistant EAC/Dox cells to doxorubicin (231). Indeed, temporary GSH depletion by CuNG enhanced tumor response of these cells to doxorubicin against cancer cell lines and in a xenograft mouse experiment (230, 231). In these studies, a combination regimen consisting of 10 mg/kg CuNG and 2 mg/kg doxorubicin increased the mean survival of male Swiss albino mice from 19 to 87 days (230). Notably, CuNG treatment alone had no antitumor effects, although increased ROS levels in tumor, liver, and kidney tissue of the treated mice were observed (254). Accordingly, oxidative stress generation by CuNG led to stimulation of SOD and catalase activity, especially in heart and kidney tissue. In contrast, basal ROS levels in lung and heart tissue of EAC/Dox-bearing animals were significantly reduced by CuNG treatment (254). It has been recently reported that CuNG treatment significantly modulates the cytokine production of tumor-associated macrophages leading to decreased interleukin 10 and TGF-β production and increased interleukin 12 levels. As these effects were reversed by addition of the ROS scavenger tocopherol (vitamin E), it seems likely that the interplay of CuNG with redox homeostasis is responsible for these observations (64).

In a recent study it has been shown that a Cu^{2+} chelate of the novel thiosemicarbazone NSC689534 induces ROS and depletes GSH as well as protein thiols. Further, microarray analysis revealed the activation of several ROS connected pathways, such as oxidative and ER stress/UPR, autophagy, and metal metabolism by these compounds. *In vitro* studies confirmed an ER stress-dependent but autophagy-independent induction of apoptosis. Moreover, anticancer activity in a mouse *in vivo* model was demonstrated for this thiosemicarbazone copper complex (143).

In case of Cu-phen, the intercalation of its ligand, 1,10-phenanthroline, into the DNA minor groove allows DNA targeting, which enables redox reactions of the Cu core with DNA and RNA (309, 353). Consequently, Cu-phen has been used as footprinting reagent for the evaluation of protein-DNA interactions as well as a probe for DNA and RNA secondary structure. Thus, the redox-mediated interaction of Cuphen and derivatives with DNA in cell-free systems has been extensively investigated (21, 72, 121, 302, 309, 354, 425). In the presence of H_2O_2, the DNA-bound Cu^{I}(phen) complex is oxidized to form presumably Cu^{II}(oxo/hydroxo) species (237, 354). Thus, the reaction of Cu-phen with nucleic acids (especially B-DNA) is not *via* a diffusible species, such as hydroxyl radicals or freely diffusible chelates, but through the non-covalent, nondiffusible Cu-oxo/hydroxo intermediate (425). The main target was shown to be the DNA C-1 site of deoxyribose located in the minor groove (21, 206, 425), which leads to the production of 3′- and 5′-phosphomonoesters, free purine and pyrimidine, and 5-methylenefuranone (the oxygen source of the carbonyl group in the latter is water). A minor alternative reaction pathway involves DNA scission *via* C-4′ and C-5′oxidation (21, 354). However, it has to be kept in mind that all of these investigations have been performed under cell-free conditions and it is so far unknown, whether these interactions of Cu-phen with DNA have any relevance for its biological activity in living cells

F. Vanadium

Vanadium (V) is a transition metal existing in eight oxidation states, of which V^{IV} and V^{V} are the most important but also V^{III} and V^{II} might occur in biological systems (106). Vanadium is a trace element and essential for diverse animals, but its importance as a micronutrient in humans is not entirely clear. Vanadium compounds have been shown to interact with numerous cellular signaling mechanisms by influencing key enzyme families starting with inhibition of protein tyrosine phosphatases, in turn activation of protein kinases, and regulation of intracellular signal pathways, which results in altered expression of multiple genes (168). Consequently, vanadium compounds exert diverse biological and physiological effects, including insulin-enhancing activity, regulation of oxygen affinity to hemo- and myoglobin, reduction of hyperlipidemia, obesity, and hypertension as well as cardioprotective properties (260). In combination with relatively minor toxicity, these characteristics open multiple possibilities for the use of vanadium drugs as medical remedies. Indeed, vanadium was already used at the beginning of the 20th century for treatment of anemia, tuberculosis, and diabetes (257). In contrast to many other metal compounds developed as potential anticancer drugs, vanadium exerts rather chemopreventive than carcinogenic activity as demonstrated in several chemically induced tumor models (39). These chemopreventive effects are believed to be based on several properties, including (i) reduced generation of carcinogen-derived reactive intermediates, (ii) specific modulation of the antioxidant capacity, and (iii) induction of phase I as well as phase II detoxifying enzymes.

Besides those cancer-preventive effects, vanadium compounds have also been shown to exert anticancer effects against already established tumors, for example, by inhibition of proliferation, apoptosis induction, blockage of invasion, as well as metastasis (106). Nevertheless, it needs to be mentioned that several vanadium(V) and vanadium(IV) compounds were characterized as genotoxic, which is probably based on the induction of oxidative stress or the inhibition of protein tyrosine phosphatases, leading, in addition to activated cell proliferation, to improper spindle formation in mitosis or meiosis and, thus, aneuploidy (35).

The chemopreventive and anticancer activities are distinctly influenced by redox processes based on the chemical and biochemical characteristics of vanadium as a transition metal. In aqueous solution, vanadium exists either as tetravalent vanadyl (VO^{2+}) or pentavalent (meta)vanadate (VO_4^{3-};VO_3^{-}), whereby different monomeric and polymeric species can exist depending on pH and drug concentration. Both the redox reactions and the polymerization state seem to have a profound impact on the cytotoxic activity of vanadium compounds (106). In the human plasma, V^{IV} and V^{V} exist, though vanadyl predominates due to the efficient reduction of vanadate by several reductive components of the blood, such as ascorbic acid. The vanadium ions are bound to plasma proteins like transferrin and albumin and are taken up in this state into cellular compartments. Vanadium (V) might be reduced not only by GSH but also by flavoenzymes, for example, GR, or in microsomes both involving NADPH (eq. 15) and connected to the generation of hydroxyl radicals (347, 348, 350). As already mentioned in Sections II.*A*. and *B*., cancer cells are characterized by an altered pH, imbalance in the cellular redox homeostasis, and enhanced oxidative stress levels supporting radical generation reactions by vanadium compounds. Consequently, V^{IV} might interact with oxygen generating a superoxide anion and V^{V} in a Fenton-like reaction (Eqs. 16 and 17).

$$V^{V}+NADPH \rightarrow V^{IV}+NADP^{+}+H^{+} \quad 15$$

$$V^{IV}+O_2 \rightarrow V^{V}+O_2^{\bullet -} \quad 16$$

$$V^{IV}+H_2O_2 \rightarrow V^{V}+OH^{-}+OH^{\bullet} \quad 17$$

Peroxovanadium complexes, which can be formed during the above described reactions, are strong and irreversible inhibitors of most tyrosine phosphatases. In contrast, vanadate is mimicking phosphate and forms reversible bonds with the thiol groups of these enzymes (257). Several important components of the anticancer mode of action of vanadium compounds are, besides the deregulation of protein tyrosine phosphorylation, directly or indirectly depending on the generated radical species. Multiple vanadium compounds have been demonstrated to cause DNA damage (39, 106, 203, 349), whereas the cell cycle arrest in G2/M phase is believed to be caused by inhibition of cyclin-B complex dephosphorylation (108). Although at least for vanadocenes, adduct formation with DNA was demonstrated (18, 147), in most cases ROS and particularly the hydroxyl radicals generated in the cells are believed to be responsible for the induction of DNA damage of exposed cells (39, 106, 257). Additionally, considering the importance of tyrosine phosphorylation in multiple cellular signaling pathways, it is not surprising that vanadium compounds cause deregulation of cellular survival pathways and induce apoptosis. The involved pathways include for example the p38, JNK/SARK, and ERK/MAPK signal cascades *via* apoptosis signal-regulating kinase (ASK-1) and, probably in turn, the NF-κB pathway (175). Moreover, cellular survival pathways, including the PI3K/AKT/PKB pathway, and the antiapoptotic bcl-2 family members are deregulated by vanadium complex exposure (36, 311). The inhibition of phosphatases and the generation of oxidative stress seem to cooperate in these activities and even enhance each other (106, 257).

Given the vast array of vanadium compounds synthesized during the last decades and the broad knowledge delivered by studies concerning diabetes, it is surprising that no vanadium compound has been approved or is even close to clinical application for the treatment of cancer so far. It has to be mentioned that many vanadium compounds, including soluble aqueous peroxovanadates formed by the oxidation of vanadate with H_2O_2, are highly unstable in aqueous solution. Moreover, multiple vanadium species might be present in solution due to a series of hydrolysis and polymerization reactions, depending on pH and concentration of the vanadates, as well as rapid redox reactions (83). Moreover, based on a labile inner coordination sphere, vanadates tend to interact with electron pair donors. This makes the identification of an active species and/or metabolite almost impossible (257). In general, the presence of ancillary ligands in the complexes confer greater stability in aqueous solution than the pure vanadates or peroxovanadates.

Consequently, with regard to specific vanadium complexes, anticancer approaches have mainly focused on organometallic vanadocenes as well as vanadium/peroxovanadate coordination compounds (Fig. 18). The molecular anticancer mechanisms of vanadium complexes involve induction of oxidative stress (compare above) and were investigated *in vitro* using human cancer cell models, including leukemia, lymphoma, and solid tumor-derived cell lines (203). In contrast, most *in vivo* studies concerned the (chemo)preventive effects of vanadium complexes [for reviews see (39, 106)], whereas reports on therapeutic activity studies are limited. For example, activity of vanadocene dichloride and a [(2-methylaminopyridine) vanadium(IV)] complex against murine mammary tumor models was shown (103). [Bis(4,7-dimethyl-1,10-phenanthroline)sulfatooxovanadium(IV)], also termed

Metvan (Fig. 18), induced potently apoptosis in tumor cell lines and demonstrated significant antitumor activity against human glioblastoma and breast cancer xenograft models in SCID mice (86). Another phenanthroline complex, namely, [(4,7-dimethyl-1,10-phenanthroline)bis(peroxo)oxovanadium(IV)] (Fig. 18), was active against transplanted breast cancer *in vitro* and *in vivo* (340). The situation in hematological malignancies seems more complicated. Vanadocene dichloride (201) and a series of vanadium(peroxo)(heteroligand) complexes (96) were demonstrated to prolong survival of lymphoid leukemia L1210-carrying mice. In contrast, only low doses of these vanadium complexes delayed progression of a lymphoma model, whereas higher doses enhanced malignant growth most likely due to an impact on drug-metabolizing enzymes (59). This complexity of pro- and anticancer activities as well as in mode of action and metabolism might be explanations why no vanadium complex is currently approved for anti-cancer therapy.

G. Rhodium

Rhodium (Rh) complexes in the oxidation states + 1, + 2, and + 3 have been tested for their tumor-inhibiting potential and often the cisplatin-like binding to DNA was proposed essential for their modes of action (188). However, only a few studies have investigated anticancer Rh complexes in the context of biological redox processes.

For several Rh^I complexes *in vivo* anticancer activity against leukemic, solid, and metastasizing tumors in mice has been shown. However, it has to be considered that Rh^I complexes are inactivated by oxidation (335, 424).

Further, a number of Rh^{III} analogs with similar structures of Ru^{III} drug candidates (i.e., the $MCl_4L_2^-$ motif) have demonstrated antineoplastic activity. Whereas Ru^{III} complexes are thought to be activated by reduction (compare Section IV.*C.*), reduction of Rh^{III} compounds to more active + 2 species was suggested improbable (91, 188). In accordance, it has been shown that *in vivo* Rh^{III} compounds do not alter biochemical pathways related to the GSH system and other enzymes involved in redox balance (56).

The discovery of the antitumor activity of Rh^{II} compounds led to various investigations of these complexes (188). It has been shown that Rh^{II} compounds have a high affinity to sulfhydryls and in particular Rh^{II} carboxylates of the general formula $[Rh_2(carboxylato)_4(H_2O)_2]$ (Fig. 19) were found to be broken down in the presence of cysteine to liberate the carboxylates (165). This might be related to a redox process causing initial formation of Rh^I–Rh^{II} mixed-valence complexes, which are further reduced to Rh^I polynuclear species, for example, observed during the reaction with ceruloplasmin, cysteine, GSH, and coenzyme A. Complexes containing 1,10-phenanthroline or 2,2′-bipyridine ligands are readily reduced by sulfhydryl groups, whereas $[Rh_2(acetato)_4(H_2O)_2]$is relatively resistant to reduction (171).

Interestingly, enzymes with sulfhydryl groups close to or in their active centers were inhibited by preincubation with Rh compounds. As the rate of enzyme inactivation correlated with toxicity and anticancer activity, the authors suggested that the activity of these Rh^{II} complexes is based on the reaction with enzymes or proteins containing sulfhydryl groups such as pyrovate kinase, aldolase, and LDH (165, 188). In contrast to Rh^I complexes, oxidation of dinuclear Rh^{II} carboxylates led to slightly more active species.

No definite trend between redox behavior and antitumor activity of $[Rh_2(carboxylato)_4(H_2O)_2]$ complexes was observed (182). In an attempt to sensitize cells to irradiation, Rh^{II} carboxylates were compared to cisplatin and metronidazole. The lower redox potential of the Rh^{II} compounds as compared to metronidazole led to the conclusion that they do not undergo electron transfer reactions upon interaction with DNA-derived radicals. The increase in radiation sensitivity with Rh^{II} carboxylates, but not cisplatin, was attributed to the ability of the rhodium compounds to deplete intracellular thiols (71).

Additionally, photoactivation of $[Rh_2(carboxylate)_4(H_2O)_2]$ with visible light in the presence of electron acceptors was analyzed. This process causes formation of one-electron-oxidized complexes of the general formula $[Rh_2(carboxylate)_4(H_2O_2)^+]$, capable of cleaving plasmid DNA (119). However, to the best of our knowledge no detailed studies on the role of redox processes or ROS formation in the modes of action of rhodium compounds have been reported. Only recently, the $[Rh_2(PheAla)_2(acetato)_2]$ complex was shown to exhibit its anticancer activity by an ROS-independent mechanism (114) and the activity of several monosubstituted $dirhodium^{II,II}$ complexes was not affected by changes in GSH levels (2).

H. Cobalt

Cobalt (Co) has two naturally occurring oxidation states, Co^{II} and Co^{III}. In general, cobalt is a very rare metal but a biologically important cofactor in vitamin B_{12}-dependent enzymes. Vitamin B_{12} (cobalamin) represents a relatively inert Co^{III} ion in a substituted corrin macrocycle (Fig. 20). In addition to the four nitrogens of the corrin macrocycle, the Co^{III} of the B_{12} coenzyme possesses an axial 5-deoxyadenosine or methyl group. In the biological context, vitamin B_{12} acts as a coenzyme in a wide spectrum of metabolic processes, including methylmalonyl CoA mutase and type II RR (found in bacteria and archea). However, the actual number of known B_{12}-dependent enzymes remains comparatively small and, therefore, most organisms need cobalamin in vanishingly small quantities. Humans require between 1 and 2 μg per day, which is ingested from our diet and is taken up by an elaborate absorption mechanism (305). Exclusively members of the *Archea* and certain eubacteria are able to synthesize cobalamin *via* a complex biosynthetic pathway (310). Further, only a few proteins containing cobalt not coordinated to the corrin macrocyclic system have been characterized.

Regarding health risks, uptake of cobalt at larger quantities has been demonstrated to be carcinogenic at least in rodents. The underlying mechanisms involve genotoxicity by both radical-mediated mechanisms as well as direct interference of cobalt with DNA repair (35). Co^{II} catalyzes the generation of hydroxyl radicals from H_2O_2 in a Fenton-like reaction (compare Section II.*C*.). After intraperitoneal injection in rats, Co^{II} evoked the formation of oxidative DNA base damage in kidney, liver, and lung (187). In case of DNA repair, Co^{II} interferes with nucleotide excision repair probably by substituting for zinc ions in zinc finger proteins, for example, XPA (200). Moreover, cobalt enhances the effects of other carcinogens like benzo[a]pyrene (362).

Despite these limitations due to adverse effects on normal cells and tissues, cobalt-containing compounds recently attracted considerable interest as systemic anticancer agents. First, cobalamin is substituted together with folic acid in chemotherapy regimens involving antimetabolites to reduce unwanted side effects. Additionally, since fast proliferating cells require higher amount of cobalamin than normal cells, cobalamin-conjugates with radioisotopes or cytotoxic compounds like, for example, nitrosylcobalamin or a cisplatincobalamin have been developed to achieve enhanced tumor accumulation *via* the respective receptor-mediated uptake system (29, 133, 325). The studies on cytotoxic/cytostatic cobalt complexes as anticancer therapeutics have more or less focused on the following types of cobalt compounds (Fig. 21): (i) hexacarbonyldicobalt complexes with alkyne ligands (cobalt alkyne complexes) containing two covalently linked Co^0 atoms (285), (ii) $[Co^{III}(NH_3)_6]Cl_3$, (iii) Co^{III} complexes with Schiff base ligands (282), including salen (135), and (iv) Co^{II} and/or Co^{III} complexes with cytotoxic mustamine (398), mithramycin (163), and thiouracil (184) ligands. Regarding the cobalt alkyne complexes, potent anticancer activity was shown *in vitro* and *in vivo* of complexes containing the propargylic ester of acetylsalicylic acid (Co-Ass, Fig. 21) especially against breast cancer cells (181). With regard to their activity, minor modifications on the molecule resulted in distinct variations, whereby profound intracellular accumulation and the higher lipophilicity of the complex as compared to the free ligand might be of great importance (285). Mode of action studies indicated that—even though binding to DNA—cobalt alkyne complexes do not substantially target DNA in living cells and several observations suggest that the activity of Co-Ass (Fig. 21) might be based on the interaction of the ligand acetylsalicylic acid (aspirin) with cyclooxygenase enzymes (COX-1 and COX-2). This would fit well with the often observed hypersensitivity of breast cancer cells against COX inhibitors. The preferential accumulation in malignant cells indicates that Co-Ass might represent a “tumor-targeted aspirin.” Indeed, its anticancer activity was distinctly higher as compared to aspirin (286). However, redox processes were not discussed to be involved significantly in the mode of action of cobalt alkyne complexes.

With regard to redox processes in the anticancer activity of cobalt complexes, two aspects are of central interest: (i) activation of Co^{III} complexes in hypoxic environment by reduction to Co^{II} and release of the ligand, and (ii) generation of ROS by a catalytic autooxidation process especially by Schiff base complexes but also $[Co^{III}(NH_3)_6]Cl_3$ (265, 266). Regarding the principal hypothesis of activation by reduction/hypoxia (similar to Pt^{IV} and Ru^{III} compounds compare Section IV.*C.*,V.*A.*2., and V.*D.*), the drug must be able to exist in an inactivated higher oxidation state (the prodrug) and an activated lower oxidation state (the effective drug). As reductants are present throughout the body, it has been assumed for Co^{III} drugs that not the reduction but the delayed reoxidation of such compounds is responsible for the hyper-activation in the hypoxic tissues (89). Several Co^{III} complexes have been demonstrated to be reduced to Co^{II} within the hypoxic tumor tissue. As Co^{II} complexes are more labile, the cytotoxic ligands may be released from the “metal chaperon” and exert their anticancer activity. The reactions that are taking place are shown in Figure 22 (285). At least in some cases this activation step was proven to be tumor specific as detected for example by X-ray absorption near edge structure (XANES) (41) and efficient activation can be further promoted by ionizing radiation (252). Such, Co^{III} complexes containing nitrogen mustard ligands were demonstrated to be active under hypoxic conditions (399, 400) and the cytotoxic ligand 8-hydroxyquinoline (5) or the potent DNA minor groove alkylator azachloromethylbenzindoline (4) were released from the Co^{III} complex in hypoxic solutions by ionizing radiation. However, other studies based on cobalt complexes of bi- and tridentate cytotoxic or fluorescent ligands (397, 411) as well as pulse radiolysis experiments (10) have indicated that hypoxia selectivity of Co^{III} complexes might not completely be based on redox cycling. Instead other mechanisms like ligand exchange without prior reduction of Co^{III} or competition with O_2 for biological reductants could be involved. Indeed, ascorbate and cysteine can reduce but also coordinate to Co^{III} (368). Yamamoto *et al.* showed that both cysteine and ascorbate were able to release fluorescent ligands from complexes even though they are—based on their reduction potentials— unlikely to be reduced by these cellular reductants (411).

The reduction step of Co^{III} complexes might not only lead to the release of cytotoxic ligands but also to generation of ROS based on a catalytic autooxidation process (281). As mentioned above, even Co^{II} ions themselves induce generation of ROS *in vivo* and *in vitro* by catalyzing the generation of hydroxyl radicals from H_2O_2 in a Fenton-like reaction (compare Section II.*C.*) (35). After exposure to $[Co^{III}(NH_3)_6]Cl_3$, enhanced lipid peroxidation and upregulation of other oxidative stress parameters were found in the kidneys of mice. With EPR spin-trapping it was demonstrated that several Co^{II} complexes are able to generate oxygen-derived free radicals under physiological conditions which were inhibited by addition of 5′-diphosphate or citrate (145). In the presence of peroxides, a nitrilotriacetate Co^{II} complex formed hydroxyl radicals, whereas in case of an EDTA–Co^{II}

complex only oxidation to Co^{III} but no ROS generation was observed. Also, cobalt metal particles in suspension and in the presence of SOD generated $OH^{\bullet}$. Chelators like anserine enhance but 1,10-phenanthroline and desferioxamine reduced $OH^{\bullet}$ generation from H_2O_2 by Co^{II}. Interestingly, in a series of cobalt(3,4-diarylsalen) complexes the oxidizing potency did not reflect the anticancer activity against human cancer cell lines, suggesting that in case of these compounds superoxide radical-mediated active species are not the major effectors. Thus, other mechanisms might be important including DNA intercalation (135). Moreover, it has been recently demonstrated that Co^{II} ions can replace Mg^{2+} in enzymatic physiological enzyme reactions, which strongly enhance DNA cleavage by topoisomerase IIα (20).

In several rodent tumor models comparable antitumor activity and DNA damage have been described as a consequence of treatment with redox-active $Co^{II/III}$ complexes with tetradentate Schiff base ligands derived from acetylacetone and ethylenediamine or biogenous and/or syntheticnitrogen-containing ligands, like phthalocyanines and vitamin B_{12} derivatives (281, 283, 391). Such redox-active complexes may act, in addition to the already mentioned cytotoxic ligand release, by other mechanisms, including binding of the histidine units of polypeptide chains like in case of $[Co(acetylacetonate\text{-}ethylenediimine)(NH_3)_2]^+$ with metmyoglobin (40). Moreover, these complexes may catalyze auto-oxidation of ascorbic acid involving generation of $O_2^{\bullet\,-}$,$OH^{\bullet}$, and H_2O_2 (391). Thus, cobalt complexes accumulated in malignant tissues should exhibit enhanced antitumor activity in cooperation with ascorbic acid as shown for the cobalt phthalocyanine complexes and Co compounds of the B_{12} series (281, 391).

In summary, cobalt complexes are mainly in the focus of interest in experimental cancer therapy research because of their ability to redox-dependent targeting the malignant tissue of solid tumors. It is surprising that despite the intense research efforts during the last decades none of these compounds has reached clinical evaluation as anticancer drug so far.

I. Manganese

Manganese (Mn) is an essential trace metal. Several enzymes have Mn cofactors, including oxidoreductases, transferases, and hydrolases. One of the best investigated enzymes is the Mn-containing SOD (compare Section II.*A*.). As oxidative stress is important in numerous diseases, including cancer, synthetic antioxidants have been extensively investigated especially in cancer chemoprevention and antiaging research. Within these, especially Mn-containing complexes as SOD mimics exhibited high antioxidative potential. From the chemical view, Mn complexes exhibit rich redox chemistry. Important examples are Mn-porphyrin compounds that have accessible oxidation states ranging from + 2 to + 5 under physiological conditions (27). Their redox potentials are similar to those of several Ru^{III} anticancer agents (compare Section V.*D*.). The primarily developed Mn-containing SOD mimics are based on corroles, porphyrins, salens, and cyclic polyamine ligand systems (Fig. 23). These SOD mimics possess tumor growth-inhibiting (27) as well as cancer-preventing properties (279) [for a recent comprehensive review see (27)].

Within the Mn compounds, Mn-porphyrin complexes are the best investigated, which appear particularly advantageous due to their low toxicity and their ability to cross cell membranes. The most potent complexes have Mn^{III}/Mn^{II} reduction potentials between the potential of $O_2^{\bullet\,-}$ reduction ($E_{1/2}$ + 0.89 V vs. NHE pH 7.0) and oxidation ($E_{1/2}$-0.16V vs. NHE pH 7.0), similar to endogenous SOD ($E_{1/2}$ ~ + 0.3 V vs. NHE) (27, 28). Further, the catalytical rate constant k_{cat} for $O_2^{\bullet\,-}$ dismutation equals nearly the k_{cat} of SOD enzymes. These properties enable Mn-porphyrins to easily donate and accept electrons from redox active compounds, such as cellular reductants (28, 110).

In the context of cancer, particularly the highly positive charged Mn-porphyrin complex Mn(III) *meso*-tetrakis(*N*-ethylpyridinum-2-yl)porphyrin (MnTE-2-PyP^{5+}) (Fig. 23) was investigated. Even though as single agent only low anticancer activity against cancer cell lines was observed, MnTE-2-PyP^{5+} had antiangiogenic properties *in vivo*, especially in combination with hyperthermia and radiation (32, 306, 418). The mode of action is thought to be related on the one hand to its anti-oxidative properties by downregulation of cellular levels of reactive nitrogen species and ROS on the other hand, to its prooxidative properties. The latter leads to oxidation of biological targets such as cysteines, for example, in signaling proteins by increased generation of H_2O_2 particularly occurring in cells with insufficient peroxide metabolism (407). Consequently, several biological functions are altered by the anti- and prooxidative properties of MnTE-2-PyP^{5+}, including inhibition of AP-1 and NF-κB activity and downregulation of HIF1α,VEGF, and TGF-β (28, 110, 385). Accumulation studies showed that MnTE-2-PyP^{5+} was able to accumulate *in vivo* in heart mitochondria to levels sufficient to exert its antioxidant activity. *In vitro* accumulation studies with macrophages and lipopolysaccharide-stimulated macrophages demonstrated that the positively charged porphyrins favor the nucleus with its anionic nucleic acids in contrast to the cytosol (27, 28, 361). Moreover, it has been shown that treatment of cancer cells in a combination regimen consisting of MnTE-2-PyP^{5+} and glucocorticoids, cyclophosphamide, or doxorubicin sensitized cells in some cases to these chemotherapeutics (174).

Beside MnTE-2-PyP^{5+}, the macrocyclic Mn(II) polyamine M40403 (Fig. 23) has been investigated in combination with chemotherapy, radiotherapy, and immune-stimulating inter-leukin-2 treatment. Prevention of side effects by the manganese compounds became obvious, and therefore M40403 has been granted orphan drug designation for prevention of radiation- or chemotherapy-induced oral mucositis in cancer patients in 2008. However, recent studies suggest that combination of M40403 with cytotoxic agents not only prevents side effects but also increases the anticancer activity by enhanced pro-oxidative effects. The M40403 produced H_2O_2 may especially target rapidly dividing cancer cells with impaired peroxide metabolism and high levels of endogenous oxidative stress (7, 208, 407). Interestingly, also mangafodipir (Fig. 24), a paramagnetic Mn^{II}-containing contrast agent for magnetic resonance imaging of the liver, enhanced cytotoxicity of anticancer agents and decreased hematotoxicity. Besides mimicking SOD, mangafodipir has also catalase- and glutathione reductase-like properties allowing interaction with several points of cellular redox homeostasis (7, 407).

In summary, Mn compounds exert a number of interesting properties that might be useful in the development of metal-based anticancer agents. However, none of them are in clinical trials for the application as cancer chemotherapeutics so far (326, 407).

J. Complexes with redox silent metal centers in clinical trials

There are currently several strategies in (pre)clinical development that use metal-containing drugs to interfere with the redox balance of cancer cells, where the central metal core is not directly involved in this “redox activity.” Among these, two promising compounds (Fig. 25), namely, motexafin gadolinium (228) and tetrathiomolybdate (47, 134, 290), have been tested in several clinical trials. Gadolinium motexafin (MGd) is a texaphyrin coordinated to a nonredox-active gadolinium(III) cation. However, the aromatic texaphyrin ring system of MGd is easily reduced (first reduction potential of −0.041 V vs. NHE in dimethylformamide), for example, $O_2^{\bullet -}$. In the presence of oxygen, this is supposed to result in redox cycling, oxidative stress, and disruption of the cellular redox homeostasis (228, 378). Indeed, ROS formation after MGd treatment has been shown in cell culture and animal experiments initiating the clinical testing to exploit these redox properties to sensitize cancer cells to radiation therapy (324). Several clinical studies were published especially on the combination therapy of whole-brain radiation and MGd in patients with brain metastases reporting in some cases encouraging response rates (54). Unfortunately, no survival benefit by addition of MGd to whole-brain radiation in patients with brain metastases from lung cancer was found in a large-scale phase III study despite an improvement in neurocognitive functions and a prolonged time to neurologic progression (247). Consequently, MGd has not been approved for clinical use as anticancer therapeutic so far.

Another clinically evaluated compound is tetrathiomolybdate (TM), which has been developed as copper chelating agent. Numerous reports describe elevated copper levels in serum and malignant tissues of cancer patients, which directly correlate with cancer progression (134). TM has been shown to interfere with the cellular redox balance by inhibition of copper-containing enzymes, such as ceruloplasmin, ascorbate oxidase, cytochrome oxidase, or Cu/Zn SODs (compare Section II.*A*.) (9). However, the binding of copper by TM does not involve any redox reaction but is based on the formation of stable ternary adducts with copper-containing proteins (9). Based on its antiangiogenic activity, TM has been evaluated against several cancer types in clinical studies indicated some clinical efficacy (244). Recently, chelation of copper by TM was demonstrated to enhanced sensitivity of tumor models against cisplatin based on augmented cisplatin uptake *via* the copper transporter CTR1 (169).

VI. Conclusion

Based on the availability of the human genome and the development of high-throughput omics methods, experimental cancer therapy research was dominated by rational drug development and molecular targeted approaches during the last decades. In parallel, studies on classical chemotherapeutics uncovered that also for such old-fashioned cytotoxic drug (including anticancer metal complexes)-specific molecular targets in addition to DNA might exist. Moreover, it was emerging that several tumor-specific biochemical/biophysical conditions, like altered pH, redox milieu, and hypoxia distinctly impact on the activity of more or less all applied anticancer drugs. Interactions with such tumor-specific conditions/mechanisms are now increasingly utilized in (pre)clinical anticancer drug development by novel and creative approaches focusing on (i) enhanced drug transport (in)to the malignant tissue, (ii) activation of prodrugs in the malignant compartment, (iii) increase of cytotoxicity against cancer cells by drug metabolism in the malignant cells, and (iv) circumvention of resistance development. All these approaches offer chances to develop better tumor-specific cancer therapeutics with enhanced activity in molecularly defined tumor entities and patient subgroups.

With regard to metal-based anticancer drugs, the great success of cisplatin but also its limitations based on side effects and resistance development were strong stimuli for the development of novel and more tumor-specific metal complexes. In that context, it has to be admitted, that—considering the enormous number of compounds synthesized—the count of clinically approved substances remains comparably low. Nevertheless, the above-mentioned developments toward an in-depth understanding of the molecular changes affecting cancer cells or the tumor microenvironment also offer novel avenues for the development of smart, tumor-targeting metal compounds. Recent success stories like the profound activity of ATO against APL based on a highly specific targeting of the oncogenic fusion protein (compare Section V.*C*.), give hope in that respect.

Alterations of the redox status and, consequently, upregulation of oxidative stress and its molecular consequences are well known for malignant tumors and now more and more recognized as platform for the development of novel cancer-targeting drugs (381). Moreover, these profound alterations in the redox status of malignant tissues might not only be a consequence of misbalance between cell proliferation, mitochondrial activity, and blood supply, but also a direct result of tumor-specific gene mutations. For example, the metabolic enzymes isocitrate dehydrogenase-1 and −2 (IDH1, IDH2) were found mutated in an extended subgroup of glioma and AML patients. The mutations were shown to alter the redox status of cancer cells with enhanced radical stress, and to activate the hypoxia-inducible factor 1 alpha (1, 412, 430).

Based on their chemical characteristics, redox-active metal-drugs are naturally in the focus of interest in this research field. This review summarizes the impact of altered redox conditions on the anticancer activity of clinically approved and innovative redox-active metal compounds. From this overview it becomes obvious that redox processes are important players both in the mode of action as well as in metabolism, transport, and distribution of anticancer metal complexes. Although for many promising drug candidates an extended array of data exist also several limitations are obvious. For example, a mode of action comparable to cisplatin is frequently anticipated for all metal drugs and, consequently, multiple studies have focused exclusively on the interaction of metal complexes with DNA. However, during the last decades increasing evidence is accumulating that such a view is too short-sighted and obviously more integrated approaches are needed. Such especially for gold, arsenic, and ruthenium compounds, important cytosolic targets are emerging (compare Section V.*B*. to V.*D*.). Moreover even in case of clinically approved platinum compounds, the modes of action might severely differ. For example, recent data suggest an important contribution of immunogenic cell death to the anticancer activity of oxali- but not cisplatin (371, 432). Moreover, the literature on redox processes in the activity of anticancer metal complexes has often focused on cell-free *in vitro* systems. Although highly informative, the translation of the gained knowledge to the *in vivo* situation—both at the level of the living (tumor) cell and the whole organism—is extremely complicated and challenging. However, the availability of modern analytical techniques as well as sophisticated, transgenic cell and animal models should severely support such integrated attempts. These considerations suggest that the molecular mechanisms underlying the anticancer activity of metal complexes need to be re-evaluated and, based on the gained knowledge, the development of more tumor-specific and less toxic anticancer metal compounds has to be further promoted by multidisciplinary research teams. Then a revival of metal-compounds to successfully fight human cancer seems not only feasible but even inevitable.

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Abbreviations Used

AML	acute myeloid leukemia
ANT	adenine nucleotide translocator
APL	acute promyelocytic leukemia
ASK-1	apoptosis signal-regulating kinase
Ass	propargylic ester of acetylsalicylic acid
ATO	arsenic trioxide
ATP7A/B	P-type ATPase
Auoxo6	$[Au_2(6,6'\text{-dimethyl-2,2'-bipyridine})(\mu\text{-O})_2]PF_6$

Auranofin	[tetra-O-acetyl-*β*-D-(glucopyranosyl) thio](triethylphosphine)gold(I)
BHA	buthylated hydroxyanisole
BPYTA	2,2′-bipyridyl-6-carbothioamide
BSO	L-buthionine-(*S,R*)-sulfoximine
COX	cyclooxygenase
COX17	cyclooxygenase 17
CTR1	copper transporter 1
CuNG	*N*-(2-hydroxyacetophenone)glycinato copper(II)
D2PYPP	bis(di-2-pyridylphosphino)propane
DACH	(*1R,2R*)-cyclohexanediamine
DMT1	divalent metal transporter
DMTU	dimethylthiourea
DNCB	dinitrochlorobenzene
DPPE	bis(diphenylphosphine)ethane
EDTA	ethylenediaminetetraacetato
GPx	glutathione peroxidase
GR	glutathione reductase
GSAO	4-(*N*-(*S*-glutathionylacetyl) amino)phenylarsonous acid
GSH	glutathione
GST	glutathione-*S*-transferases
$\mathbf{H_2O_2}$	hydrogen peroxide
HO-1	heme oxigenase-1
HSAB	hard and soft acids and bases
Iproplatin	*cis,trans,cis*-[PtCl$_2$(OH)$_2$(isopropylamine)$_2$]
JM118	*cis*-amminedichlorido-(cyclohexylamine)platinum(II)
LIP	labile iron pool
MER1	*S*-dimethylarsino-thiosuccinic acid
METVAN	[Bis(4,7-dimethyl-1,10-phenanthroline)sulfatooxovanadium(IV)]
MGd	gadolinium motexafin
MnTE-2-PyP^{5+}	Mn(III) meso-tetrakis(*N*-ethylpyridinum-2-yl)porphyrin
MOA	mode of action
MRP	multi-drug resistance
NAC	*N*-acetylcysteine
NHE	normal hydrogen electrode
$\mathbf{O_2^{\bullet\,-}}$	superoxide radical
$\mathbf{OH^{\bullet}}$	hydroxyl radical

Phen	1,10-phenanthroline
ROS	reactive oxygen species
RR	ribonucleotide reductase
Satraplatin	*cis,trans*-[$PtCl_2(OAc)_2(NH_3)$(cyclohexylamine)]
SOD	superoxide dismutases
Tetraplatin	[$PtCl_4$(d,l-cyclohexane-1,2-diamine)]
Tf	transferrin
TfR1	transferrin receptor
TGR	thioredoxin glutathione reductase
TM	tetrathiomolybdate
TrxR	thioredoxin reductase
TSC	*α*-*N*-heterocyclic carboxaldehyde thiosemicarbazonates
UPR	unfolded protein response
XANES	X-ray absorption near edge structure
ZIO-101	darinaparsin
***γ*-GT**	*γ*-glutamyl transpeptidase

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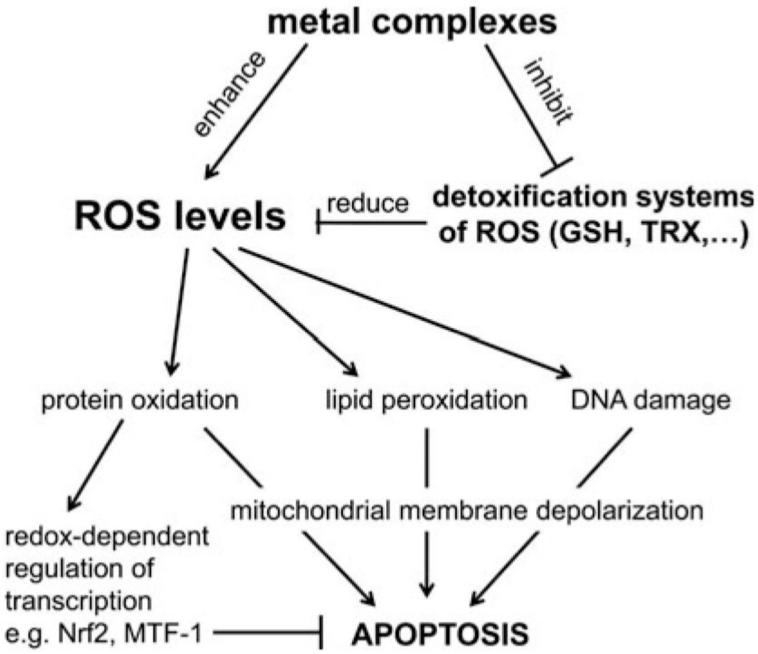


FIG. 1.

General overview on the role of ROS in the activity of anticancer metal drugs.

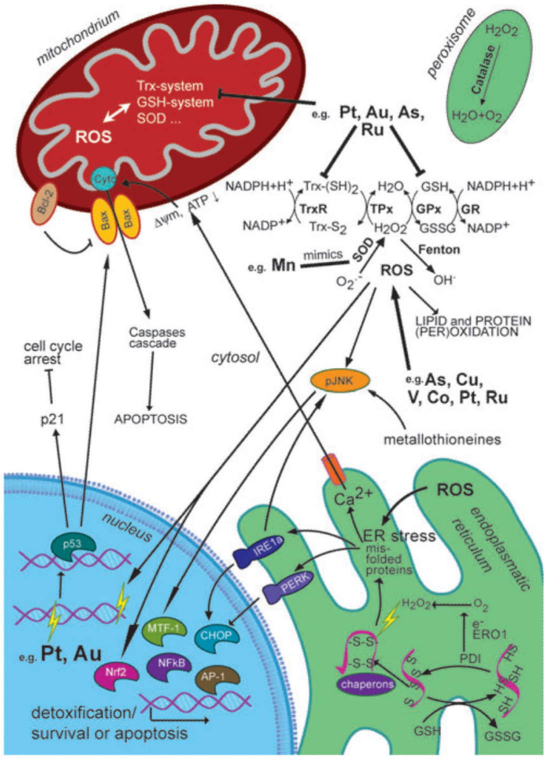


FIG. 2.

Main interaction sites of anticancer metal complexes with cellular redox and oxidative stress pathways. Several metal compounds produce directly reactive oxygen species (ROS) and activate several ROS-dependent signaling and protection pathways (e.g., mediated by stress responsive transcription factors Nrf2, NF-κB, and AP-1). Sustained stress can induce apoptosis, for example, *via* the intrinsic mitochondrial pathway resulting in caspase-mediated cell death. Beside ROS-induced DNA damage, lipid peroxidation and protein oxidation also direct interactions with redox-regulatory mechanisms can disturb cellular redox homeostasis. Examples are the interaction of metal complexes with the thioredoxin (Trx) and glutathione (GSH) systems in the cytosol as well as in other cellular compartments such as mitochondria and endoplasmic reticulum (ER). Further, direct DNA damage by metal complexes and induction of ER stress due to accumulation of misfolded proteins can again lead to apoptosis (e.g., mediated by the transcription factors p53 and CHOP, respectively, as well as Ca^{2+} release after ER stress) and/or p53-mediated cell cycle arrests. In general, the different pathways are highly cross-linked and metal compounds target different sites. Metal complexes are indicated in bold face; cellular compartments in italic face; TrxR, thioredoxin reductase; TPx, thioredoxin peroxidases; GPx, glutathione peroxidases; GR, glutathione reductase; SOD, superoxide dismutase.

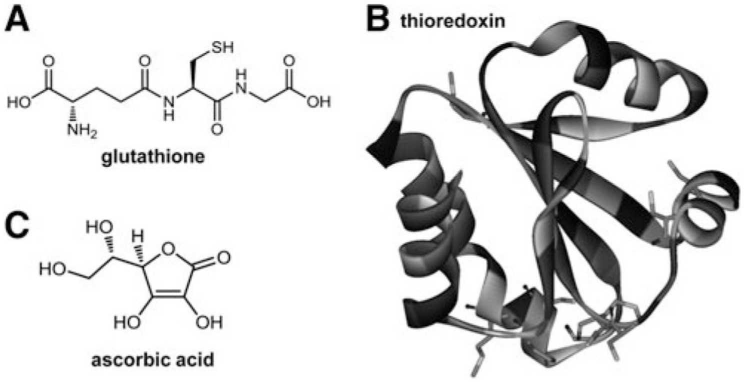


FIG. 3.

Major cellular nonenzymatic antioxidants. Structures of (A) the tripeptide glutathione (built from L-glutamic acid, L-cysteine, and glycine), (B) thioredoxin (1AIU) (16), and (C) ascorbic acid.

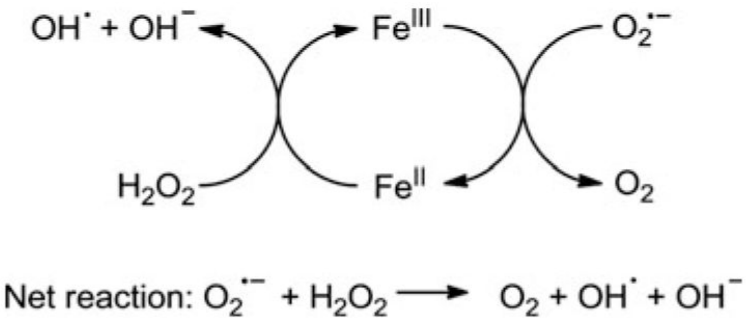


FIG. 4.
Iron-catalyzed production of hydroxyl radicals. The Haber-Weiss reaction is shown, whereby the left part depicts the Fenton reaction.

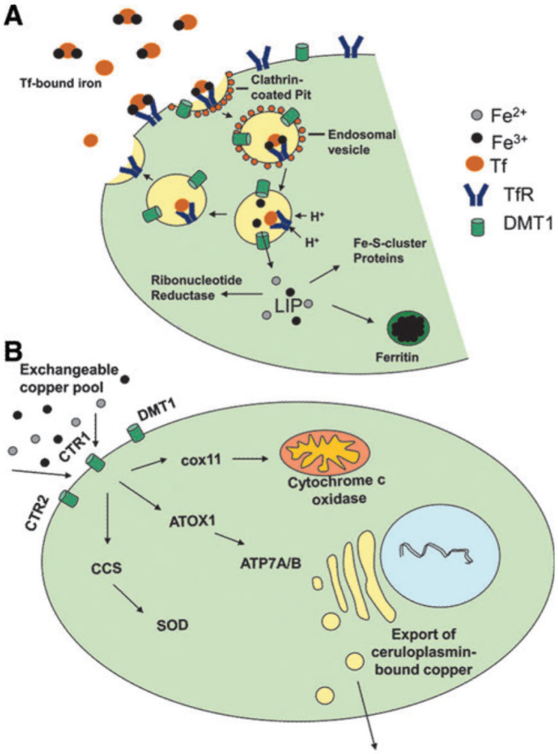


FIG. 5.

Metal homeostasis in human cells. (A) Iron homeostasis: iron is accumulated in cells *via* transferrin-mediated endocytosis. Upon acidification iron is released from endosomal vesicles and becomes part of the labile iron pool (LIP) in the cytosol. Iron is utilized as cofactor, for example, in ribonucleotide reductases or proteins with Fe-*S*-clusters. Excess iron is stored in ferritin. (B) Copper homeostasis: a model of cellular copper transport and chaperoning is shown. Copper is taken up at the plasma membrane by diverse transporters (e.g., CTR1, CTR2, and DMT1). Once in the cell, copper is further distributed by intracellular chaperons. For example, copper is transported to the mitochondrial inner membrane *via* cox11. ATOX1 delivers excess copper to the *trans*-Golgi network where it is packed into vesicles by ATP7A/B and bound to ceruloplasmin for excretion. Finally, CCS chaperons copper for use in Cu/Zn-SODs.

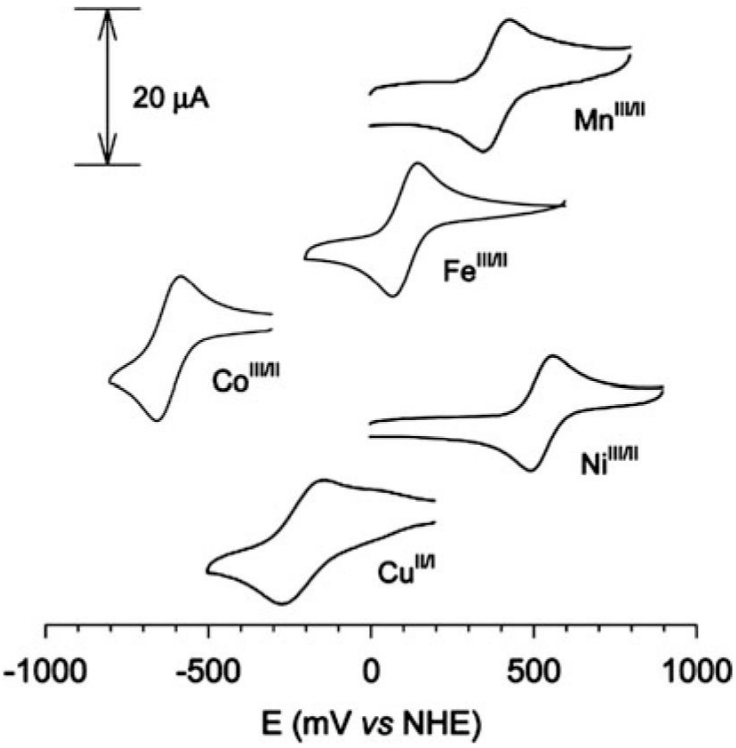


FIG. 6.

Impact of the central metal ion on the redox potential of metal complexes. As an example the cyclic voltammograms of complexes of the type M(Dp44mT)$_2$ with different metal centers are shown (M = manganese, iron, cobalt, nickel, copper; Dp44mT = di-2-pyridylketone 4,4-dimethylthiosemicarbazone) (33). The figure illustrates the strong impact of the central metal ion on the redox potential of structurally similar complexes.

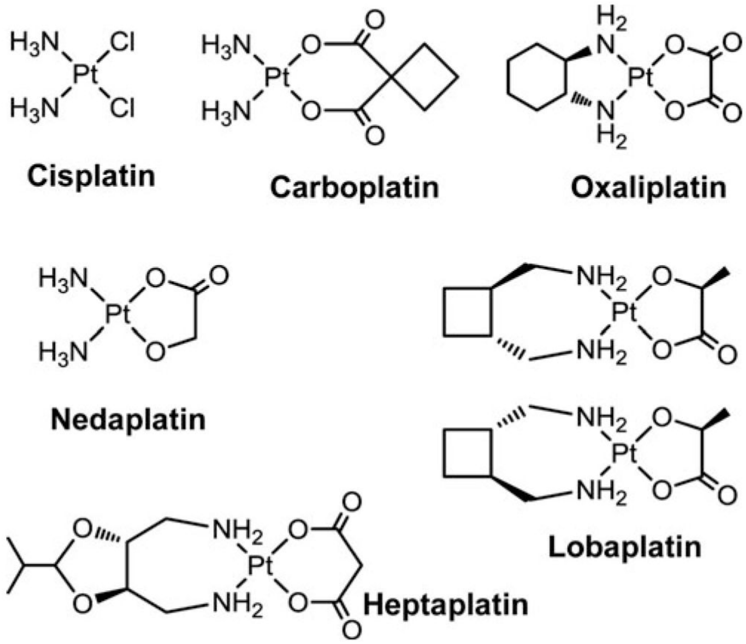


FIG. 7.

Clinically approved Pt^{II} drugs.

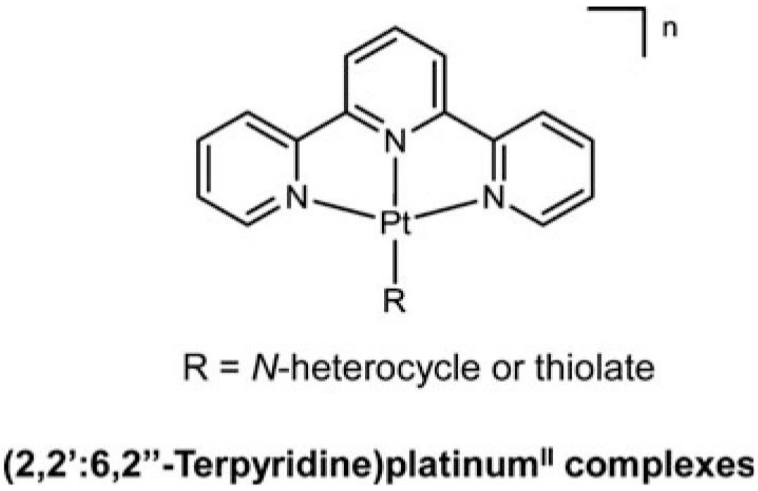


FIG. 8.
General structure for terpyridine-Pt^{II} complexes.

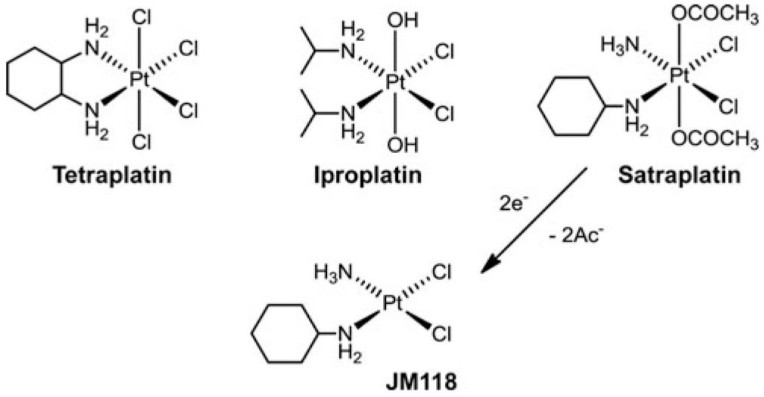


FIG. 9.

Pt^{IV} drug candidates. Tetraplatin, iproplatin, and satraplatin, together with the major reduced Pt^{II}-metabolite of satraplatin (JM118) are shown.

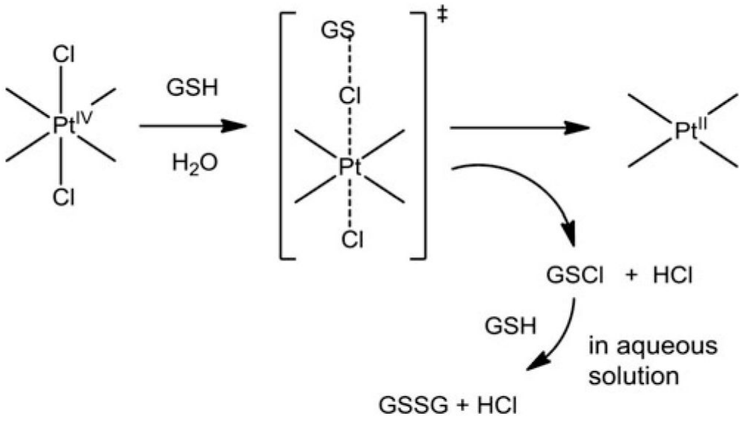
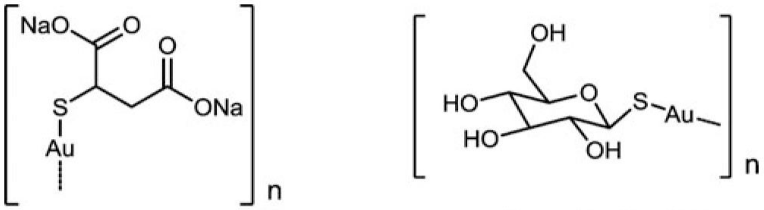
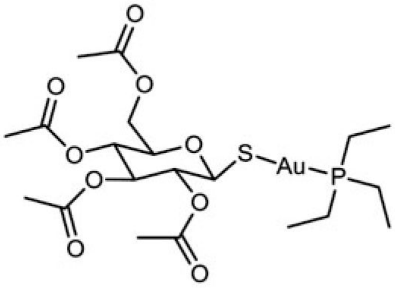


FIG. 10.
Possible reduction mechanism of tetraplatin and other Pt^{IV} complexes. In the case of Pt^{IV} drugs like tetraplatin it is assumed that reduction with GSH occurs *via* a halide bridged electron transfer from GSH to Pt^{IV} resulting in GSCl and the corresponding Pt^{II} species. GSCl further reacts in aqueous solution with GSH yielding GSSG and HCl. Adapted from refs. (138, 210).



Aurothiomalate

Aurothioglucose



Auranofin

FIG. 11.
Au^I drugs relevant for rheumatoid arthritis therapy additionally harboring anticancer activity.

Auro(bis)thiosulfate

[Chlorido(triethylphosphine)gold^I]

[Bis{(diphenylphosphine)ethane}-gold(I)] chloride (R = phenyl)

[Bis{di-2-pyridylphosphino)propane}-gold(I)] chloride (R = pyridyl)

FIG. 12.

Experimental Au^I drugs.

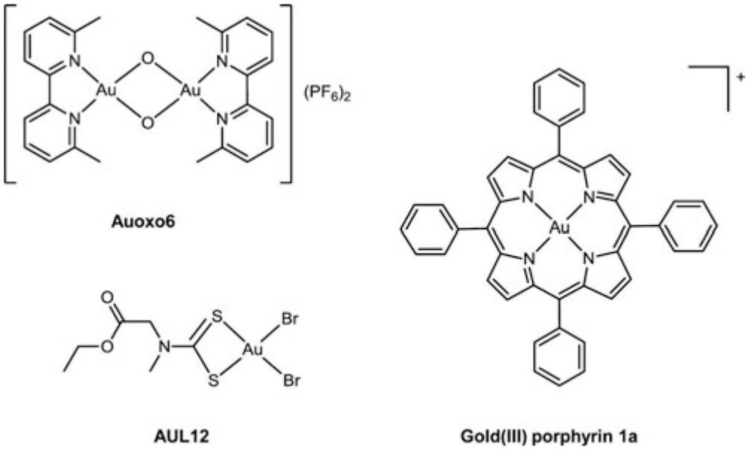


FIG. 13.
Experimental Au^{III} drugs.

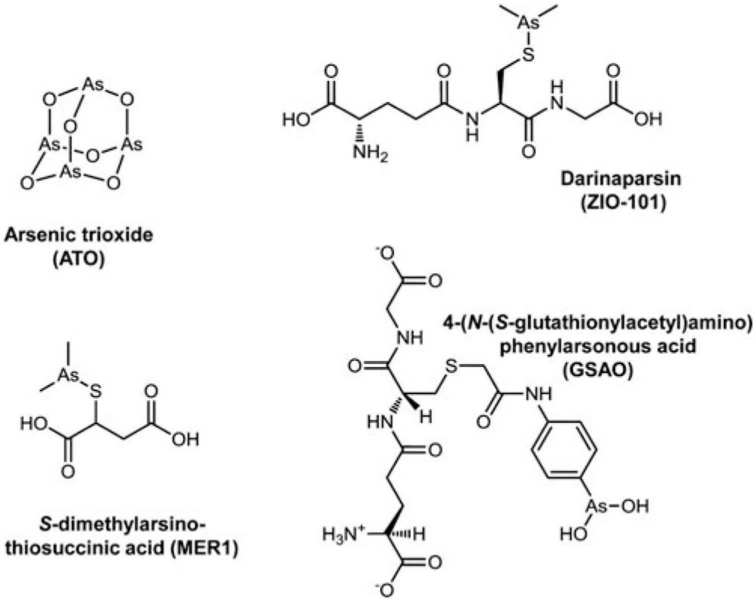


FIG. 14.

As^{III} drugs. ATO is approved for treatment of acute promyelocytic leukemia, whereas the other compounds are in (pre)clinical development.

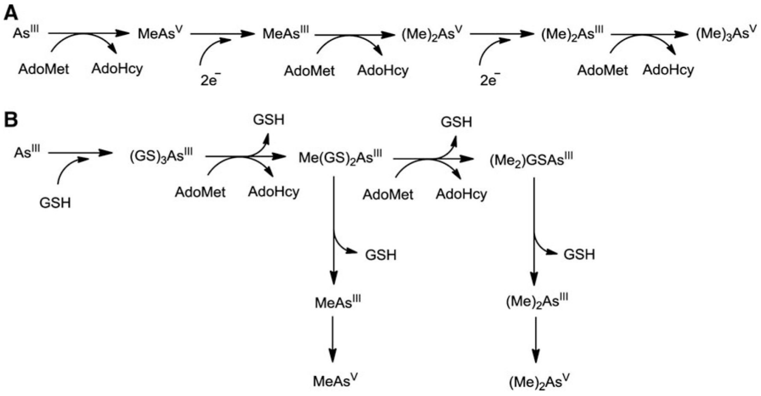


FIG. 15.

Arsenic Metabolism. (A) The classical oxidative methylation pathway of arsenic is shown involving sequential reactions of reduction and oxidative methylation steps. (B) Alternative pathway scheme for methylation of arsenic involving generation of arsenic-glutathione (GSH) complexes. From ref. (373).

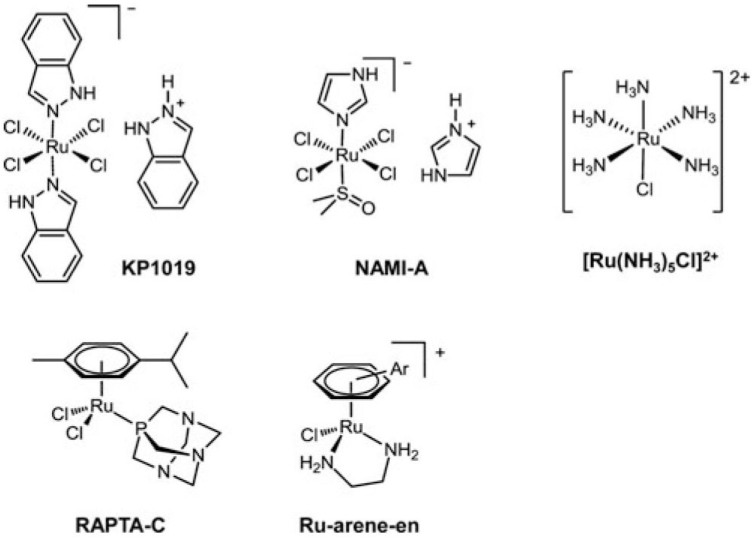
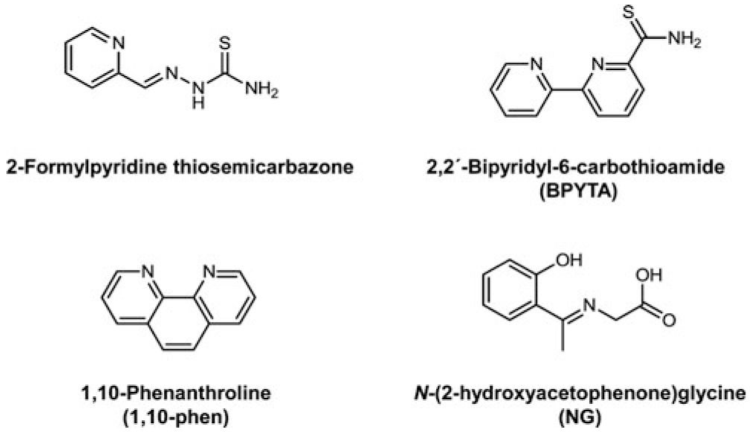


FIG. 16.

Ruthenium drugs. KP1019 and NAMI-A have been already evaluated in clinical trials, whereas all others are under preclinical investigation.



2-Formylpyridine thiosemicarbazone

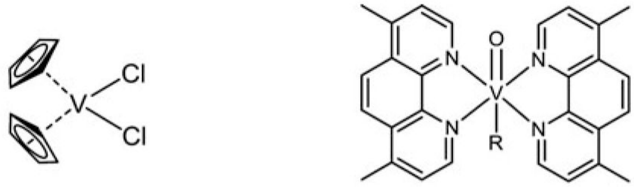
2,2´-Bipyridyl-6-carbothioamide (BPYTA)

1,10-Phenanthroline (1,10-phen)

***N*-(2-hydroxyacetophenone)glycine (NG)**

FIG. 17.

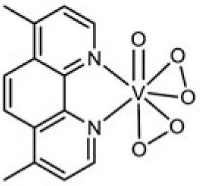
Ligands of the best investigated anticancer Cu^{II} complexes.



Vanadocene dichloride

R = SO_4^{2-}

[Bis(4,7-dimethyl-1,10-phenanthroline) sulfatooxovanadium^{IV}] (Metvan)



[(4,7-Dimethyl-1,10-phenanthroline)bis(peroxo)oxovanadium^{IV}]

FIG. 18.

Vanadium drugs with anticancer potential.

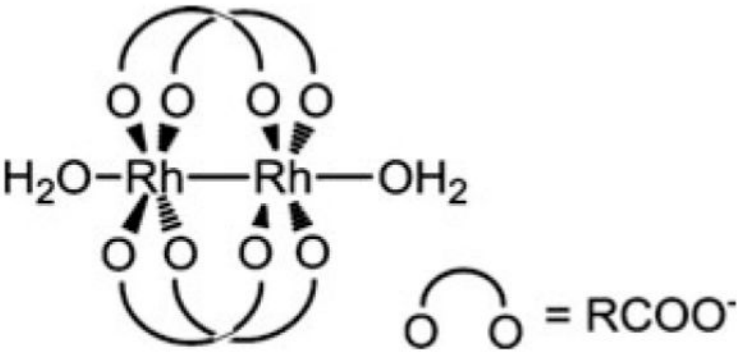
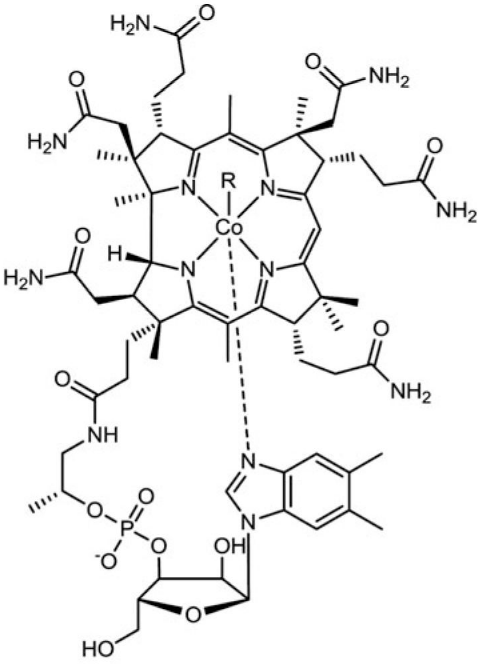


FIG. 19.
General structure of Rh^{II} carboxylato complexes.



R = CH_3, OH, H_2O, 5`-deoxyadenosyl

FIG. 20.

Vitamin B12 (Cobalamin).

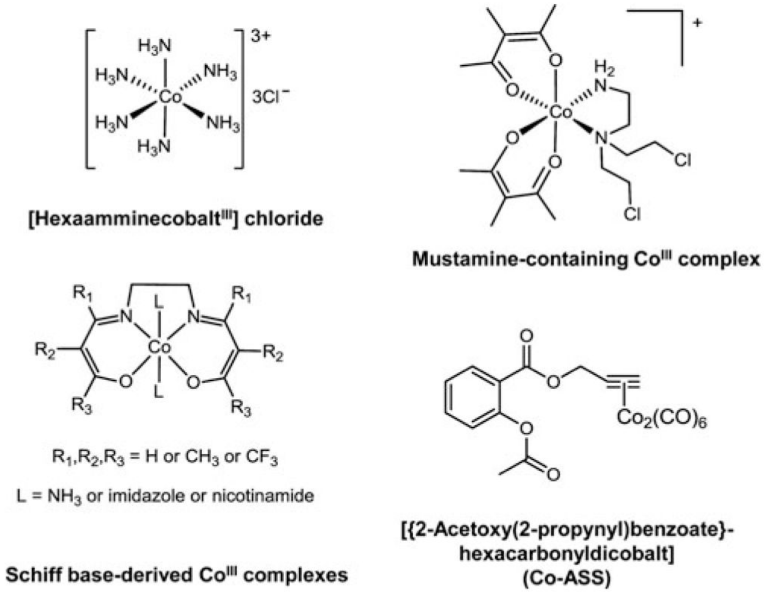


FIG. 21.

Anticancer cobalt compounds.

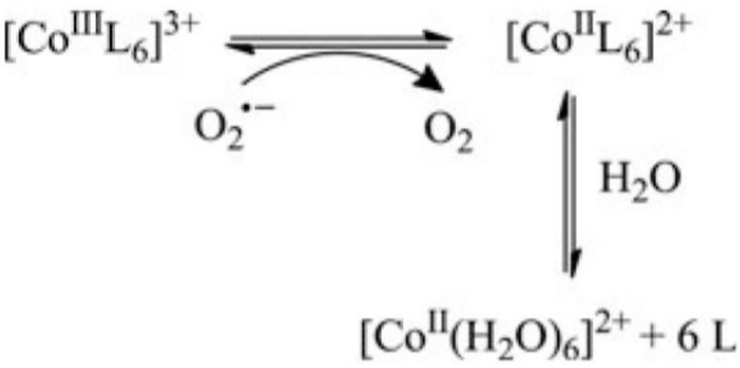
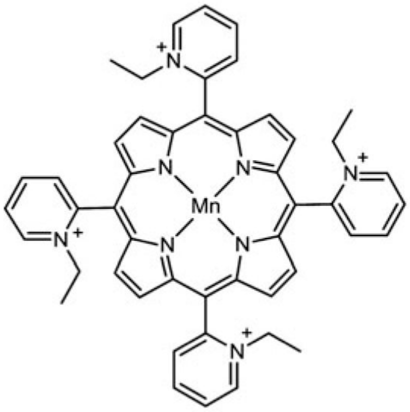
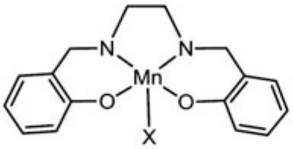


FIG. 22.

Ligand release after reduction of Co^{III} complexes (285). In the case of Co^{III} complexes it is assumed that in the hypoxic tumor tissue the Co^{III} metal center can be reduced to Co^{II}, for example, by superoxide radicals. Due to the lower stability of the Co^{II} complexes the cytotoxic ligands are released under formation of $[Co^{II}(H_2O_2)_6]^{2+}$.



Mn^{III}-porphyrin complex
MnTE-2-PyP^{5+}



Mn^{III}-salen complexes

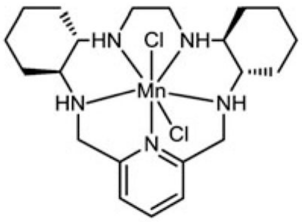


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FIG. 23.
Manganese drugs under preclinical development as SOD mimics.

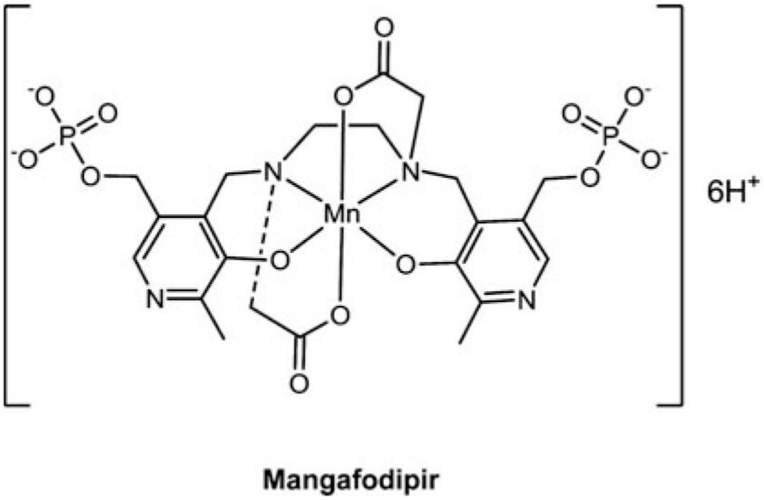

FIG. 24.

Structure of Mangafodipir. This compound is in clinical use as contrast agent.

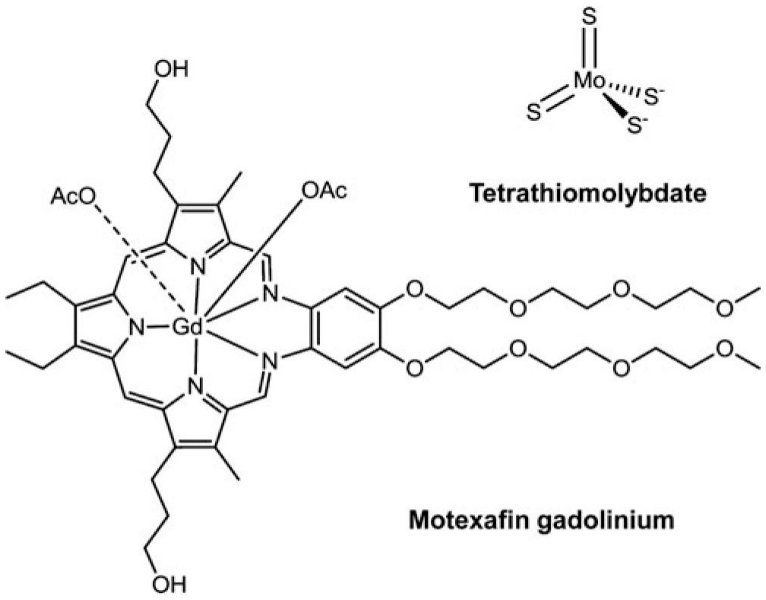

FIG. 25.

Anticancer complexes with redox-silent metal centers under clinical investigation.

Table 1

Overview of Physicochemical and Biological Properties of the Most Important Reactive Oxygen Species[a]

	Reactivity	*Reactions in cells*	*$E^{o\prime}$ [V]*[b]	*Antioxidative defense*
$OH^{\bullet}$	Most reactive oxygen radical, which reacts immediately at its origin	Reacts immediately with almost every molecule found in living cells, including sugars, amino acids, phospholipids, and DNA bases	+ 2.31 $[OH^{\bullet} + e^{-} + H^{+} \leftrightarrow H_2O]$	Glutathione
$O_2^{\bullet -}$	Low reactivity in aqueous solution at pH 7.4, damage is based on reactions with other radicals or metal ions; membrane impermeable but can cross cell membranes *via* anion channels (379)	Reaction with [Fe-S] clusters and radicals such as $NO^{\bullet}$ generating peroxynitrit ($ONOO^{-}$)	+ 0.94 $[O_2^{\bullet -} + e^{-} + 2H^{+} \leftrightarrow H_2O_2]$ or −0.16 $[O_2 + e^{-} \leftrightarrow O_2^{\bullet -}]$(336)	Superoxide dismutase; glutathione; nonenzymatic dismutation
H_2O_2	Weak oxidizing and reducing agent; generally poorly reactive; very diffusible between cells	Oxidation of cysteine and methionine; can be reduced to $OH^{\bullet}$ by transition metals like Fe^{II} (Fenton reaction)	+ 0.32 $[H_2O_2 + e^{-} + H^{+} \leftrightarrow H_2O + OH^{\bullet}]$	Catalase; peroxidases; peroxiredoxins (319)

[a] Unless otherwise stated the data are from ref. (140).

[b] Redox potentials versus NHE at pH 7, with 1 *M* concentrations of oxidized and reduced form.

Table 2

Influence of Ligand Exchange on the Redox Potential[a]

Compound	***$E_{1/2}$ (Ru^{III}/Ru^{II}) V vs. NHE[b]***
$[Ru^{III}Cl_6]^{3-}$	− 1.36[c]
$[Ru^{III}Cl^{5}(Hind)]^{2-}$	− 0.87[c]
trans-$[Ru^{III}Cl_4(Hind)_2]^{-}$	− 0.43
mer-$[Ru^{III}Cl_3(Hind)_3]^{0}$	+ 0.10
trans-$[Ru^{III}Cl_2(Hind)_4]^{+}$	+ 0.59

[a] Values taken from ref. (318).

[b] Redox potentials in V± 0.02, measured at a scan rate of 0.20 V/s in [*n*-Bu_4N][BF_4]/dimethylformamide.

[c] Adequate detection was hampered by rearrangement of the complexes in dimethylformamide; therefore, the potentials were estimated using Lever's parametrization approach (213): $E_{1/2} = S_M \cdot \sum E_{Ligand} + I_M$ (with $S_M = 1.14$; $E_{Cl} = -0.24$ and $E_{Hind} = 0.26$; $I_M = -0.35$).