Drug Resistance Updates 58 (2021) 100778

Contents lists available at ScienceDirect

Drug Resistance Updates

journal homepage: www.elsevier.com/locate/drup

Metal- and metalloid-based compounds to target and reverse cancer multidrug resistance

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ARTICLE INFO

Keywords:
Platinum
ruthenium
copper
iridium
organoselenium
metal drugs
drug resistance
collateral sensitivity

ABSTRACT

Drug resistance remains the major cause of cancer treatment failure especially at the late stage of the disease. However, based on their versatile chemistry, metal and metalloid compounds offer the possibility to design fine-tuned drugs to circumvent and even specifically target drug-resistant cancer cells. Based on the paramount importance of platinum drugs in the clinics, two main areas of drug resistance reversal strategies exist: overcoming resistance to platinum drugs as well as multidrug resistance based on ABC efflux pumps. The current review provides an overview of both aspects of drug design and discusses the open questions in the field. The areas of drug resistance covered in this article involve: 1) Altered expression of proteins involved in metal uptake, efflux or intracellular distribution, 2) Enhanced drug efflux via ABC transporters, 3) Altered metabolism in drug-resistant cancer cells, 4) Altered thiol or redox homeostasis, 5) Altered DNA damage recognition and enhanced DNA damage repair, 6) Impaired induction of apoptosis and 7) Altered interaction with the immune system. This review represents the first collection of metal (including platinum, ruthenium, iridium, gold, and copper) and metalloid drugs (e.g. arsenic and selenium) which demonstrated drug resistance reversal activity. A special focus is on compounds characterized by collateral sensitivity of ABC transporter-overexpressing cancer cells. Through this approach, we wish to draw the attention to open research questions in the field. Future investigations are warranted to obtain more insights into the mechanisms of action of the most potent compounds which target specific modalities of drug resistance.

1. Introduction

1.1. Anticancer metal drugs in clinical use and development

Since the beginning of medicine, metal drugs have been key remedies to treat various diseases. Important examples include gold and copper complexes, which have been used by ancient Egyptians and Chinese cultures against several maladies such as syphilis and cancer (Faa et al., 2018; Ndagi et al., 2017). In addition, arsenic trioxide (ATO, Trisenox, Fig. 1) has a long history of almost 2000 years in Traditional Chinese Medicine as a medication against diverse diseases, including cancer (Pötsch et al., 2019). In fact, ATO is still used, as it has been approved for the treatment of acute promyelocytic leukemia (APL) in 2000 (Sanz et al., 2019). The clinical success of metal drugs in modern cancer therapy started with the discovery of cisplatin in the 1970s. To date, the three platinum complexes cisplatin, oxaliplatin and carboplatin are among the most important anticancer drugs (Fig. 1), with one of these drugs applied in basically every second therapeutic regimen. The importance of these three platinum compounds is also indicated by their inclusion in the "list of essential medicines" of the World Health Organization (WHO, www.who.int). However, severe adverse effects and drug resistance remain the main obstacles of this therapy, especially at

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https://doi.org/10.1016/j.drup.2021.100778
Received 31 March 2021; Received in revised form 18 June 2021; Accepted 3 August 2021
Available online 6 August 2021

the advanced stage of the disease (Cheff and Hall, 2018; Heffeter et al., 2008). Consequently, various platinum drugs have been clinically investigated, but only nedaplatin, heptaplatin, and lobaplatin have gained regional approval in Japan, Korea, and China, respectively (Johnstone et al., 2016) (Fig. 1). Moreover, inspired by the potent biological activities of many drug candidates, a multitude of new metal compounds have been (and still are) designed and (pre)clinically developed (Gibson, 2019; Johnstone et al., 2016; Kenny and Marmion, 2019; Simpson et al., 2019; Yeo et al., 2018). Especially noteworthy are the platinum(II) drug picoplatin and the platinum(IV) derivative, satraplatin, as these cytotoxic drugs were tested in phase III clinical trials against small cell lung cancer (SCLC) and hormone-refractory prostate cancer, respectively (Choy et al., 2008; Ciuleanu et al., 2010; Johnstone et al., 2016; Pötsch et al., 2019) (Fig. 1). Apart from these drugs, more than a dozen additional platinum compounds, and several complexes based on other metals such as ruthenium, gold, copper and gallium or metalloids like arsenic and selenium (but also radiopharmaceuticals, which are not discussed in this review), have entered clinical trials during the last decades (Pötsch et al., 2019). Well-known examples are the ruthenium complexes (Fig. 1): NAMI-A (imidazolium *trans*-[tetrachlorido(dimethyl sulfoxide)(imidazole)Ru(III)]) developed by Sava and co-workers, KP1019 (indazolium *trans*-[tetrachloridobis (indazole)Ru(III)]) and its sodium salt NKP1339/IT-139/BOLD-100 (sodium *trans*-[tetrachloridobis(indazole)Ru(III)]) developed by Keppler and co-workers (Alessio and Messori, 2019; Lipponer et al., 1996; Trondl et al., 2014), which recently entered a phase IB clinical trial in combination with the FOLFOX regimen for advanced solid tumors (NCT04421820) or TLD1433 ([Ru(4,4′-dimethyl-2,2′-bipyridine)$_2$(2-(2′,2″:5″,2‴-terthiophene)-imidazo[4,5-f][1,10]phenanthroline)]Cl_2) (Fig. 1), which is currently tested in a phase II trial against invasive bladder cancer (NCT03945162). Moreover, the gold complex auranofin (Fig. 1), a well-known thioredoxin reductase (TrxR) inhibitor, has entered clinical phase I and II trials for the treatment of gynecological (NCT01747798 and NCT03456700), non-small cell lung cancer (NSCLC, NCT01737502) as well as chronic lymphocytic leukemia (NCT01419691), while gold sodium thiomalate is in phase I testing against advanced NSCLC (NCT00575393). Other examples which have been tested/developed in respect to the treatment of drug-resistant cancer cells will be discussed in greater detail in the respective subchapters of the current review.

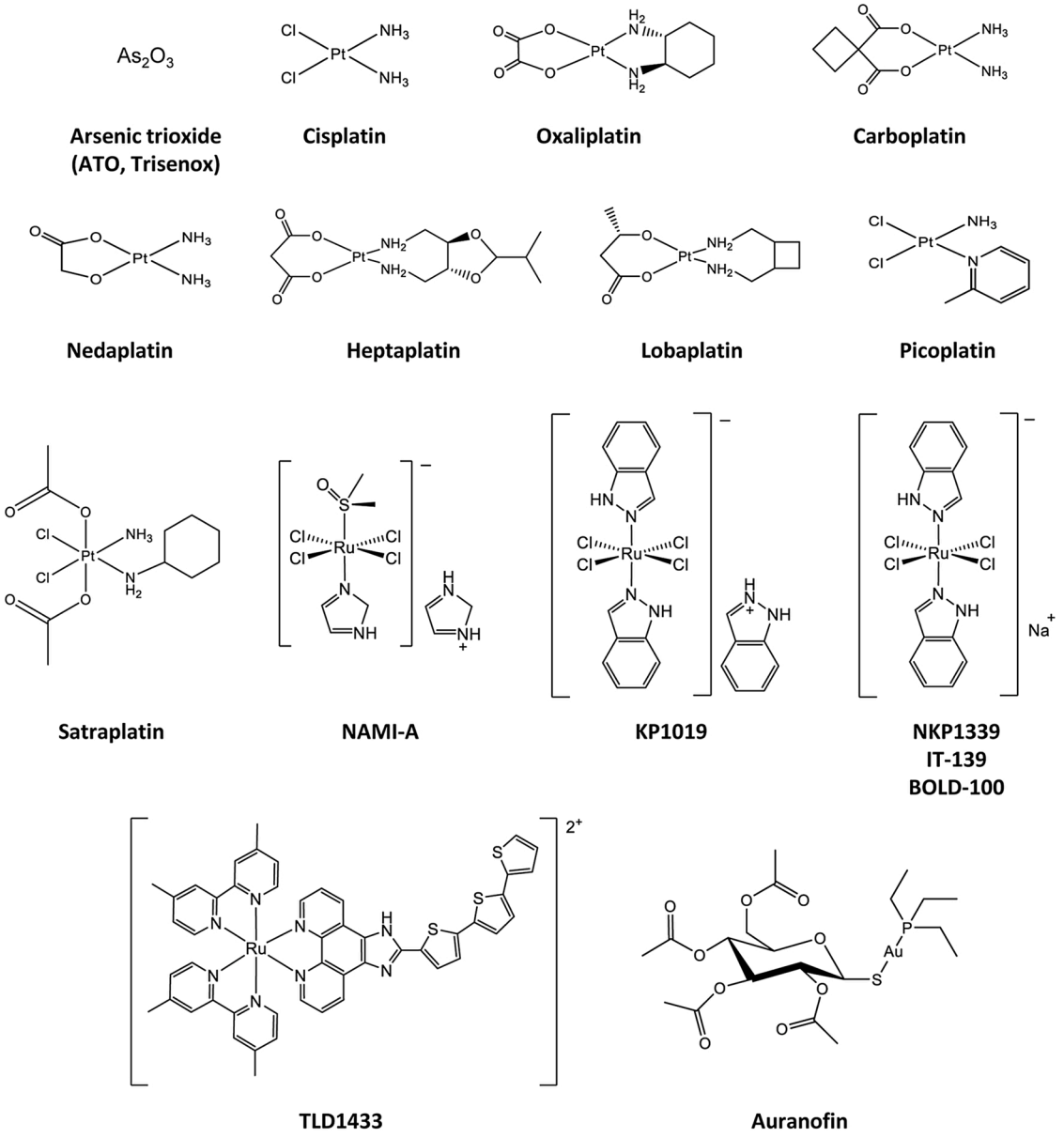


Fig. 1. Overview of approved or clinically investigated metal drugs.

1.2. Metal compounds are anticancer drugs with multi-faceted modes of action

Due to their multi-faceted biological activity, a clear-cut target is not always easy to identify for metal or metalloid drugs. For example, clinically approved platinum drugs are widely accepted to target DNA and, hence, their activities are known to be influenced by DNA damage response pathways or respective repair mechanisms (Makovec, 2019). However, even in the case of cisplatin, only a small amount of platinum finally ends up at the DNA in the cancer cell nucleus (Makovec, 2019). The majority of platinum molecules is interacting with other nucleophilic targets already in the circulation, the plasma membrane, the cytoplasm or within organelles like mitochondria (Jungwirth et al., 2011; Lai et al., 2018; Makovec, 2019). Besides their role in drug resistance and adverse effects such as nephrotoxicity (Englinger et al., 2019; Makovec, 2019; Riddell, 2018), there is increasing evidence that such protein targets are central to the activity of several metal or metalloid drugs (Bose, 2002; Cubo et al., 2010; Flocke et al., 2016; Roder and Thomson, 2015; Tomaz et al., 2012). In line with the assumption that DNA damage is not the only mode of action of metal drugs, it has become progressively clear that many metal drugs exert complex and distinct impacts on the patient's immune system. As one impressive example, oxaliplatin must be mentioned, which has distinctly reduced anticancer activity under immunosuppressed conditions (Englinger et al., 2019).

In general, one needs to discriminate between simple metal salts and coordination complexes. In the latter respect, the central metal is bound to ligands in a mono- or multidentate fashion by heteroatoms such as O, N, S, Cl (see for example cisplatin, Fig. 1). In addition, there is an important subclass of coordination compounds, namely organometallic compounds, containing at least one bond between a carbon atom and a metal (sometimes broadened to include metalloids), such as e.g. ruthenium(II) arene compounds. The choice of ligands to complete the coordination sphere of the metal compounds also dictates their overall solubility, stability, ligand exchange kinetics, as well as their ability to interact with biological targets.

However, the underlying biological modes of action appear to strongly depend on the chemical/physical properties of the central metal ion. Especially the hardness/softness of a metal ion has a strong impact on the behavior of the complexes in biological systems (LoPachin et al., 2019). In more detail, 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 (Jungwirth et al., 2011; LoPachin et al., 2019). Consequently, soft acids react more easily and form stronger bonds with soft bases, whereas hard acids have a preference for hard bases. The biological consequence of this chemical concept is, for example, that soft acids like Pt(II), As(III), or Au(I) easily react with soft bases like the sulfur-containing tri-peptide glutathione (GSH) or other cysteine-rich molecules, such as thioredoxin (Trx) and metallothioneins (MT) (Raab and Feldmann, 2019).

One central characteristic in the mode of action of several metal drugs is their redox reactivity, as in contrast to most organic anticancer therapeutics being redox-inactive in the cellular environment, many metal-containing drugs can undergo redox processes and/or interact with the redox homeostasis of the cancer cell (Jungwirth et al., 2011). Noteworthy, reduction/oxidation often significantly influences and alters the physiological properties of some metal complexes (e.g. platinum (IV), ruthenium(III), cobalt(III)) including geometry, charge and reactivity. Consequently, there are several metal-based prodrug systems, which are currently exploited to enhance the tumor specificity of therapy and to allow selective targeting of resistant tumors (Johnstone et al., 2016; Jungwirth et al., 2011; Simpson et al., 2019). Here, the concept named "activation by reduction" is of special importance (Fig. 2). In a nutshell, this concept is based on the idea of a less cytotoxic prodrug,

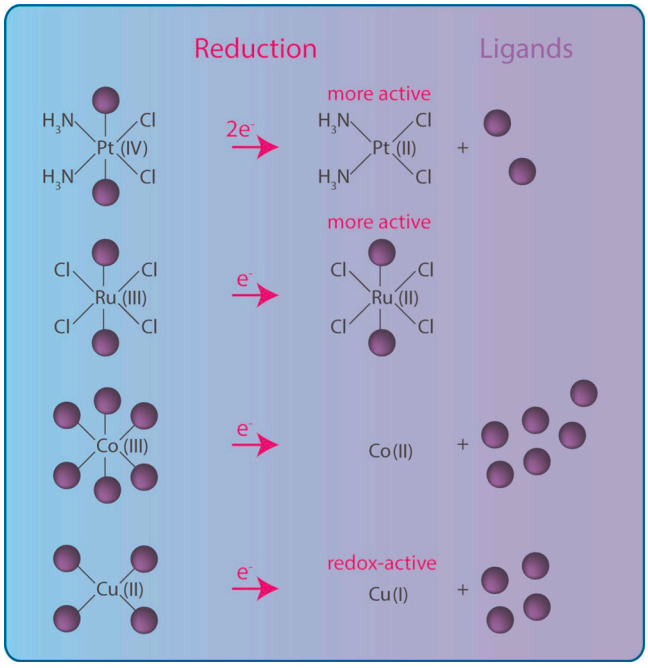


Fig. 2. Consequences of reduction on the diverse metal drugs ("Activation by reduction principle").

which is then activated in the tumor tissue by reduction. Particularly in the case of platinum(IV), ruthenium(III), cobalt(III), and copper(II) drugs, activation by reduction is believed to be important for their modes of action. Noteworthy, reduction frequently results in labilization/dissociation of attached ligands, which is exploited with the aim of tumor-specific delivery and release of specific bioactive (inhibitory) ligands. Hydrolysis too is a very common mechanism of bioactivation for drugs containing transition metals. This involves the displacement of weakly bound ligands by aqua ligand. The bestknown compound with such a mechanism of activation is cisplatin (Anthony et al., 2020).

In addition to metal drugs, in the field of metal therapeutics there are several attempts to use metal or metalloid cores (e.g. gold and selenium) for the preparation of nanoformulations. However, as there are diverse excellent reviews on this subject area, metal-based nanoformulations are not discussed in the present review. Moreover, we would like to stress that in this introduction section, it was neither our aim to list all anticancer metal-based drugs that are currently used in clinical practice nor to describe all their known mechanisms of action. Many excellent reviews on these topics are available (for example (Anthony et al., 2020; Boros et al., 2020)). We have focused mainly on data that are relevant to the field of multidrug resistance (MDR).

2. Common mechanisms of MDR

As already mentioned, drug resistance is one of the major obstacles towards the curative treatment of advanced and disseminated cancers (Assaraf et al., 2019; Bar-Zeev et al., 2017; Das et al., 2021; Gonen and Assaraf, 2012; Li et al., 2016b; Livney and Assaraf, 2013; Zhitomirsky and Assaraf, 2016). In general, there are two types of drug resistance. On the one hand, cancer cells can be intrinsically resistant to therapy, which is often observed when the disease arises from a tissue that is already physiologically highly protected from toxins and metabolites such as the liver or the kidneys. On the other hand, initially (chemo)sensitive cancer cells can rapidly develop "acquired" drug resistance as a response to the applied therapy regimen. One very problematic phenomenon here is the so-called MDR, which indicates that the malignant cells become not only resistant against the applied antitumor agent but develop resistance to a broad array of compounds with different structures and modes of action

(Andrei et al., 2020; Assaraf et al., 2014; Cui et al., 2018; Lepeltier et al., 2020; Li et al., 2016b; Robey et al., 2018; Szakacs et al., 2014; Wang et al., 2021). A summary of the most frequently emerging mechanisms of drug resistance against cisplatin is shown in Fig. 3.

Anticancer drug resistance can arise from a multitude of underlying mechanisms including for example impaired drug uptake into the tumor (cell), enhanced drug efflux, altered drug target, changed damage recognition/enhanced DNA repair, impaired induction of apoptosis as well as drug sequestration away from its target (Fig. 4) (Marin et al., 2019; Rottenberg et al., 2021; Zhou et al., 2020). Moreover, there is increasing evidence that not only alterations in cancer cells themselves mediate chemoresistance. The entire composition of the tumor microenvironment (TME), containing multiple cell types such as fibroblasts or immune cells, has a strong impact on therapy success and failure (Englinger et al., 2019; Petanidis et al., 2019; Rottenberg et al., 2021). As metal drugs are versatile tools to interact with multiple aspects of (multi)drug resistance, the following sub-chapters provide an overview of the most important factors which have been in the focus of metal drug design during recent years. Notably, two main areas of drug resistance reversal by metal or metalloid drugs exist: 1) overcoming resistance to platinum-based therapy, and 2) surmounting classical MDR. This review provides an overview regarding both aspects of drug design.

2.1. *Altered expression of proteins involved in metal uptake, efflux or intracellular distribution*

One of the main mechanisms of MDR is the marked decrease in the intracellular drug concentration that leads to diminished drug cytotoxicity. Membrane transporters are responsible for the bioavailability of different anticancer drugs through the regulation of drug uptake and efflux (DeGorter et al., 2012). Several transport mechanisms have been discussed for the uptake of metal drugs (Spreckelmeyer et al., 2014; Zhitomirsky and Assaraf, 2016). For example, some studies have demonstrated that proteins controlling copper, for example CTR1, could be involved in the regulation of the cellular levels of basically all clinically used platinum drugs (Ferreira et al., 2016; Howell et al., 2010; Kuo et al., 2007; Lai et al., 2018; Song et al., 2004). CTR1 is a high-affinity transporter responsible for energy-independent copper transport (Lee et al., 2002). This transporter is abundantly expressed in the choroid plexus, renal tubules and connective tissues of the eye, ovary and testis (Kuo et al., 2001). A study by Larson et al., showed that mouse embryonic fibroblasts lacking CTR1 exhibited reduced uptake of cisplatin, carboplatin, and to a lesser extent, oxaliplatin (Larson et al., 2009). However, novel platinum drugs, such as satraplatin and JM118, were not transported by CTR1 (Safaei and Howell, 2005; Samimi and Howell, 2006). Moreover, CTR1 plays a clinically important role in the cellular uptake of cisplatin (Kuo et al., 2007), and consequently, its expression is associated with the responsiveness of patients to platinum therapy (Sun et al., 2017; Zhitomirsky and Assaraf, 2016). In contrast, CTR1 showed only low transport activity for other metals such as iron or zinc. Other metal drugs were also suggested to be transported by CTR1 (Novohradsky et al., 2014), indicating that its downregulation as a mechanism of resistance could also impact these drugs. An additional transporter, which needs to be mentioned with respect to platinum drugs, is the copper-transporting exporter ATP7B. This protein, which is usually localized at the Golgi apparatus, has been also shown to facilitate

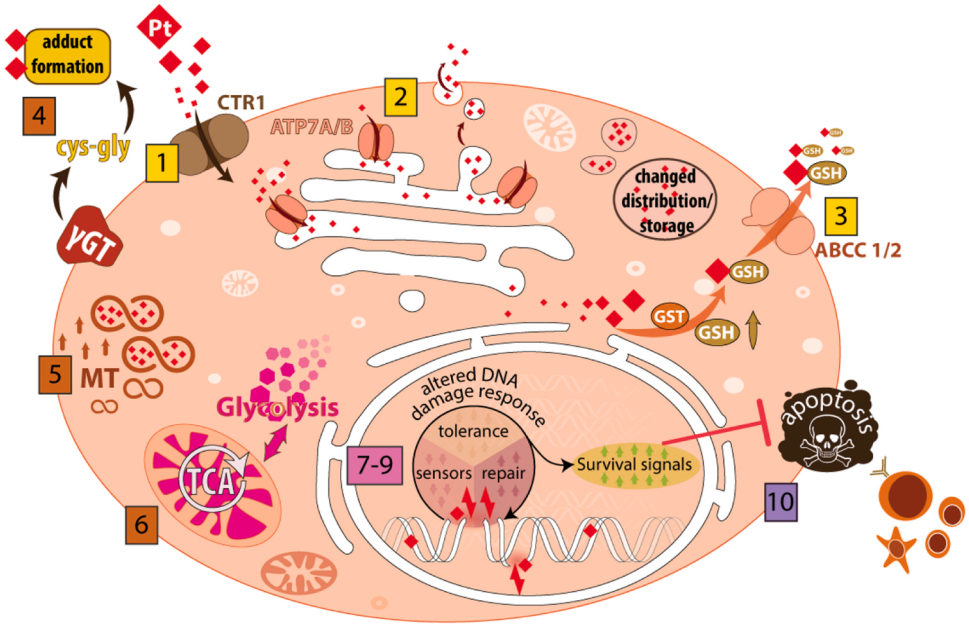


Fig. 3. Overview on the most common mechanisms of drug resistance against platinum drugs.

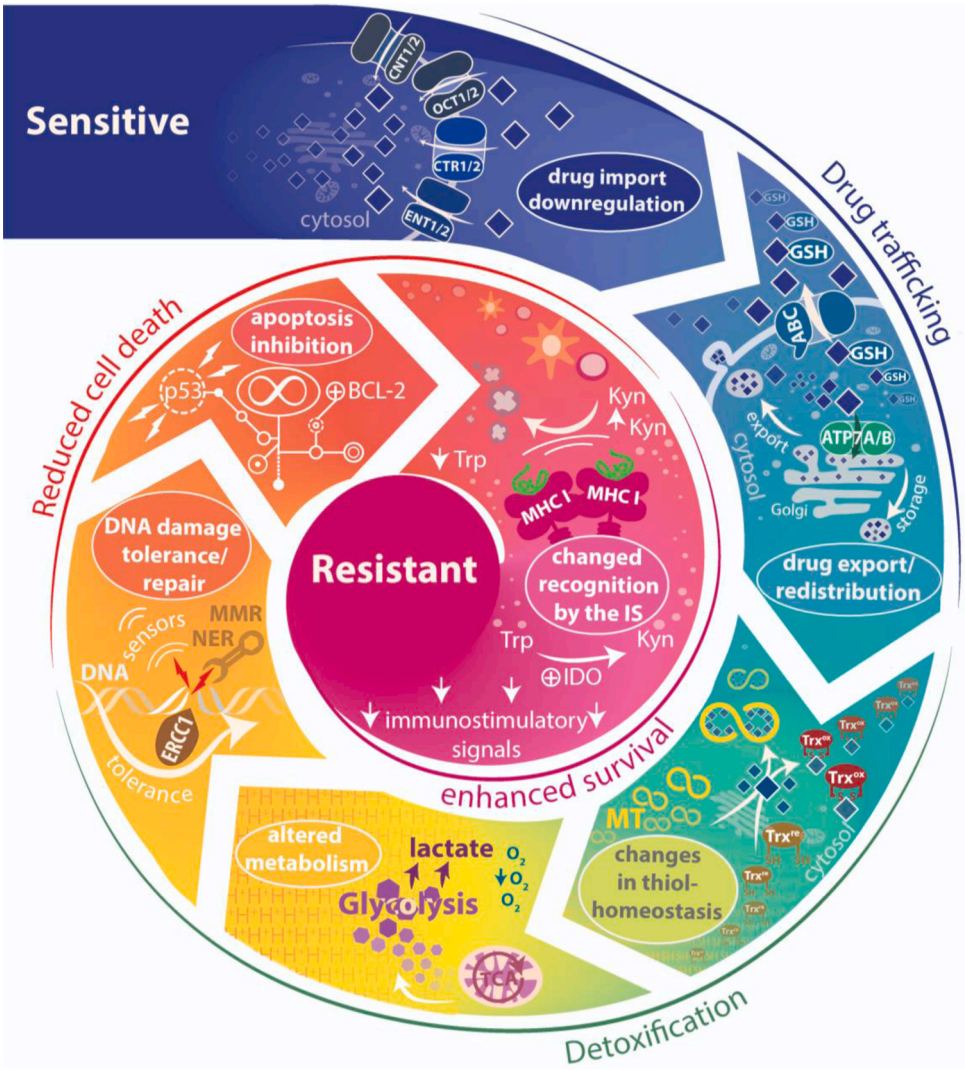


Fig. 4. Cancer cells can develop drug resistance (against metal drugs) on all steps from drug entry to cell death induction.

lysosomal exocytosis, which in turn results in resistance to platinum drugs due to enhanced drug efflux (Lai et al., 2018; Zhitomirsky and Assaraf, 2016). Noteworthy, while there is some literature on platinum drugs, these aspects, especially with respect to drug resistance are widely unexplored for most non-platinum drugs.

2.2. Enhanced drug efflux by ABC transporters

ATP-binding cassette (ABC) transporters are the most extensively studied efflux transporters involved in MDR development. The human ABC transporter superfamily comprises 48 members distributed into seven subfamilies (ABCA-G) (Cui et al., 2018; Domenichini et al., 2019; Robey et al., 2018; Szakacs et al., 2014). These transmembrane proteins utilize the energy from ATP hydrolysis to transport xenobiotics, metabolites and signaling molecules against a concentration gradient across the cell membrane. Most common members of the ABC superfamily that efflux anticancer drugs are ABCB1 (P-glycoprotein/P-gp/MDR1), ABCC1 (multidrug resistance protein 1/MRP1) and ABCG2 (breast cancer resistance protein/BCRP) (Dinic et al., 2018).

The first described and maybe the best-characterized member of the ABC transporter superfamily is ABCB1 due to its important role in the development of MDR (Ambudkar et al., 1999). This 170 kDa glycoprotein, encoded by the *ABCB1* gene, is normally expressed at physiological barriers and in excretory tissues, including the blood-brain barrier, gastrointestinal tract, kidney, lung and liver (Fletcher et al., 2016). ABCB1 displays a broad substrate specificity with a multitude of compounds identified as its transport substrates. A highly flexible drug-binding pocket enables different compounds to bind ABCB1 simultaneously, and the same compound could bind several distinct sites on ABCB1 (Stankovic et al., 2018). ABCB1 regulates the efflux of various neutral or positively charged hydrophobic compounds, including a wide range of clinically important chemotherapeutics such as paclitaxel or vincristine (Fletcher et al., 2016).

ABCC1, a 190 kDa protein, plays an important role in protecting various tissues from xenobiotics and therefore is widely expressed in physiological barriers including oral epithelium, kidneys, testes, and peripheral blood mononuclear cells (Podolski-Renic et al., 2016; Wang et al., 2021). Due to its role in MDR and drug efflux, ABCC1 is also known as multidrug resistance protein 1 (MRP1). ABCB1 and ABCC1 have broadly similar substrate specificity. However, besides hydrophobic molecules, ABCC1 is also able to export organic anions conjugated to GSH, glucuronate or sulfates. Moreover, the efflux of many hydrophobic compounds by ABCC1 is highly dependent on GSH (Deeley and Cole, 2006). Many important cancer chemotherapeutics are ABCC1 substrates, including etoposide, doxorubicin, vincristine, irinotecan, mitoxantrone and methotrexate (Fletcher et al., 2016).

ABCG2, a small (70 kDa) half-transporter that functions as a homodimer, was first identified in a MDR breast cancer cell line and,

therefore, is also called breast cancer resistance protein (BCRP) (Doyle et al., 1998). However, ABCG2 is expressed in various normal tissues including the gastrointestinal tract, excretory tissues and blood-tissue barriers with the highest levels found in the placenta (Podolski-Renic et al., 2016). Although ABCG2 transports a wide range of conventional chemotherapeutics such as doxorubicin, daunorubicin, mitoxatrone and irinotecan (Bram et al., 2009), it is also capable of transporting tyrosine kinase inhibitors (Hegedus et al., 2012; Mao and Unadkat, 2015). ABCG2 is also overexpressed in a subpopulation of cancer cells with stem cell-like properties such as self-renewal capacity and high chemoresistance (Podolski-Renic et al., 2016).

Although metal-based compounds are generally poor substrates for ABC transporters, several studies suggested that ABCC2 and ABCC4 might be involved in the transport of some platinum compounds (Heffeter et al., 2008; Lai et al., 2018; Martinez-Balibrea et al., 2015). Moreover, ABCB1-overexpressing cell lines displayed resistance to several ruthenium compounds (Aird et al., 2002; Heffeter et al., 2005). Noteworthy, ABCC1/2 transport could be of relevance for copper complexes, as we were able to show that some were able to form ternary complexes with GSH, in turn leading to their recognition by these GSH-conjugate transporters (Bormio Nunes et al., 2020).

2.3. Alterations in metabolism of drug-resistant cancer cells

Based on its enhanced proliferation rate, cancer is a disease characterized by the constant generation of new biomass. Consequently, to satisfy their high demand for new building blocks, it is not surprising that malignant cells differ in their nutrient acquisition and metabolic pathways from healthy tissues (Palm and Thompson, 2017). For example, a shift towards increased glycolytic metabolism even in the presence of oxygen (the so-called Warburg effect) is observed (Icard et al., 2018; Palm and Thompson, 2017), which is also associated with the upregulation of glucose uptake via the glucose transporters GLUT1 or GLUT4. In addition, enhanced receptor-mediated endocytosis of nutrient carriers (e.g., the iron transport protein transferrin) or catabolism of plasma proteins like albumin as an amino acid source are characteristic of malignant tissues (Palm and Thompson, 2017; Torti and Torti, 2013). Notably, there is increasing evidence that this shift in metabolism is also associated with therapy resistance (Icard et al., 2018). For example, Harper et al., reported that drug-resistant cancer cells (cisplatin-resistant as well as MDR cells) were characterized by low mitochondrial potential and the use of non-glucose carbon sources (such as fatty acids) for mitochondrial oxygen consumption based on high levels of the mitochondrial uncoupling protein 2 (Harper et al., 2002). Moreover, in another study, cisplatin-resistant patient-derived xenografts were characterized by a different metabolic make up (Ricci et al., 2019). In detail, upregulation of glycolysis, tricarboxylic acid cycle and the urea cycle were found. In addition, the oxygen consumption rate and mitochondrial respiration were increased upon acute stress. Carboplatin resistance was shown to partially depend on enhanced glucose metabolism based on PKM2 overexpression (Liu et al., 2017b). In a study on ascitic cells collected from epithelial ovarian cancer patients, cancer cells with glucose-independent metabolism were characterized by carboplatin resistance (Pasto et al., 2017). Finally, a recent study on cisplatin-resistant ovarian carcinoma cells showed that these cells undergo a shift towards a more oxidative metabolism together with a general increase in the mitochondrial compartment (Zampieri et al., 2020). Collectively, these findings indicate that metabolic alterations might represent an Achilles heel, which could be exploited for the treatment of drug-resistant cancers.

2.4. Altered thiol or redox homeostasis

Redox homeostasis is essential for maintaining normal cellular functions. Imbalance in redox homeostasis leads to oxidative stress due to increased ROS production (Perry et al., 2000). Many types of cancer have increased ROS levels (Szatrowski and Nathan, 1991). In order to adapt to oxidative stress, cancer cells have developed an enhanced antioxidant capacity through activation of GSH detoxification and the Trx systems (Fig. 5) (Galadari et al., 2017). The GSH detoxification system is composed of GSH, GSH peroxidase (GPx), GSH reductase (GR), GSH-S-transferases (GSTs) as well as GSH export pumps (e.g. ABC transporters like ABCC1/2) (Bredel, 2001). GSH is a tripeptide (L-γ-glutamyl-L-cysteinyl-glycine) with various functions in living organisms. As a carrier of the active thiol group in the form of a cysteine residue, GSH acts as an antioxidant directly, by interacting with reactive molecules or as a cofactor of numerous enzymes (Lushchak, 2012). Moreover, GSH can detoxify many metal drugs e.g. platinum or ruthenium complexes by direct interaction between its thiol and the metal center (Hrabeta et al., 2016; Jungwirth et al., 2011; Lai et al., 2018). Consequently, enhanced intracellular GSH levels have been frequently found in many metal drug-resistant cell models (Table 1). However, GSH is also discussed as an intracellular reducing agent responsible for activation via reduction of several metal drugs (Fig. 5) (Heffeter et al., 2008; Jungwirth et al., 2011). Consequently, the role of GSH is not always easy to assess and might even constitute an Achilles heel of cancer cells for drug targeting.

GPx uses GSH as the substrate to reduce hydrogen peroxide and lipid hydroperoxides. GR then reduces the oxidized disulfide form of GSH (GSSG), thereby recycling the GSH molecule (Cui et al., 2018; Kearns and Hall, 1999). GSH participates in phase II metabolism of xenobiotics, including anticancer agents as well as in reactions catalyzed by GSTs (Lushchak, 2012), leading to the formation of less toxic and more soluble conjugates that are actively transported by GSH export proteins (including ABCC1/2). Therefore, the higher expression and activity of GSTs play a role in resistance to platinum compounds. This resistance is based on the enhanced formation of non-covalently bound complexes between platinum compounds and GSH, which produces more inactive metabolites and reduces intracellular concentration of active drugs (Bredel, 2001; Cui et al., 2018; Lai et al., 2018; Marin et al., 2019; Surowiak et al., 2005).

Another enzyme involved in GSH metabolism is the γ-glutamyltransferase (γGT), a transferase that catalyzes the transfer of γ-glutamyl groups from e.g. GSH to diverse acceptor molecules (Ramsay and Dilda, 2014). Consequently, γGT has been linked to drug resistance, e.g. against platinum drugs (Fig. 5) (Corti et al., 2010).

Trx, TrxR, and NADPH are components of a highly conserved system that has an important role in redox homeostasis and regulation of various cellular processes such as DNA replication, cell proliferation and cell growth (Zhang et al., 2017). Three isoforms of TrxR have been identified so far, cytosolic isoform TrxR1, mitochondrial isoform TrxR2 and testis-specific isoform TrxR3 (Gasdaska et al., 1996). TrxR are selenoenzymes that maintain Trx in its reduced state (Fig. 5). In turn, Trx exerts its function by reducing peroxiredoxin (Prx), responsible for the detoxification of hydrogen peroxide, lipid peroxides, and peroxynitrite, or by reducing various target proteins and consequently affecting their activity (Zhang et al., 2017). TrxR1 contains a selenocysteine sequence at the C-terminal active site essential for the enzyme activity (Lu and Holmgren, 2009). Besides Trx, TrxR1 has several other substrates including selenium-containing compounds (Björnstedt et al., 1992). TrxR and Trx are overexpressed in cancer cells, contributing to cancer progression either via promotion of cell growth or inhibition of cell death (Berggren et al., 1996; Lincoln et al., 2003). Additionally, increased levels of the Trx protein system are associated with the development of resistance to various chemotherapeutic agents, including cisplatin (Cui et al., 2018; Sasada et al., 1996). Targeting the TrxR/Trx system in cancer cells has become a rational anticancer strategy (Cui et al., 2018; Kladnik et al., 2021; Kladnik et al., 2019). Currently, the gold complex auranofin, a known inhibitor of TrxR1, is under investigation as a potential anticancer drug (Li et al., 2016a).

Finally, overexpression of MTs, a class of small cysteine-rich proteins, is observed as a physiological protection mechanism against

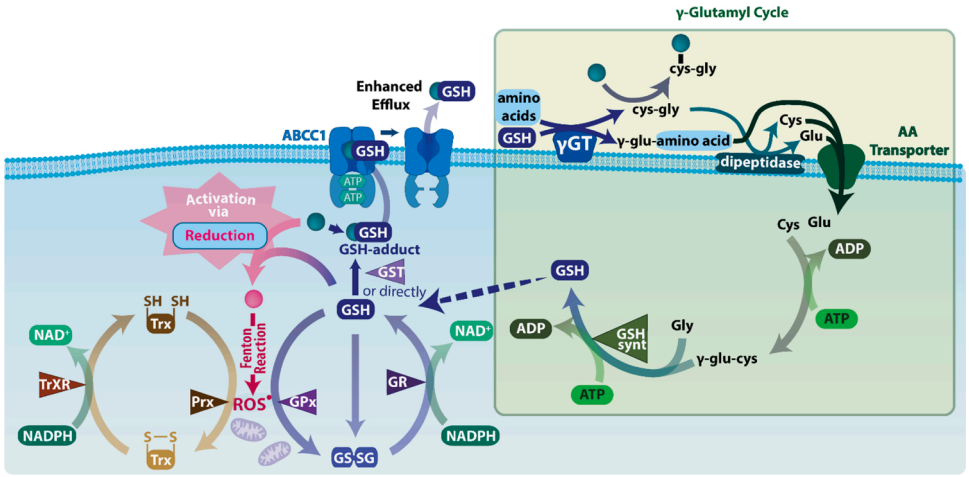


Fig. 5. Metal drugs and the redox homeostasis of the (cancer) cell.

metal-induced stress (Golan and Assaraf, 2020; Golan et al., 2017). Consequently, it is not surprising that there are several reports indicating that resistance to metal chemotherapeutics is accompanied by upregulation of MTs (Fig. 3) (Holford et al., 2000; Hrabeta et al., 2016; Hrubisko et al., 1993; Perego et al., 2003; Surowiak et al., 2005).

2.5. Altered DNA damage response and enhanced DNA repair

Although there is increasing evidence that protein targets also play a significant role in the anticancer activity of metal drugs, DNA damage is still considered crucial in the mode of action of various anticancer agents including platinum drugs (especially cis-, carbo- and oxaliplatin) (Brabec and Kasparkova, 2005; Poti et al., 2019; Riddell, 2018). Moreover, in the case of several other metal and metalloid therapeutics, e.g. ruthenium, gallium and silver complexes as well as selenium drugs, induction of DNA damage has been reported at least *in vitro* (Allison et al., 2017; Fast et al., 2019; Fischer-Fodor et al., 2014; Gandin et al., 2018; Kryeziu et al., 2013; Letavayova et al., 2006; Pluim et al., 2004; Stevens et al., 2013; Tanaka et al., 2013). Accordingly, in several cell culture-based resistance models, alterations in the DNA repair capacity have been reported (Jakupec et al., 2003; Kelland et al., 1993; Mellish and Kelland, 1994). Moreover, the nucleotide excision repair (NER) capacity of cancer cells (e.g. in the excision repair cross-complementation group 1 (ERCC1) or *Xeroderma pigmentosum* group proteins), or the BRCA 1/2 status have been repeatedly suggested as biomarkers for prediction of sensitivity or intrinsic resistance to platinum-based therapy in the clinics (Basourakos et al., 2017; Beheshti et al., 2018; Dabholkar et al., 2000; Damia and Broggini, 2019; Martinez-Balibrea et al., 2015; Tanaka et al., 2013).

Besides increased DNA repair, increased tolerance to DNA damage plays a central role in platinum drug resistance. Loss of the mismatch repair pathway (MMR) has been shown to confer low-level resistance to cisplatin and carboplatin, as it helps the cells to avoid unsuccessful repair cycles leading to DNA strand breaks and apoptosis (Damia and Broggini, 2019; Martinez-Balibrea et al., 2015; Riddell, 2018). Interestingly, oxaliplatin seems to be less affected by MMR loss, which could be the reason for the enhanced efficiency of this drug in the frequently MMR-deficient colon cancer (Martinez-Balibrea et al., 2015; Riddell, 2018).

During the last decades there has been increasing evidence that DNA damage leads to upregulation of immunostimulatory signals (e.g. attracting natural killer cells) on cancer cells (Englinger et al., 2019). Consequently, it can be expected that resistance to metal drug-induced DNA damage, also results in drug resistance due to impaired activation of the immune cells against the malignant cells.

2.6. Impaired induction of apoptosis

Dysfunction of apoptotic cell death is one of the main characteristics of cancer cells, thus posing a major obstacle to effective cancer treatment (Adams and Cory, 2007; Martinez-Balibrea et al., 2015; Shahar and Larisch, 2020). Chemotherapy initiates apoptosis mainly via two independent pathways: the extrinsic pathway activated through the death receptor on the cell membrane and the intrinsic or mitochondrial pathway mediated by the Bcl-2 protein family. The first pathway is stimulated by the binding of TNF-α or Fas ligand to their receptors (so-called death receptors) leading to activation of the initiator caspase 8. This caspase transmits a pro-apoptotic signal to the effector caspases 3 and 7, which induce apoptosis through proteolytic degradation of different enzymes (Ashe and Berry, 2003). The intrinsic pathway depends on the delicate balance between the pro-apoptotic (Bax, Bak, Bok, Bid, Bad, Bim, Taurus, Blk, Noxa and Puma) and anti-apoptotic (Bcl-2 and Bcl-XL) members of the Bcl-2 protein family (Shahar and Larisch, 2020; Youle and Strasser, 2008). The function of pro-apoptotic proteins is regulated by anti-apoptotic proteins. Pro-apoptotic proteins participate in the opening of the mitochondrial permeabilization pores leading to the release of cytochrome C into the cytosol. Cytochrome C induces oligomerization of Apaf 1 into a caspase activation complex. In turn, Apaf 1 binds and promotes the activation of initiator caspase 9, which cleaves and activates caspase 3 and 7, thus triggering apoptotic cell death (Adams and Cory, 2007; Shahar and Larisch, 2020). In either case of apoptotic cell death, activation of caspases results in chromatin condensation, fragmentation of the nucleus and formation of apoptotic bodies with intact organelles (Green, 2005). Since the balance between members of the Bcl-2 protein family is required for proper apoptotic signaling, alterations in the balance between these proteins leads to the development of drug resistance. Increased expression of anti-apoptotic proteins and/or reduced expression of pro-apoptotic proteins limit the effectiveness of most chemotherapeutics (Longley and Johnston, 2005; Martinez-Balibrea et al., 2015), including metal drugs such as oxaliplatin (Gourdier et al., 2004), picoplatin (Pestell et al., 1998) or BBR-3464 (Harris et al., 2006; Perego et al., 2003). Moreover, drug-resistant cancer cells express so-called inhibitors of apoptosis proteins (IAPs) which can be exploited by specific combination therapy (Thibault et al., 2018).

One of the key molecules in the regulation of apoptosis is the zinc-finger protein and transcription factor p53, which upon stabilization e.g. by DNA damage, leads to cell cycle arrest, activation of DNA repair proteins and, if the stress persists, induction of apoptosis via the mitochondrial pathway (Cao et al., 2020; Stiewe and Haran, 2018). Consequently, mutations in the *p53* gene that impair the function of this important tumor suppressor are widespread in cancer. As dysfunctional

Table 1
Overview on diverse tumor cell lines with acquired resistance to platinum drugs.

Cell model	Mode of resistance	Sensitive to	(Cross)resistant to
41 McisR	changed drug uptake (Holford et al., 1998b)	- picoplatin (Holford et al., 1998b) - trans-platinum acetonimine complexes (Boccarelli et al., 2006)	Cisplatin transplatin
A2780/cisR	enhanced GSH levels, reduced drug uptake and increased DNA damage repair/ tolerance (Holford et al., 1998b)	- albumin adducts of PL-04 and PL-07 (Garmann et al., 2008) - picoplatin (Holford et al., 1998b) - trans-platinum acetonimine complexes (Boccarelli et al., 2006) - RAED-type compounds (Aird et al., 2002) - ruthenium cyclopentadienyl compounds with bipyridine based ligands (Corte-Real et al., 2018; Morais et al., 2016; Moreira et al., 2019; Tomaz et al., 2012) - ruthenium(II) and osmium (II) iodide complexes of (p-cymene)(azo/imino-pyridine) (Romero-Canelon et al., 2013) - rhenium(I) tricarbonyl complexes bearing diimine ligands (Konkankit et al., 2019) - gold complexes based on phosphane and thionate co−ligands (Vergara et al., 2010) - [(η^5-Cp*)Ir(bq)]Cl (Novohradsky et al., 2014) - copper(II) thiosemicarbazone complexes (Ohui et al., 2020)	cisplatin transplatin (in part ethacraplatin)
A2780cp8	Loss of MMR proteins (hMLH1 and hPMS2)	BBR-3464 (Colella et al., 2001)	cisplatin
A2780/ CP70	Reduced drug uptake due to reduced expression of hCTR1 and enhanced levels of ABCB1, ERCC1, ATP7A/B (Peng et al., 2017)	- transferrin-bound cisplatin (Peng et al., 2017) - Non-covalent albumin-binding platinum(IV) drugs (Zheng et al., 2014) - [Pt(BDI^{QQ})]Cl (Suntharalingam et al., 2014) - rhenium(V) oxo complexes (Suntharalingam et al., 2015)	cisplatin
A2780R	unknown	- gold(I) complexes with NHC 1,3-substituted imidazole-2-ylidene and benzimidazole-2-ylidene ligands (Schuh et al., 2012). - silver(I) NHC complexes bearing a fluorescent anthracenyl ligand (Citta et al., 2013)	cisplatin
A2780/DDP	Reduced uptake due to reduced hCTR expression, increase GSH levels and enhanced repair capacity (Zhang et al., 2015)	DCA-releasing platinum(II) (Zhang et al., 2015)	cisplatin carboplatin
A431−Pt			cisplatin

Table 1 (*continued*)

Cell model	Mode of resistance	Sensitive to	(Cross)resistant to
	decreased cisplatin accumulation and increased DNA damage repair/ tolerance (Lanzi et al., 1998)	gold complexes based on [Au(PEt_3)]$^+$ synthon and additional simple co−ligands (Gandin et al., 2010).	
A549R	Enhanced GSH levels (Han et al., 2018) Resistance to apoptosis and induction of autophagy (Wang et al., 2019)	- platinum(IV) complexes with a protected lactose ligand (Ma et al., 2018) - asplatin (Cheng et al., 2014) - [Ru(7,8-benzoquinoline)$_2$(PIP)]$^{2+}$ (Zeng et al., 2016) - rhenium(I) dinuclear compounds with phenanthroline based ligands and a bridged 1,2-bis(4-pyridyl)-ethane (Ye et al., 2016) - heteroleptic ruthenium(II) organometallic complex with three bidentate ligands (Zeng et al., 2016) - hetero-binuclear iridium (III)-platinum(II) complex [(ppy)$_2$Ir(dpp)PtCl$_2$]$^+$ (Ouyang et al., 2018) - cyclometalated iridium(III) complexes with benzothiazole substituted ligands (Guan et al., 2018)	cisplatin, oxaliplatin, satraplatin
BEL7404/ CP20	decreased cisplatin accumulation and DNA damage tolerance (Johnson et al., 1996) Overexpression of GST-P (Li et al., 2017b)	ethacraplatin (Li et al., 2017b)	cisplatin
CH1cisR	increased DNA damage repair/ tolerance (Holford et al., 1998b)	picoplatin (Holford et al., 1998b)	cisplatin
HCT116Ox	unknown	ruthenium(II) and osmium(II) iodide or chlorido complexes of (p-cymene)(azo/imino-pyridine) (Romero-Canelon et al., 2013) - Pt-Oqn (Hayashi et al., 2016)	Oxaliplatin cisplatin
MKN28 (CDDP)	unknown	- glycoconjugated $PdCl_2$(L) (L = 2-deoxy-2-[(2pyridinylmethyllene) amino-α-D-glucopyranose) (Tanaka et al., 2013)	cisplatin carboplatin glycoconjugated $PtCl_2$(L)
MKN45 (CDDP)	increased mRNA levels of ABCB1 and DNA damage repair genes (Tanaka et al., 2013)	- Pt-Oqn (Hayashi et al., 2016) - glycoconjugated $PdCl_2$(L) - (L = 2-deoxy-2-(2pyridinylmethyllene) amino-α-D-glucopyranose) (Tanaka et al., 2013)	Cisplatin carboplatin glycoconjugated $PtCl_2$(L)
MM98R	unknown	ethacraplatin (Zanellato et al., 2011)	cisplatin
OAW42MER	loss of MMR proteins (hMLH1 and hPMS2) and enhanced NER (ERCC1/2 mRNA levels)	BBR3464 (Colella et al., 2001; Orlandi et al., 2001)	Mephalan cisplatin
			cisplatin

(*continued on next page*)

Table 1 (*continued*)

Cell model	Mode of resistance	Sensitive to	(Cross)resistant to
OV2008/C13*	low mitochondrial potential (Hirama et al., 2006), increased glucose uptake and consumption (Catanzaro et al., 2015)	- gold complexes based on $[Au(PEt_3)]^+$ synthon and additional simple co–ligands (Gandin et al., 2010). - azolate gold(I) phosphane complexes (Galassi et al., 2012) - gold(III)/palladium(II) pincer complexes with bis (diphenylphosphino) ferrocene/non-ferrocene-based ligands (Tabrizi and Chiniforoshan, 2017)	
SK-OV-3/DDP	unknown	DCA-releasing platinum(II) drugs, where the DCA moiety is attached to the leaving group via an ester bond (Liu et al., 2015; Liu et al., 2013)	Cisplatin carboplatin

Bq, 7,8-benzoquinoline; DCA…dichloroacetate, NHC…N-heterocyclic carbine, PIP… 2-phenylimidazo[4,5-f][1,10]phenanthroline, ppy…2-phenylpyridine, dpp… 2,3-bis(2-pyridyl)pyrazine, oqn… N-(8-hydroxoquinoline-2-ylmethylidene)-β-D-glucosamine, BDI^{QQ}… N-((1Z,3E)-3-(quinoline-8-ylimino)prop-1-en-1-yl)quinolin-8-amine

p53 protein changes the sensitivity of cancer cells to chemotherapy, it also plays an important role in (intrinsic) drug resistance (Cao et al., 2020; Lowe et al., 2004; Martinez-Balibrea et al., 2015; Stiewe and Haran, 2018). There are currently some attempts to use (metal-based) chaperon drugs to restore the wild-type function of p53 (Yu et al., 2017; Zaman et al., 2019). In addition, induction of non-apoptotic cell death forms might be a possible approach to overcome apoptosis resistance. One such form of cell death could be necrosis, which is characterized by cytoplasmic swelling, the rupture of the plasma membrane and cell lysis, followed by inflammatory reactions. Unlike apoptosis, necrosis is typically not associated with the activation of caspases (Leist and Jaattela, 2001). However, necrosis can also function as a programmed cell death, called necroptosis, and is triggered by the same death signals that induce apoptosis. Several death receptors that typically induce apoptosis, such as TNFR1, FAS, TNFR2, TRAILR1 and TRAILR2, have also been shown to induce necroptosis via distinct signaling pathways (Nikoletopoulou et al., 2013). Namely, upon TNFR1 activation, PARP1 and AKT are directly activated by RIP1, contributing to the necroptosis by reducing ATP levels and activating JNK, respectively (Nikoletopoulou et al., 2013). Another non-apoptotic form of cell death discussed for the circumvention of apoptosis resistance is paraptosis, a form of programmed, caspase-independent cell death that is morphologically characterized by the formation of perinuclear vesicles originating from the ER (Fontana et al., 2020; Lee et al., 2016). It was first mentioned by Sperandio et al., in 2000, who described paraptosis as inducible by overexpression of insulin-like growth factor I receptor (Sperandio et al., 2000). This cell death was characterized by cytoplasmic ER-derived vesicles, mitochondrial swelling, resistance to caspase inhibitors and lack of typical apoptotic morphology (Sperandio et al., 2000). Finally, oncosis is also a type of programmed cell death, which differs from apoptosis in both morphological changes and inner pathways. This type of cell death is characterized by whole cell swelling, accompanied by severe damage to mitochondria, vacuolization of cytoplasm, blebbing of the plasma membrane and collapse of cytoskeleton (Guan et al., 2018). The calcium-activated protease calpain and the surface receptor porimin are the key molecules mediating oncotic cell death (Guan et al., 2018).

2.7. Alterations in interaction with the immune system

During the last decades, there was an increasing awareness, that avoidance of recognition by the patient's immune system is a fundamental trait in cancer development (Hanahan and Weinberg, 2011). Consequently, all cancer cells can be assumed as "intrinsically resistant to immune recognition". Noteworthy, diverse therapeutic options such as platinum drugs also help to re-activate and re-direct immune cells against the malignant tissues (Guan et al., 2018). For example, as already mentioned above, apoptotic stress signals, e.g. after DNA damage, lead to attraction of natural killer (NK) cells (Englinger et al., 2019). On the other hand, several treatment options including oxaliplatin, doxorubicin or radiation therapy, lead to the induction of immunogenic cell death (ICD), which finally results not only in enhanced immune-based clearance of the cancer cells but also a long-lasting memory effect (vaccination) against the cancer cells (Galluzzi et al., 2017; Tesniere et al., 2010). Moreover, immunosuppressive players of the tumor immune cell population such as regulatory T-cells (Tregs) and myeloid-derived suppressor cells (MDSC) are especially sensitive to several metal therapeutics (Chang et al., 2013; Montani et al., 2016; Xu et al., 2018). Consequently, a shift to a more anti-tumorigenic immune cell population has been observed in several studies in platinum-treated patients (Englinger et al., 2019). Finally, most recently, platinum-based therapy has been suggested to induce the expression of neo-antigens on the cancer cells, which support their recognition by the immune system. That these effects can also be efficiently exploited for combination therapies has been impressively shown by the recent approval of immune checkpoint inhibitors (ICIs) such as pembrolizumab together with cisplatin or carboplatin in NSCLC and SCLC (Diesendruck and Benhar, 2017; Hays and Bonavida, 2019; Kon and Benhar, 2019; Leonetti et al., 2019; Perez-Ruiz et al., 2020).

Evidence exists that the development of drug resistance can influence the sensitivity of the malignant tissue to immune recognition in both directions. For example, a cisplatin-resistant ovarian carcinoma cell line (SKOV3-A2) displayed higher levels of several MHC class I-presented peptides and an altered resistance-specific peptide repertoire. These selected resistance-associated epitopes were significantly better recognized by cytotoxic T-cells in the cisplatin-resistant subline as compared to the sensitive parental model (Shetty et al., 2012). On the other hand, chemoresistance in mesenchymal lung cancer tissues was correlated with high Treg presence in the TME (Zhang et al., 2019). Moreover, there are several reports that alterations in the chemokine profile of the malignant tissue lead to drug resistance (e.g. against platinum drugs) (Reyes et al., 2020); for example, by interleukin-6- and prostaglandin E_2-induced monocyte differentiation into tumor-promoting M2 macrophages (Dijkgraaf et al., 2013). Finally, it seems logical that resistance to apoptosis by enhanced DNA damage repair will protect cells from attack by immune cells (Bonavida and Chouaib, 2017; Englinger et al., 2019). However, all in all, the changes in and contributions of the immune cell composition to the development of drug resistance are surprisingly underexplored and warrant more in-depth studies.

3. Novel drugs to treat drug-resistant cancer cells

3.1. General comments

As platinum drugs have been successfully used in the clinic for decades and as drug resistance represents a major obstacle for the successful application of these drugs, new platinum drugs, but also many other metal candidates, are frequently tested in cell models with intrinsic or acquired platinum resistance (Cheng et al., 2014; Gupta et al., 2013; Hoffmann et al., 2017; Konig et al., 2018; Lord et al., 2015; Margiotta et al., 2006; Morais et al., 2016; Novohradsky et al., 2014; Ohui et al., 2020; Pellei et al., 2011; Romero-Canelon et al., 2013; Santini et al., 2011; Song et al., 2017; Starha et al., 2018a; Tomaz et al., 2012; Wang et al., 2015; Wang et al., 2020; Ye et al., 2017a). Thus, in many cases the compounds are not especially designed to circumvent a specific form of drug resistance. Moreover, the tumor cell lines used

often have not been characterized for the mechanisms underlying their drug resistance, or the selected cell model is not resistant via the mechanism, which is inhibited by the new drug. This unspecific approach is useful to discover promising drug candidates for further preclinical development and to obtain indications for interesting patient collectives for clinical trials. However, this also means that we often do not know why certain drug-resistant tumor cell lines might be hypersensitive to specific therapeutics. This knowledge-gap could be improved by better characterization of the cell models employed. In fact, many publications on the biology of the tested cell models exist, which would allow a meta-analysis of the available data. In the current article, in order to allow the generation of such mechanistic hypothesis, we generated a summary Table 1 on platinum-resistant models.

However, we need to point out, that very often the exact source of the tumor cell model is missing in the manuscripts. In addition, several cell line names (e.g. A549R or A2870cis) are repeatedly used in the literature to describe independently generated cell clones (Hsieh et al., 2012; Liu et al., 2017b; Mihatsch et al., 2011), as well as different terms being used for the same cell line (e.g. A2780R, A2780cis, A2780/cis, A2780/cisR). Consequently, one cannot always guarantee that the same cell model has indeed been used for the biological analysis and the investigation of the new drugs.

Finally, there are publications where the compounds of interest have been analyzed in-depth only in the drug-resistant cell clone without using the chemosensitive parental cells as a reference. Such reports do not allow any assessment of the role of the resistance-associated changes of the cell models. Hence, data has only been included in this review for analyses that have been performed in both drug-resistant and cognate parental cell line.

In addition to the rather unbiased approaches, several attempts to rationally design novel metal drugs to specifically circumvent the most frequently emerging modalities of platinum or multidrug resistance will be discussed in the subsequent chapters.

3.2. Metal drugs to overcome impaired drug uptake or enhanced efflux in platinum-resistant cancer cells

An attractive modality to circumvent drug resistance and at the same time enhance tumor-specific drug uptake into cancer cells is the use of alternative uptake mechanisms. As mentioned in the introduction, (platinum)-resistant cancer cells are frequently characterized by reduced levels of hCRT, OATs or enhanced drug efflux; in the case of platinum, for example, ATP7B and ABCC1/2 (Buß et al., 2018; Choi and Kim, 2006; Heffeter et al., 2008; Oguri et al., 2016; Spreckelmeyer et al., 2014; Ueda et al., 1999). At the same time, cancer cells are known for their enhanced requirement and consumption of nutrients, including glucose, fatty acids, amino acids and nucleosides, resulting in frequently occurring alterations in their metabolism (Harper et al., 2002; Pasto et al., 2017; Ricci et al., 2019). Hence, exploiting these mechanisms is especially attractive for the targeting of drug-resistant cancer cells. To this end, there have been multiple attempts to design platinum(II) and platinum(IV) drugs, which enter the cancer cell in a glucose-dependent manner (Johnstone et al., 2016; Kenny and Marmion, 2019; Liu et al., 2017a; Patra et al., 2016). Interestingly, despite the expectation that such drugs could be more effective in drug-resistant cancer cells (Liu et al., 2017a), only a few derivatives have also been investigated with respect to platinum resistance. Among these is a panel of diverse platinum(IV) glycoconjugates containing different mono- or disaccharides (Ma et al., 2018), which were compared for their biological activity also against the platinum-resistant cell model A549R (Fig. 6). In this study, the authors convincingly showed that a glucose derivative (6d) is taken up by MCF-7 breast cancer cells via the glucose uptake transporter (GLUT). This drug (as well as a mannose and a rhamnose derivative) was also able to circumvent the cisplatin- and oxaliplatin-resistance of A549R cells, at least to some extent. However, as the GLUT expression level in the drug resistance model has not been evaluated, it is unclear whether this is based on differences in the drug uptake. Interestingly, the resistant cell clone displayed strong collateral sensitivity against two derivatives carrying a protected lactose ligand. Likewise, the group of Joh et al., investigated the efficacy of several glycosylated platinum(II) and palladium(II) complexes in two platinum-resistant models of gastric cancer for which it is unknown whether impaired platinum uptake is involved in the mode of resistance. [PtCl(Onq)] (Onq = N-(8-hydroxoquinoline-2-ylmethylidene)-β-D-glucosamine (Hayashi et al., 2016), as well as $[PdCl_2(L)]$ (L = 2-deoxy-2-[(2pyridinylmethyllene)amino]--α-D-glucopyranose) efficiently circumvented platinum resistance *in vitro* and *in vivo*, while $[PtCl_2(L)]$ remained significantly less efficient in the drug-resistant cell line model (Tanaka et al., 2013).

Several ruthenium glycoconjugates have been reported in the last years (Berger et al., 2008; Böge et al., 2015; Florindo et al., 2014; Florindo et al., 2015; Valente et al., 2013). However, only one study on a series of Ru(II)-cyclopentadienyl glycoconjugates explored their GLUT-mediated cellular uptake in cancer cells (Fig. 6) (Florindo et al., 2016). The findings revealed that the cellular uptake of the derivatives with methyl α-D-mannopyranoside or methyl α-D-glucopyranoside was indeed D-glucose-dependent (but not L-glucose-dependent) suggesting that these glycoconjugates might enter the cell via a GLUT-dependent uptake. However, it remains unclear whether this route of drug uptake is also able to circumvent drug resistance for ruthenium drugs.

Apart from the attachment of sugar moieties, the design of drugs with specific protein-binding properties has recently attracted attention, as this would also achieve the circumvention of drug resistance based on drug accumulation via another mode of drug uptake into the cancer cell. The promising activity of such strategies has already been indicated for diverse organic drugs (Daniels et al., 2012). For example, conjugation to the iron transport protein transferrin, the receptor of which has been reported to be upregulated in some drug-resistant cancer models, proved to be successful (Kazan et al., 2017). Conjugation of doxorubicin to transferrin and, consequently, transferrin receptor-dependent drug uptake was able to circumvent resistance mediated by ABCB1 (Fritzer et al., 1992; Fritzer et al., 1996). This effect could even be enhanced by using a doxorubicin-gallium-transferrin conjugate (Wang et al., 2000). The first attempt to use such a strategy for platinum drugs was in the 1990's with MPTC-63, where cisplatin was chemically conjugated to transferrin (Elliott et al., 1988). This conjugate showed promising anticancer activity in tumor cell culture and rat tumor models *in vivo*. Subsequent analysis also revealed strong activity in several breast cancer patients, including several complete remissions based on enhanced platinum accumulation in the malignant tissue (Elliott and Head, 2006; Elliott et al., 1988). However, this conjugate was never tested with respect to drug resistance. More recently, Peng et al., developed a new technique to stably load up to 41 cisplatin molecules onto one transferrin protein (Tf-cisplatin) (Peng et al., 2017). This new preparation was subsequently more efficient against A2780/CP40 cells compared to their chemosensitive parental counterpart, based on enhanced drug uptake and consequently increased induction of apoptotic cell death in cell culture. Moreover, it showed significantly improved activity compared to free cisplatin in A2780/CP40 xenografts *in vivo*. Transferrin-mediated drug targeting has also been investigated for several ruthenium(II) cyclopentadienyl compounds with heteroaromatic ligands (Corte-Real et al., 2014), however, not in association with drug resistance.

Another interesting serum protein in this respect is the human serum albumin (HSA), as there is strong evidence that cancer cells differ in their albumin uptake and catabolism from healthy tissues (Finicle et al., 2018; Palm and Thompson, 2017). There are several examples of metal drugs where non-covalent binding to albumin is considered crucial for their anticancer activity. Here, KP1019 and its sodium salt KP1339, which efficiently and rapidly bind to serum albumin in mice, as well as in cancer patients, might be the best-studied drug candidates (Trondl et al., 2014). Moreover, several ruthenium(II) arene compounds with heteroaromatic ligands have exhibited the potential to use non-covalent

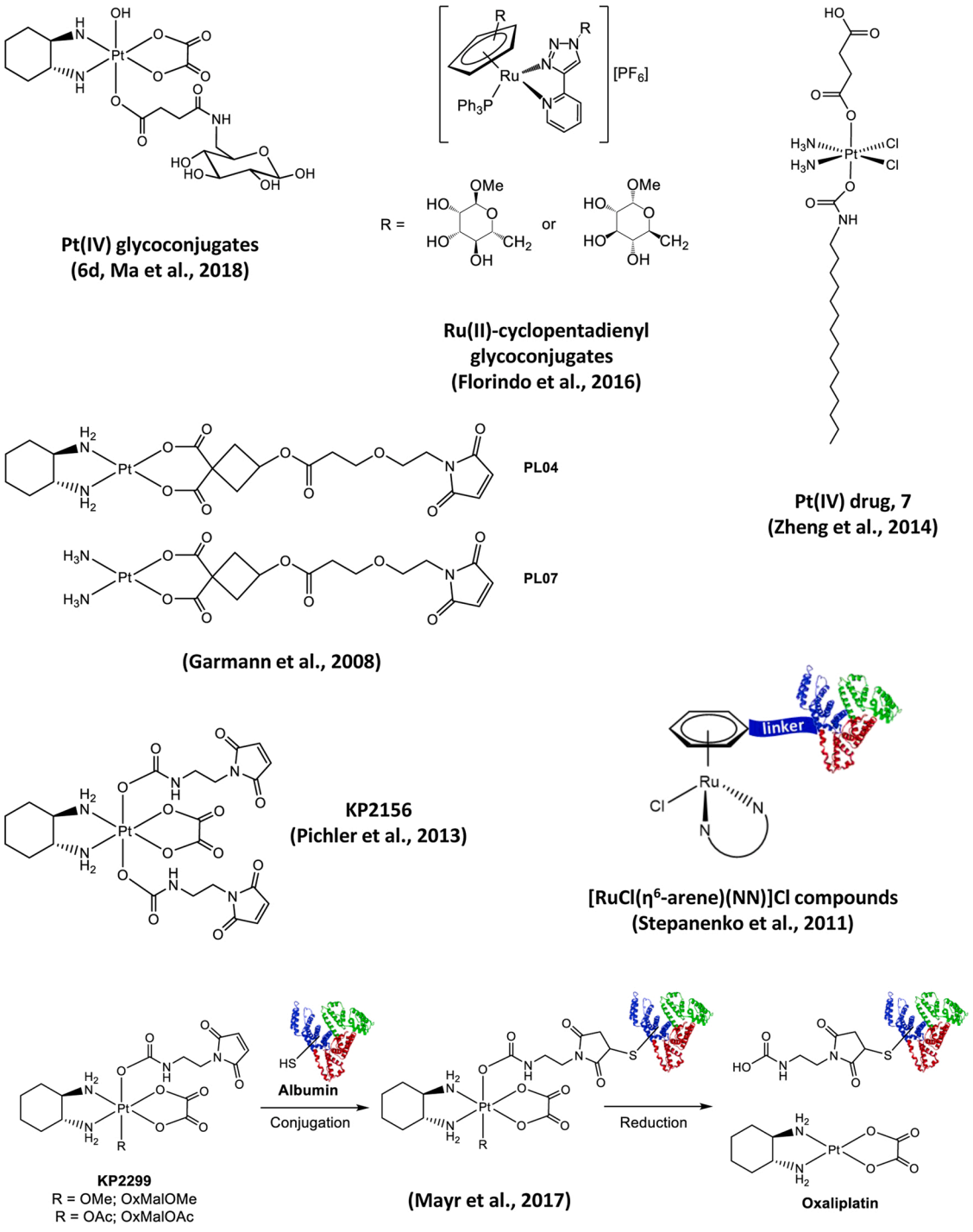


Fig. 6. Metal drugs with changed uptake routes circumventing reduced drug uptake or enhanced efflux in platinum-resistant cancer cells.

albumin binding for the selective tumor delivery (Kladnik et al., 2019; Markovic et al., 2020; Morais et al., 2013; Tomaz et al., 2012). In this case, the interaction is expected to result in an increase or retention of cytotoxicity towards cancer cells for the Ru-HSA adducts compared to the free complexes. The use of the A2780/A2780cisR cells for some complexes confirmed that the uptake is retained even in the drug-resistant strain.

In order to allow for more specific and controlled binding to albumin, several strategies have been explored in metal drug design over the years. One example is the synthesis of drugs able to bind albumin due to fatty acid mimetic properties such as the platinum(IV) drug **7** (Fig. 6), which then results in non-covalent albumin binding (Zheng et al., 2014). This strategy efficiently circumvented cisplatin resistance in A2780/CP70 cells. The most specific targeting of albumin is probably the introduction of maleimide moieties into the molecule, which results in reaction with the free thiol group at the cysteine 34 and, consequently, a covalent attachment of the compounds to the albumin molecule (Hoogenboezem and Duvall, 2018; Kratz, 2008). Here, several drug candidates have been evaluated (Fig. 6). On the one hand, there are platinum(II) compounds, such as PL04 and PL07, where the maleimide moiety is attached to the leaving group (Garmann et al., 2008). On the other hand, several platinum(IV) drugs (e.g. KP2156 (Pichler et al., 2013) and KP2299 (Mayr et al., 2017)) have been designed, where the maleimide moiety is attached to the axial leaving group, which allows

the release of the unmodified platinum(II) species from the albumin molecule after reduction of the platinum core (Fig. 6). Due to the distinctly improved anticancer activity of such drug candidates, two platinum(IV) drugs have been developed following this approach for clinical use (BTP-114 by Placon Therapeutics and Albuplatin by P4 Therapeutics, however, in both cases the structures are not disclosed). Thus, BTP-114 is currently tested in a phase I study (NCT02950064) in patients with advanced solid tumors with BRCA mutations (Moreau et al., 2015).

In addition to platinum, several attempts have been made to use maleimide-mediated albumin targeting for selective tumor delivery of other metal compounds such as ruthenium and osmium η^6-arene complexes (den Heeten et al., 2010; Hanif et al., 2016; Hanif et al., 2012). Unfortunately, in most cases, these compounds were not tested with respect to drug resistance. Some [RuCl(η^6-arene)(NN)]Cl compounds (arene = 4-formylphenoxyacetyl-η^6-benzylamide; NN = cyclin-dependent kinase (Cdk) inhibitor) were covalently attached to HSA through an hydrazone linkage formed between the succinimidyl 4-hydrazidoterephthalate hydrochloride (SHTH) linker of the recombinant protein[2] and the aldehyde of the (η^6-arene) ligand. It was shown that this significantly increased the cytotoxicity of the drugs against A2780 cells as well as its resistant variant A2780cisR (Fig. 6) (Stepanenko et al., 2011). These studies therefore indicate that albumin binding has the potential to overcome metal drugs resistance and should be further investigated in future studies.

3.3. Development of metal-based ABC efflux inhibitors

As already discussed, ABCB1 and ABCC family members are important players in cancer MDR. Surprisingly, there is no literature on platinum-based compounds developed to selectively inhibit the transport function of ABC efflux pumps (either directly or by the release of attached modulatory ligands). In contrast, for other metals (especially ruthenium), a great deal of research has been dedicated to the development of MDR modulators that could block the drug efflux out of cancer cells. In this respect, Juillerat-Jeanneret, Dyson and coworkers used modified phenoxazine- and anthracene-based MDR modulator ligands bound to a ruthenium(II) organometallic scaffold to originate new MDR-reverting agents (Fig. 7) (Vock et al., 2007). The resulting compounds showed moderate to good cytotoxicity against A549 lung, HT29 colon, and T47D breast carcinoma. ABCB1 inhibition assays in the A549 cell line revealed that the compound with the anthracene derivative was the best at a concentration of 80 μM showing similar efficiency as the pioneering ABCB1 and ABCC1 inhibitor verapamil. Overall, the coordination of the anthracene-based MDR modulator ligand to the ruthenium(II) organometallic scaffold led to an increase in the cytotoxic activity and ABCB1 inhibition, however, at the expense of *in vitro* selectivity towards cancer cells.

In another approach, Valente and coworkers developed a family of compounds aimed at blocking ABC efflux pumps with the general formula [Ru(η^5-CpR)(PPh_3)(4,4′-R'-2,2′-bpy)]$^+$ (Fig. 7) (Corte-Real et al., 2019; Corte-Real et al., 2018; Moreira et al., 2019). Studies with the pump proteins ABCB1, ABCC1/2 and ABCG2 for a set of compounds allowed structure-activity relationships to be deciphered: the substitution on the bipyridine ligand dictates, whether the ruthenium compound behaves like a substrate or an inhibitor of these ABC pumps. This was found to be also related to the compounds' cytotoxicity. Thus, when the η^5-methylcyclopentadienyl ligand is used and the substituent on the bipyridine is a more hydrophobic group (CH_3), the compound is an inhibitor of ABCC1/2. In contrast, when CH_3 is replaced by H or a hydroxymethyl group, the compounds become ABC pump substrates (either for ABCB1 or for all the pumps tested, respectively) (Corte-Real et al., 2018). The behavior as a substrate observed for the hydroxymethyl group was also confirmed, when η^5-C_5H_5 was used instead (pmc79) (Corte-Real et al., 2019; Moreira et al., 2019). In this respect, the studies revealed that the presence of a long leg substituent on the bipyridine (such as biotin (LCR134) or polylactide (pmc78)) is key to afford compounds acting as strong ABCB1 inhibitors. Importantly, results also confirmed that these two compounds are no substrates for any other ABC pumps. Overall, these studies disclosed a family of compounds with a dual-action as cytotoxic agents that can also overcome MDR caused by ABC transporters. Additional studies in NSCLC confirmed the involvement of ABC pumps in the mechanism of action of these compounds and revealed unprecedented collateral sensitivity for cisplatin-resistant lung cancer cells (Teixeira et al., 2021), which will be discussed in the next section.

Finally, a ruthenium coordination compound (RuF, Fig. 7) was designed to inhibit ABCG2 (Zeng et al., 2019). In this study the authors showed that RuF was able to overcome mitoxantrone resistance in H460/MX20 cells by down-regulating ABCG2 expression and inhibiting ABCG2 ATPase activity. Preliminary *in vivo* studies in athymic nude mice xenografted with H460/MX20 cancer cells and treated with RuF via intratumoral injection, showed a slower tumor growth compared to controls together with a good tolerability of the drug.

Besides these examples for ruthenium drugs, the copper complex, copper *N*-(2-hydroxy acetophenone)glycinate (CuNG, Fig. 7) is noteworthy. This drug was found to inhibit drug efflux by direct binding to the ABCB1 molecule. Consequently, CuNG increased cellular accumulation of doxorubicin in ABCB1-expressing cells and significantly stimulated ABCB1 ATPase activity in isolated membrane preparations from NIH MDR1-G185 cells. However, CuNG did not compete with ABCB1 substrate binding in a photoaffinity labeling assay. Thus, the drug seems to have a different interaction site to verapamil, vinblastine and progesterone on the ABCB1 protein. As treatment with CuNG resulted in downregulation of the transporter expression on both the mRNA and protein levels (Ghosh et al., 2012; Majumder et al., 2006b), this compound (together with similar complexes formed with other metals) will be discussed in this aspect in the following chapter on collateral sensitivity. Based on the interesting properties, the same group also prepared the manganese and zinc derivatives of CuNG (Ghosh et al., 2013). Here too, ZnNG was able to enhance the activity of the ABCB1 substrate vincristine in MDR cells (Ghosh et al., 2011). In contrast, MnNG led to rapid reduction of ABCB1 expression in the drug-resistant cell clone but had no "modulatory" activity, as it did not sensitize ABCB1-overexpressing CEM/adr cells to vincristine.

Domínguez-Álvarez et al. reported a series of selenoanhydrides and selenoesters (Fig. 7) with cytotoxic activities against MDR mouse T-lymphoma cells within the low micromolar-submicromolar activity range (Dominguez-Alvarez et al., 2016) with enhanced activity compared to sensitive tumor cell lines, as well as good cancer cell selectivity. Furthermore, an MDR-reversing effect was also observed in rhodamine 123 accumulation assays. Interestingly, synergistic pro-apoptotic activity and inhibition of the ABCB1 efflux pump were found to be the key modes of action, leading to an improvement in the inhibitory properties (1.7-3.6-fold) compared to verapamil, used as a reference inhibitor (Gajdacs et al., 2017). These findings suggest that apart from being potent cytotoxic agents, organoselenium derivatives could also be used as adjuvants for reducing the resistance of classical chemotherapeutic agents.

3.4. Collateral sensitivity of ABC transporter-overexpressing cells to certain metal drugs

Collateral sensitivity (CS) is the ability of compounds to be more efficient in MDR cancer cells than in their drug-sensitive counterparts. Thus, CS constitutes an "Achilles' heel", which can be exploited as a target for developing MDR-selective compounds (Gottesman et al., 2006; Szakacs et al., 2014). Although there are reports on CS of

[2] The SHTH linker is attached to the amine groups on the lysine residues of HSA.

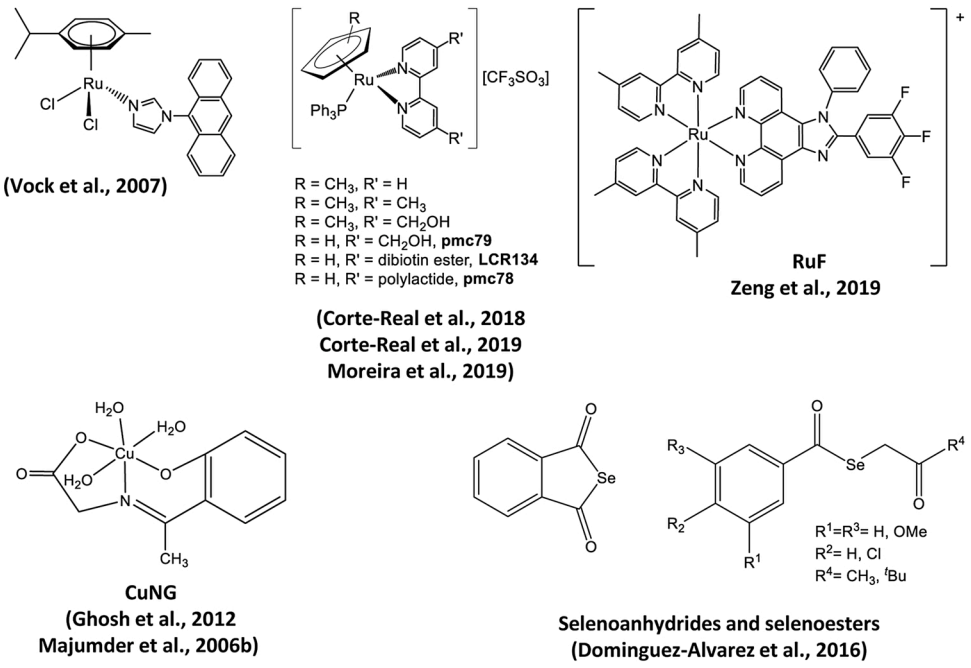


Fig. 7. Metal drugs targeting ABC transporter-overexpressing cancer cells and metal-based ABC transporter inhibitors.

platinum-resistant cells (Gatti et al., 2004; Kotoh et al., 1994; Perego et al., 1998), in most cases, the term CS is used for targeting ABC transporter (mainly ABCB1)-overexpressing cancer cells. Notably, there are reports that drug-resistant cancer cells display CS to treatment with diverse MDR modulators, which inhibit (ABCB1) transport function (Karwatsky et al., 2003). Moreover, there is increasing evidence that not all forms of CS are dependent on the ABCB1 function *per se* but could be associated with general alterations in the course of the resistance development (ABCB1-dependent vs ABCB1-associated CS). However, it is not always easy to differentiate between effects associated with direct ABC transporter interactions and CS of MDR cancer cells due to more indirect mechanisms. The picture is even more complicated as, up to now, the mechanisms underlying the observed effects are still heavily disputed (although there are multiple reports on drugs against which MDR cells are collateral-sensitive to). Thus, several mechanisms have been proposed to account for CS. For example, modification of intracellular redox status yielding the production of reactive oxygen species (ROS), increased sensitivity to changes in energy levels, extrusion of an endogenous substrate (for instance, verapamil dramatically increased GSH efflux in ABCC1-overexpressing cells, causing ROS generation and subsequent apoptosis). Further examples include membrane perturbation (Pluchino et al., 2012) and changes/interaction with the cellular iron homeostasis (Turk et al., 2009). All in all, the underlying mechanisms of CS presumably depend on cell type and/or applied drug (family).

Interestingly, although there are some rather old reports on CS of specific MDR cells to platinum drugs (Cho et al., 1995; Doherty et al., 2014), this aspect never seemed to be a major focus in the design of new platinum derivatives. In contrast, there are multiple reports on novel metal-based complexes which elicited CS in ABCB1- or ABCC1-overexpressing cell lines (Ganguly et al., 2010; Heffeter et al., 2007; Majumder et al., 2006b; Teixeira et al., 2021). This chapter together with Table 2 gives an overview of diverse metal drug systems inducing CS in ABC transporter-overexpressing tumor cells.

One mechanism, which is frequently discussed for CS of MDR cells, is an enhanced sensitivity to oxidative stress, as the *MDR1* gene expression seems to be influenced by ROS (Cort et al., 2016). There are several examples of ROS-inducing drugs characterized by CS induction, such as the ferrocene-quinidine epimers, which exerted significant selectivity towards MDR colorectal carcinoma DLD1-TxR and glioblastoma U87-TxR cells compared to their sensitive cells DLD1 and U87, respectively (Podolski-Renić et al., 2017). In more detail, ferrocene complexes displayed greater potential to increase ROS production and provoke mitochondrial damage in MDR cancer cells. This effect was accompanied by inhibition of autophagy and induction of apoptosis. Additionally, simultaneous treatments of ferrocene-quinidine epimers with paclitaxel increased the sensitivity of MDR cancer cells to the conventional chemotherapeutic and ABCB1 substrate paclitaxel (Podolski-Renić et al., 2017).

Another example was reported by Palanichamy and coworkers, who prepared a gold(III) polypyridyl complex $[Au(DPPZ)Cl_2][PF_6]$, (DPPZ = dipyrido[3,2-a:2′,3′-c] phenazine), which showed an ability to circumvent platinum-resistance in human ovarian carcinoma A2780/CP70 cells thus resulting in CS (Palanichamy et al., 2012). However, this ability to overcome platinum-resistance was not based on enhanced drug accumulation, which is noteworthy, as A2780/CP70 cells are characterized by reduced CTR1 and increased ABCB1 expression. In contrast, this compound increased ROS production in both cell clones. Consequently, the CS could be explained by the very low basal ROS level in A2780/CP70, which could render them more vulnerable to changes in the redox homeostasis induced by $[Au(DPPZ)Cl_2][PF_6]$ (Palanichamy et al., 2012).

The intracellular redox balance can also be impacted by the downregulation of antioxidant molecules such as GSH. Thus, it is not surprising that several CS-inducing compounds have been reported to deplete intracellular GSH, thus supporting the formation of ROS (Ganguly et al., 2010; Majumder et al., 2003; Mookerjee et al., 2006b)). However, theoretically, these agents could generate ROS in both MDR and non-MDR cancer cells, indicating the inherent vulnerability of some MDR cells to increased ROS level. This might be especially true for selenodrugs as mechanistic studies revealed that selenocompounds could downregulate the expression of GST genes and reduce the levels of GSH, which is conjugated to various xenobiotics, allowing their elimination (Wang et al., 2017). In this context, Choi and coworkers showed that sodium selenate (Na_2SeO_4) induced higher cell growth inhibition in MDR oral squamous carcinoma cells KBV20C compared to their parental KB cells. Selenate provoked cell growth inhibition in a dose- and time-dependent manner in ABCB1-overexpressing KBV20C cells,

Table 2
Metal drugs inducing CS in ABC transporter-overexpressing cancer cells.

Cell model	Overexpression of	(Collateral)Sensitive to	Selected against
A2780/CP70	reduced CTR1 and enhanced ABCB1 expression (Palanichamy et al., 2012)	gold(III) polypyridyl complex $[Au(DPPZ)Cl_2]PF_6$ (Palanichamy et al., 2012)	cisplatin
A549	ABCB1 and ABCC1 (Teixeira et al., 2021)	ruthenium cyclopentadienyl compounds with bipyridine based ligands (Teixeira et al., 2021)	cisplatin
BJAB BiBo	ABCB1	$[Re(CO)_3(bpm)]^+$ (Konig et al., 2018)	vincristine
Calu-3	ABCB1 (Teixeira et al., 2021)	ruthenium cyclopentadienyl compounds with bipyridine based ligands (Teixeira et al., 2021)	cisplatin
CEM/ ADR5000	ABCB1 (Efferth et al., 2008)	- CuPHMBA (Banerjee et al., 2016a) and Cu-5-SMAG (Banerjee et al., 2016b) - FeNG (Ganguly et al., 2010)	doxorubicin
DLD1-TxR	ABCB1 (Podolski-Renic et al., 2013)	ferrocene-quinidine epimers (Podolski-Renić et al., 2017)	paclitaxel
EAC/Dox	ABCC1 (Mookerjee et al., 2006b)	- CuPHMBA (Banerjee et al., 2016a) - FeNG (Ganguly et al., 2012)	doxorubicin
GLC(4)/ADR	ABCC1 (Versantvoort et al., 1995)	sodium selenite (Björkhem-Bergman et al., 2002)	doxorubicin
HCT15/ CLO2	enhanced ABCB1 expression?? (Lee et al., 2003)	arene–ruthenium metallarectangle bearing a 5,8-dihydroxy-1,4-naphthaquinonato unit (Dubey et al., 2013)	doxorubicin, cisplatin
H460/MX20	ABCG2	RuF (Zeng et al., 2019)	mitoxantrone
KBC-1	ABCB1	KP772 (Heffeter et al., 2007)	colchicine
KB-V1	ABCB1	- platinum-phenanthroline and KP772 (Turk et al., 2009) - Cu-Dp44mT (Jansson et al., 2015) - Cu-DpC (Seebacher et al., 2016)	colchicine
KBV20C	ABCB1 (Kim et al., 2007)	sodium selenate (Choi et al., 2015)	vincristine
MES-SA/Dx5	ABCB1 (Wesolowska et al., 2005)	ruthenium and rhodium complexes of 8-hydroxyquinoline derivatives (Domotor et al., 2017)	doxorubicin
Nalm-6/DAU	ABCB1	$[Re(CO)_3(bpm)]^+$ (Konig et al., 2018)	daunomycin
NCI-H228	ABCB1 and ABCC1	ruthenium cyclopentadienyl compounds with bipyridine based ligands (Teixeira et al., 2021)	cisplatin
SW480/Tria	ABCB1 (Miklos et al., 2015) Loss of PDE4D (Miklos et al., 2016)	iron(III) complex of COTI-2 (Bormio Nunes et al., 2020)	triapine
U-1285dox	ABCC1 (Jonsson-Videsater et al., 2003)	sodium selenite (Björkhem-Bergman et al., 2002)	doxorubicin
U87-TxR	ABCB1 (Podolski-Renic et al., 2013)	ferrocene-quinidine epimers (Podolski-Renić et al., 2017)	paclitaxel

Bpm … 4-[(bis(6-phenanthridinylmethyl)amino)methyl]benzoic acid methyl ester, DPPZ … dipyrido[3,2-a:2′,3′-c] phenazine, NG = N-(2-hydroxy acetophenone) glycinate, PHMBA … N-(2-hydroxy-3-methoxy-benzaldehyde)-alaninate, SMAG … N-(2-hydroxy-5metoxy-acetophenone) glycinate;

without inhibitory effect on ABCB1. Cell growth inhibition was accompanied by G2/M phase cell cycle arrest and an increase in early apoptosis (Choi et al., 2015).

Sodium selenite (Na_2SeO_3) also proved to be more efficient against doxorubicin-resistant ABCC1-overexpressing SCLC U-1285dox and GLC (4)/ADR cell lines than in sensitive U-1285 and GLC(4) cell lines. The main difference between sensitive and drug-resistant tumor cell lines was the higher activity of TrxR in drug-resistant cell lines, while GR activity was practically the same between sensitive and resistant cell lines. However, selenite significantly increased the activities of both TrxR and GR in sensitive U-1285 cells, whereas, in resistant U-1285dox cells, activities of these enzymes were unaltered. Upregulation of the key enzymes in selenium metabolism after selenite exposure probably lead to a survival advantage in sensitive cells. This could be a possible mechanism explaining the differential cytotoxicity of sodium selenite in sensitive and resistant cancer cells (Björkhem-Bergman et al., 2002).

Interestingly, there is a considerable amount of literature on CS-inducing metal complexes containing Schiff base-derived ligands: 1) several metal complexes contain the aforementioned NG ligand or its derivatives. Here, the metals are coordinated via an O,N,O coordination sphere. The most-investigated representative of this compound class is the above described CuNG, which is assumed to target MDR cells mainly via direct interaction with the ABCB1 protein. However, this drug also displayed CS-inducing properties. In contrast, MnNG had no ABCB1-modulatory properties, but CS of ABCB1-overexpressing CEM/adr cells *in vitro* and ABCC1-overexpressing AEC/Dox cells in female Swiss albino mice was observed (Ghosh et al., 2013). Concerning the mode of action, ROS induction was suggested for MnNG. However, as no direct comparison between resistant and sensitive cancer cells has been performed yet, it is difficult to estimate whether this is the mode of action underlying the CS of MDR cancer cells to this drug. Similarly, the redox-active iron complex, FeNG, displayed cytotoxic activity in the doxorubicin-resistant T lymphoblastic leukemia cells CEM/ADR5000 (Ganguly et al., 2010). FeNG also provoked ROS and intracellular GSH depletion in these resistant cells. Induction of redox imbalance led to nuclear fragmentation, DNA condensation and apoptosis through mitochondrial pathway (Ganguly et al., 2010). Additionally, FeNG potentiated the cytotoxic effect of doxorubicin in EAC/DOX cancer cells *in vitro* and increased survival of ABCC1-overexpressing EAC/DOX xenografts (Ganguly et al., 2012). *In vivo* administration of FeNG induced GSH depletion and ROS production in EAC/Dox cancer cells, without alteration in ABCC1 expression. FeNG also enhanced intracellular doxorubicin accumulation in EAC/Dox cells in a time-dependent manner *in vivo* (Ganguly et al., 2012). Derivatives of CuNG, copper(II) *N*-(2-hydroxy-3-methoxy-benzaldehyde)-alaninate (CuPHMBA, Fig. 8) and copper(II) *N*-(2-hydroxy-5-methoxy-acetophenone) glycinate (Cu-5-SMAG, Fig. 8), also showed redox activity and potential to overcome MDR in doxorubicin-resistant cell lines expressing ABCB1 based on CS (Banerjee et al., 2016a; Banerjee et al., 2016b). While in the case of CuPHMBA, most experiments on the mode of action of this drug were performed in the drug-resistant cell model only, there is a more elaborated study on Cu-5-SMAG. Here, the data indicated that the CS of ABCB1-overexpressing CEM/ADR5000 cells (in comparison to their chemosensitive counterpart) is based on more rapid and pronounced induction of apoptosis. Interestingly, while there are some indications that the ROS induction was similar between drug-resistant and -sensitive cell lines with CuPHMBA, regarding Cu-5-SMAG, drug-resistant cells experienced stronger GSH depletion together with slightly increased redox stress. Finally, ABCC1-overexpressing EAC/Dox cells were characterized by CS (in comparison to EAC/S cells) in Swiss albino mice *in vivo*. All in all, this makes this class of compounds interesting for further development against drug-resistant cancer cells.

2) There are some reports on thiosemicarbazone complexes, where the metal center is coordinated via a N,N,S donor set (Turk et al., 2009). Examples are the iron(III) complex of the clinically investigated COTI-2 (Bormio Nunes et al., 2020) but also several copper(II) complexes of, e.g. Dp44mT and the clinically tested DpC (Fig. 8) (Hager et al., 2020; Park et al., 2016). In more detail, CS of ABCB1-overexpressing KBV-1 cells to

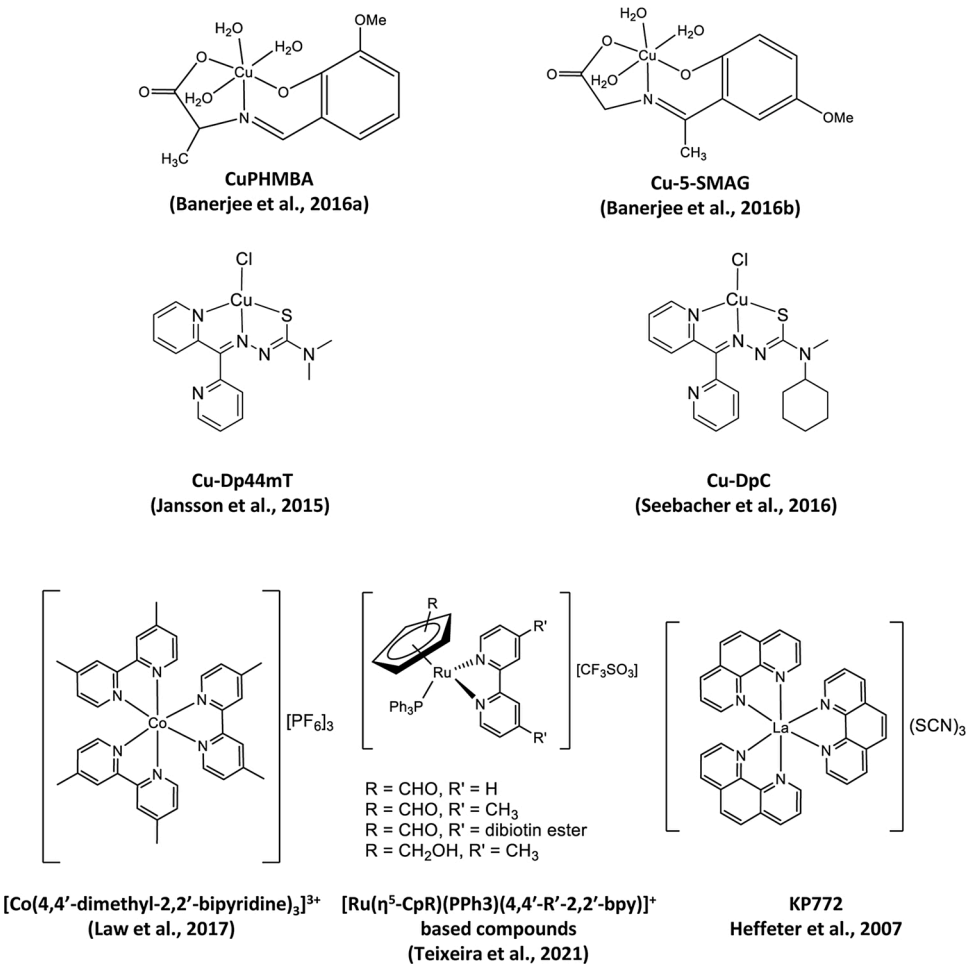


Fig. 8. Metal drugs inducing CS in ABC transporter-overexpressing cancer cells.

Cu-Dp44mT and Cu-DpC was ABCB1-dependent and characterized by enhanced loss of lysosomal integrity (Jansson et al., 2015; Seebacher et al., 2016). In contrast, Fe-Dp44mT did not induce such effects in resistant or sensitive cell clones. In general, there is far more literature on CS of ABCB1-overexpressing cells for metal-free thiosemicarbazone derivatives (Heffeter et al., 2019). However, based on the very strong metal-chelating properties of this compound class, an important role of intracellularly formed metal complexes in these CS-inducing effects can be hypothesized. Interestingly, the phenomenon of CS in ABCB1-overexpressing cancer cells is not a general feature of thiosemicarbazones (Bormio Nunes et al., 2020; Hager et al., 2020; Turk et al., 2009). In contrast, this feature seems to be associated with specific physicochemical properties of the respective thiosemicarbazone ligands. Overall, the structure-activity relationships predicting chemical features responsible for thiosemicarbazone-mediated CS are still not entirely understood. For example, it has been suggested that only α-*N*-heterocyclic thiosemicarbazones with electron-withdrawing substituents at the imine carbon mediate enhanced ABCB1-dependent cytotoxicity (Stacy et al., 2016). Also, for isatin-β-thiosemicarbazones, a specific pharmacophore model was suggested to identify chemical features that fine-tune selective toxicity towards ABCB1-expressing cells (Hall et al., 2011; Hall et al., 2009). However, it should be noted that this model could not be validated in a more extended library of more diverse thiosemicarbazones (Pape et al., 2016), suggesting that a more complex structure-activity relationship exists for the class of thiosemicarbazones as a whole. Interestingly, in addition to their induction of CS, several metal thiosemicarbazone complexes (e.g. copper and iron complexes of Dp44mT, Bp44mT, DpC, and Triapine) were shown to directly interact with the ABCB1 protein resulting in stimulation of its ATPase activity comparable to the known substrate and competitive inhibitor verapamil (Jansson et al., 2015; Stacy et al., 2016).

In addition to metal complexes containing Schiff base-derived ligands, there are also several drugs containing an N,N-coordination sphere (e.g. bipyridine-, phenanthroline-, pyrimidinylhydrazone-derived ligands), for which CS of MDR cells has been reported (Heffeter et al., 2007; Law et al., 2017; Turk et al., 2009). For example, the potential of a family of cobalt(II) and cobalt(III) tris(bipyridine) compounds to induce CS in ABCB1-overexpressing cancer cell models has been disclosed (Law et al., 2017). In contrast, in several platinum-resistant models the compounds were equally effective in the parental and resistant subclones (Law et al., 2017). Subsequent analysis of $[Co(4,4'\text{-dimethyl-}2,2'\text{-bipyridine})_3]^{3+}$ (Fig. 8) demonstrated that in addition to its CS-inducing potential, this drug also had an ABCB1-inhibitory potential. Concerning its mode of action, the authors showed that $[Co(4,4'\text{-dimethyl-}2,2'\text{-bipyridine})_3]^{3+}$ inhibited cell cycle progression and induced autophagy in an Atg7-dependent manner.

4,4'-Dimethyl-2,2'-bipyridine has also been identified as a potential ligand to endow $[Ru(\eta^5\text{-CpR})(PPh_3)(4,4'\text{-R'-}2,2'\text{-bpy})]^{+}$-based compounds with ABCC1/2-inhibitory properties (Corte-Real et al., 2018). The importance of the methyl substituent was further confirmed for a new set of compounds where the substituent at the cyclopentadienyl ring (R) is a formyl or a hydroxyl group (Fig. 8) (Teixeira et al., 2021). In this study, the ruthenium(II) compounds exhibited CS for NSCLC cells resistant to cisplatin expressing high levels of ABCC1 (A549 and NCI-H228) and ABCB1 (Calu-3), being non-cytotoxic for the cisplatin-sensitive cell line, NCI-H1975. When co-administered at

non-cytotoxic doses (IC_{25}) with cisplatin, these compounds increased cisplatin cytotoxicity up to ~1400-fold by directly impairing the catalytic activity of ABCC1 and ABCB1.

Similarly to $[Co(4,4'\text{-dimethyl-}2,2'\text{-bipyridine})_3]^{3+}$, the lanthanum 1,10-phenantroline complex KP772 (Fig. 8) also induced strong cell cycle arrest in G0/G1 (based on inhibition of ribonucleotide reductase) together with pronounced apoptosis induction in ABCB1- as well as ABCC1-overexpressing cell lines (Heffeter et al., 2007). Interestingly, in contrast to the ROS production described for several CS-inducing compounds above, KP772 did not induce oxidative stress but rather had ROS-scavenging properties (Heffeter et al., 2009). Finally, Pape et al., reported potent CS-inducing properties for the copper complex of a new pyrimidylhydrazone derivative (Pape et al., 2015). In a rare study, the authors also investigated the dependency of these effects on functional ABCB1, characterizing this compound as an ABCB1-associated CS inducer. Interestingly, the CS-inducing potential was also shared already by the metal-free ligand, and the effect of ROS scavenging was similar in chemosensitive and -resistant cells.

CS of ABCB1-overexpressing MDR cancer cells has also been described for several 8- hydroxyquinoline-based iron chelators (Turk et al., 2009). Here, comparable to reports on thiosemicarbazones, induction of CS was not a general feature but occurred only for selected derivatives indicating a specific structure-activity relationship. Although most of the reports focus on metal-free ligands, e.g. NSC29736, there are indications that the formation of intracellular iron complexes plays a crucial role in CS of ABCB1-overexpressing cancer cells (Cserepes et al., 2020). In more detail, the iron complex of NSC29736 (but not the metal-free ligand) was demonstrated to be, in fact, an ABCB1 substrate. Consequently, it is currently hypothesized that the continuous efflux of the iron complex leads to selective iron depletion in ABCB1-overexpressing cells. In line with this hypothesis, the iron complex of NSC29736 did not induce CS *per se* (Cserepes et al., 2020). On the other hand, the complexation of ruthenium even enhanced the CS-inducing potential of a (η^6-*p*-cymene) 8-hydroxyquinoline complex, while the ruthenium (η^6-*p*-cymene) complex of the substituted 7-(1-piperidinylmethyl) derivate appeared to be an ABCB1 substrate (Domotor et al., 2017).

These data, taken together, indicate that metal complexes as well as interaction with the metal homeostasis, have the potential to induce CS in MDR cancer cells. However, the exact mechanisms underlying these effects are widely unknown and urgently warrant further investigations. The precise mechanism is even more complicated because there seems to be complex structure-activity relationships and probably multiple modes of action, which are currently unexplored in most cases.

3.5. Targeting altered tumor metabolism in drug-resistant cells

As described above, cancer drug resistance is frequently associated with changes in the metabolic profile (Bhattacharya et al., 2016; Harper et al., 2002; Ricci et al., 2019). This central aspect in cancer biology could be exploited for anticancer therapy, as indicated in several studies on metformin (Saraei et al., 2019). Metformin inhibits mTOR activity and subsequently adenosine monophosphate-activated kinase (AMPK), a central pathway in the metabolic shift associated with the Warburg effect (Saraei et al., 2019). Metformin is currently clinically tested in combination with several approved drugs including platinum compounds (Saraei et al., 2019). Metformin is highly synergistic with platinum drugs in chemosensitive but also in drug-resistant cell models in cell cultures and in xenograft models (Liu et al., 2017b; Ricci et al., 2019). Interestingly, although there are some attempts to co-deliver metformin with cisplatin using nanocarriers (Saber et al., 2018; Xiong et al., 2016), no dual-action platinum drug currently exists. However, first complexes with other metals such as ruthenium (Gopalakrishnan et al., 2017), nickel (Elshami et al., 2020), and gold (Babak et al., 2021) have been designed and it will be interesting to see, how they act against drug-resistant cancer cells.

For several years, diverse metal compounds with dichloroacetate (DCA) ligands have been designed to specifically target drug-resistant cancer cells with mitochondrial dysfunction. DCA is a drug that has been clinically tested for diverse metabolic disorders based on its pyruvate dehydrogenase kinase (PDK)-inhibitory properties (Kankotia and Stacpoole, 2014). PDK1 is an enzyme that inhibits pyruvate dehydrogenase by shifting the metabolism from oxidative to reductive (e.g. the fermentation of glucose into lactate) (Icard et al., 2018). One of the first DCA-releasing drugs was mitaplatin, a cisplatin-releasing platinum(IV) drug with two DCA ligands in axial position (Fig. 9) (Dhar and Lippard, 2009). Indeed, mitaplatin was able to partly overcome the resistance of several cisplatin-resistant cell lines (KB/CP20, BEL7404/CP20, A2780/CP20, characterized among others, by changes in their mitochondrial activity) based on enhanced drug accumulation, changes in the mitochondrial integrity and reduction of the cellular glucose consumption (Dhar and Lippard, 2009; Xue et al., 2012). However, it was reported by Wexselblatt et al., that platinum(IV) derivatives of cisplatin, carboplatin or oxaliplatin having two axial ligands of DCA are not stable under biological conditions, e.g. in cell culture medium (Wexselblatt et al., 2015). Thus, these complexes undergo hydrolysis, which results in premature loss of one or both axial DCA ligands. Regarding mitaplatin, its half-life was less than 1 h. Similar behavior was also reported in the case of a DCA-releasing platinum(IV) derivative of kiteplatin (Savino et al., 2018). To improve the pharmacological properties of mitoplatin, besides diverse nanoformulations (Johnstone et al., 2013; Yang et al., 2016), several other DCA-releasing platinum drugs have been synthesized and tested for their chemical and biological properties. On the one hand, there are platinum(II) derivatives, where, e.g. the DCA moiety has been directly linked to the platinum center (Zhang et al., 2015) or attached to the leaving group via an ester bond (Liu et al., 2015; Liu et al., 2013). On the other hand, platinum(IV) drugs like oxaliplatin derivatives with axial hydroxido ligands (Zajac et al., 2016) or the biotinylated cisplatin variant DPB (Jin et al., 2019) have been designed. However, in most cases, the evaluation of their potential to overcome drug resistance was only preliminary evaluated by MTT assays in one platinum-resistant cell model or is still missing. Moreover, the selection of the tested drug resistance models was rarely based on alterations in metabolism. Thus the data generated do not allow the assessment of whether the new compounds are indeed more active in cisplatin-resistant cells due to their anti-metabolic activity. However, an in-depth understanding of these facets in the mode of action of these new drugs is urgently needed. For example, in the study on the platinum(IV) drugs with axial hydroxido ligands (Fig. 9) (Zajac et al., 2016), it was already shown that the improved efficacy against A2780/cis cells was at least in part due to conversion of oxaliplatin into its platinum(IV) analogue and, consequently, changed hydrophilicity, which allowed circumvention of the uptake deficiency of the used resistance model. With regard to other metal complexes, recently, Brabec and co-workers described the effect of metal-based, DCA-bearing half-sandwich complexes, $[M(\eta^6\text{-pcym})(bphen)(DCA)][PF_6]$ (M = Os or Ru; pcym = *p*-cymene; bphen = 4,7-diphenyl-1,10-phenanthroline) on several cancer cell lines, with the osmium compound being slightly better than the ruthenium derivative (Fig. 9) (Pracharova et al., 2018; Starha et al., 2018b). The differences in activity were attributed to the quicker release of the DCA ligand for the ruthenium compound before entering the cells. Of particular relevance for this review is the fact that both compounds were equally cytotoxic in A2780 vs A2780/cis cells. Further mechanistic studies in MDA-MB-231 cells revealed that the osmium complex seems to behave like a glycolytic inhibitor by reversing the Warburg's effect.

3.6. Changed reactivity with thiols

With the aim to design a new platinum(II) drug able to overcome thiol-mediated resistance of cisplatin-resistant cells, picoplatin (AMD473, JM-473, ZD0473) was designed by introducing a bulky methylpyridine ring which sterically hindered its interaction with GSH

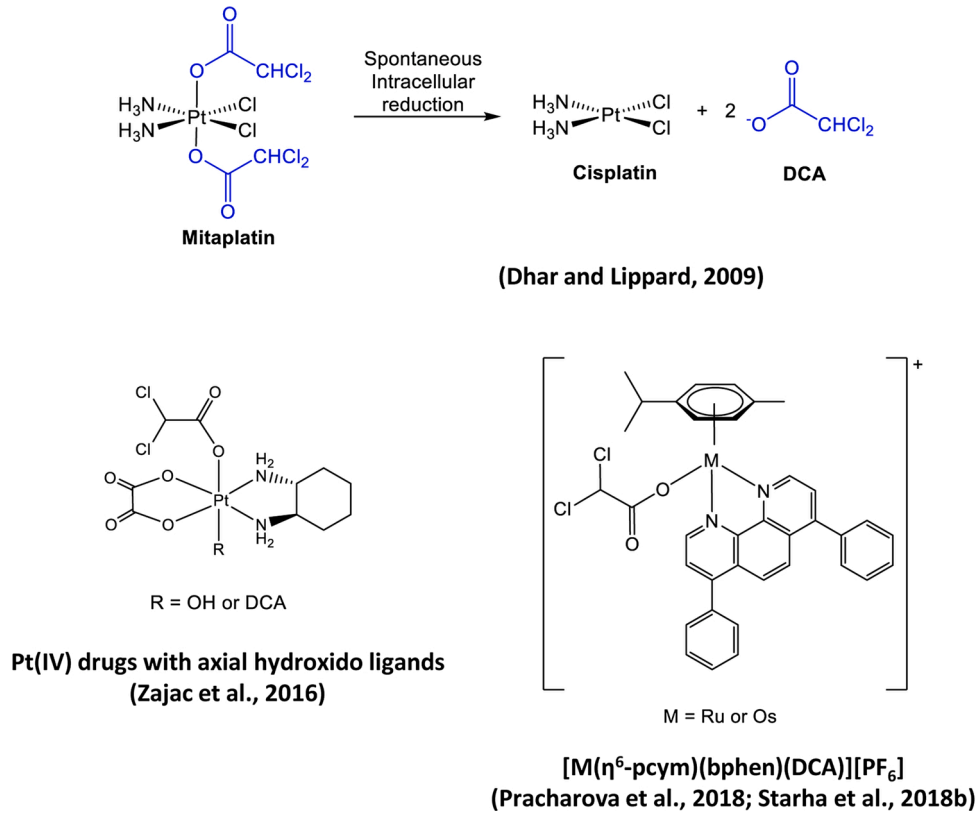


Fig. 9. Metal drugs targeting the changed tumor metabolism in resistant cells.

(Fig. 10). Consequently, picoplatin has been shown to be less conjugated to GSH and MT than cisplatin in cell-free systems. Moreover, enhanced GSH levels (Holford et al., 1998a; Holford et al., 1998b) as well as overexpression of MT, had a significantly lower impact on the anticancer activity of picoplatin compared to cisplatin. The drug subsequently circumvented resistance in three models of acquired cisplatin resistance: 41 M/41 McisR (resistance due to changed drug uptake), CH1/CH1cisR (resistance due to increased DNA damage repair/tolerance) and A2780/A2780cisR (resistance due to enhanced GSH levels, reduced drug uptake and increased DNA damage repair/tolerance) (Holford et al., 1998b). Moreover, elevated MT levels did not protect cells from picoplatin activity (in contrast to cisplatin, carboplatin and satraplatin) (Holford et al., 2000). Based on promising anticancer activity of the drug also *in vivo* against cisplatin-resistant ovarian carcinoma models (Raynaud et al., 1997), the compound was clinically tested in several phase I and II studies on platinum-sensitive ovarian cancer and cisplatin-resistant

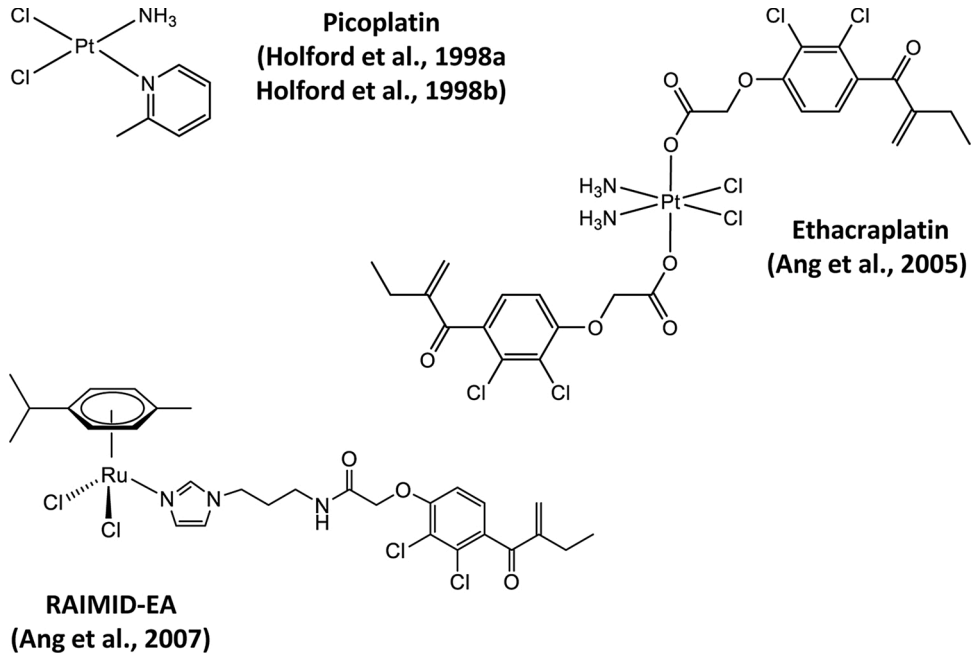


Fig. 10. Metal drugs with a changed reactivity with thiols or targeting changed thiol metabolism in resistant cells.

SCLC (Eckardt et al., 2009). However, a clinical phase III study in SCLC failed to show a significantly improved overall survival of picoplatin-treated patients (Ciuleanu et al., 2010; Hamilton, 2013). Noteworthy, this study did not assess the molecular characteristics between responding and non-responding patients (Hamilton, 2013). Consequently, it is unknown, whether the failure of picoplatin is based on the selection of a too broad patient cohort without application of appropriate biomarkers, or on the general failure of the drug concept of circumventing GSH-mediated drug resistance. The latter would be supported by a study on acquired resistance to picoplatin, which revealed that resistance development was associated with significantly reduced cellular drug accumulation and, in the case of A2780ZD0473R cells, loss of the MMR protein hMLH1 as well as increased GSH levels (Holford et al., 2000).

3.6.1. Targeting GST

GST comprises an important class of enzymes, the main function of which is detoxification of toxic compounds, thus playing an important role in the cellular defense against exogenous toxic small molecules (Habig and Jakoby, 1981). Several studies correlated MDR with the overexpression of GST enzymes (Townsend et al., 2005). In particular, the GST P1-1 isozyme is known to regulate the mitogen-activated protein (MAP) pathway, involved in cellular survival and death signaling (Tew and Ronai, 1999). Ethacrynic acid (EA) is a well-described and effective inhibitor of all GST isozymes (Hayes et al., 2005) and there have been several attempts to attach this molecule to metal-based (pro) drugs. In this respect, one of the most investigated drug candidates is ethacraplatin, a *trans*-platinum(IV) carboxylate prodrug that was designed to release two EA molecules from their axial positions upon reduction (Fig. 10) (Ang et al., 2005). Unexpectedly, however, ethacraplatin turned out to have GST-inhibitory properties, which were even superior to EA itself (~20-fold more active) (Parker et al., 2011). Subsequent studies revealed that ethacraplatin does not act as a prodrug, but instead, the intact EA-containing platinum(IV) complex strongly binds to the enzyme. Moreover, this interaction resulted in a reduction of the Pt center and subsequent binding of the platinum(II) complex at the dimer interface of the enzyme and the release of EA moieties at both H-sites (Parker et al., 2011). These direct "suicidal" interaction of the platinum(IV) complex could be prevented by preparation of a platinum (IV) derivative, which contained only one EA moiety and, thus, was characterized by a more easy reduction (Lee et al., 2018). In line with the cell-free experiments, ethacraplatin showed a strong GST inhibition and anticancer activity in GST-P1-overexpressing hepatocellular carcinoma BEL7404/CP20 cells, which led to the overcoming of the strong cisplatin resistance in this cell model (Li et al., 2017b). Interestingly, ethacraplatin as well as its platinum(II) analogue also circumvented the drug resistance of platinum-resistant MM98R mesothelioma cells, which did not display enhanced GST activity in comparison to its chemosensitive parental counterpart. This indicates that other factors might contribute to the efficacy of these drugs against platinum-resistant cells (Zanellato et al., 2011). An observation also supported by the reduced cross-resistance of A2780/cisR cells (Lee et al., 2018). One explanation could be that the attachment of the EA ligand(s) results in increased lipophilicity and thereby increased drug uptake in comparison to cisplatin (Lee et al., 2018).

In addition to platinum, several ruthenium(II) and a few osmium(II) η^6-arene complexes were conjugated to EA with the aim to develop new GST inhibitors (Ang et al., 2007). In more detail, EA was conjugated to the complexes either by using arene-, phosphane-, imidazole- or pyridine-based ligands or by direct coordination to the metal (Agonigi et al., 2016; Agonigi et al., 2015; Ang et al., 2007; Ang et al., 2009; Nowak-Sliwinska et al., 2011). Since not all studies reported on the ability of compounds to inhibit GST activity or investigated the cytotoxicity in resistant cancer cell lines, it is not possible to perform an overall discussion in terms of structure-activity relationships. Yet, regarding the ability of compounds to inhibit GST activity, the first compound reported, RAIMID-EA (Fig. 10), seems the most potent GST P1-1 inhibitor with similar or slightly better inhibitory activity than EA, resulting in similar IC_{50} values for A2780cisR and A2780 cells (Ang et al., 2007). Using cysteine-modified GST P1-1 mutants and ESI-MS studies, the authors subsequently showed that there was a covalent binding between the ruthenium compound and the enzyme after loss of the chloride ligands. The functionalization of the η^6-arene ligand with EA does not seem advantageous for GST inhibition (Ang et al., 2009). Functionalization of the pyridine and phosphane ligands in ruthenium and osmium compounds led to modest GST-inhibitory properties; however, no comparison with EA was shown (Agonigi et al., 2016; Agonigi et al., 2015). Finally, the impact of the presence of two EA or two metal centers (ruthenium or osmium) on the compounds' structure was studied relatively to their cytotoxic activity in A2780 and A2780cisR cells, but, unfortunately, inhibitory studies were not reported (Nowak-Sliwinska et al., 2011). Thus, the improved cytotoxic activity observed when the compounds bear two EA entities cannot be directly correlated to their GST-inhibitory potential. Yet, this set of results suggests that these metal compounds conjugated to EA have potential as GST inhibitors.

Besides conjugation to EA, metal compounds can also have intrinsic GST-inhibitory activity, which allows them to act against drug-resistant cancer cells by reducing the intracellular GSH levels. One example is the already mentioned CuNG (compare Fig. 7), which was reported to reduce cellular GSH levels *in vivo* even more efficiently than EA (Majumder et al., 2003). With regards to the mode of action, CuNG depletes cellular GSH levels at non-toxic concentrations through conjugation (Majumder et al., 2006a). Consequently, CuNG was able to overcome doxorubicin resistance and to increase the lifespan of EAC/-DOX xenograft mice, overexpressing GST and the GSH-conjugate efflux transporter ABCC1 (Majumder et al., 2006a).

3.6.2. Targeting γGT-overexpressing cancer cells

γGT is a key enzyme involved in GSH metabolism and its expression is often significantly increased in diverse human cancer types (Corti et al., 2010). Moreover, there is evidence that the development of drug resistance is associated with γGT, presumably due to its detoxification activity. Noteworthy, there have been several attempts to use the enzymatic functions of this membrane-located protein for the tumor-specific activation of prodrugs (Ramsay and Dilda, 2014). Concerning this review, three arsenicals need to be mentioned, three of which have been already tested in clinical trials: 4-(N-(S-glutathionylacetyl)amino)phenylarsonous acid (GSAO), 4-(N-(S-penicillaminyl)-amino)phenylarsonous acid (PENAO) and Darinaparsin (S-dimethylarsion-glutathione, ZIO-101, SP-02 L). The proposed mode of action of GSAO and PENAO is shown in Fig. 11. Briefly, the pro-drug is applied in a non-permeable form, which is activated by γGT at the cell surface by cleavage of the γ-glutamyl group. Subsequently, the dipeptide metabolite is able to enter the cancer cell, where it is further processed by dipeptidases to its single amino acid form. This, in turn, was shown to crosslink the cysteine residues of the mitochondrial adenine nucleotide translocator (ANT), resulting in loss of mitochondrial integrity and cell death (Ramsay and Dilda, 2014). However, although GSAO was investigated with respect to γGT expression (Ramsay et al., 2014), no studies on its potential to act in drug-resistant cancer cells have been performed. Moreover, GSAO and PENAO were both ABCC1 substrates comparable to ATO (Dilda et al., 2009).

Darinaparsin is an organic arsenical, which has been originally developed with the aim to design a better tolerated arsenic-based drug. Subsequent analysis revealed that Darinaparsin was not only more active against cancer cells than ATO in cell culture - but also exerted a different spectrum of activity (Matulis et al., 2009). Thus, while the PML/RARα fusion gene, a known ATO target, remained unaffected, Darinaparsin activity was based on ROS generation and oxidative damage in a manner different from ATO. Accordingly, the drug was also not affected by the acquired resistance of AR2 cells to ATO, and showed

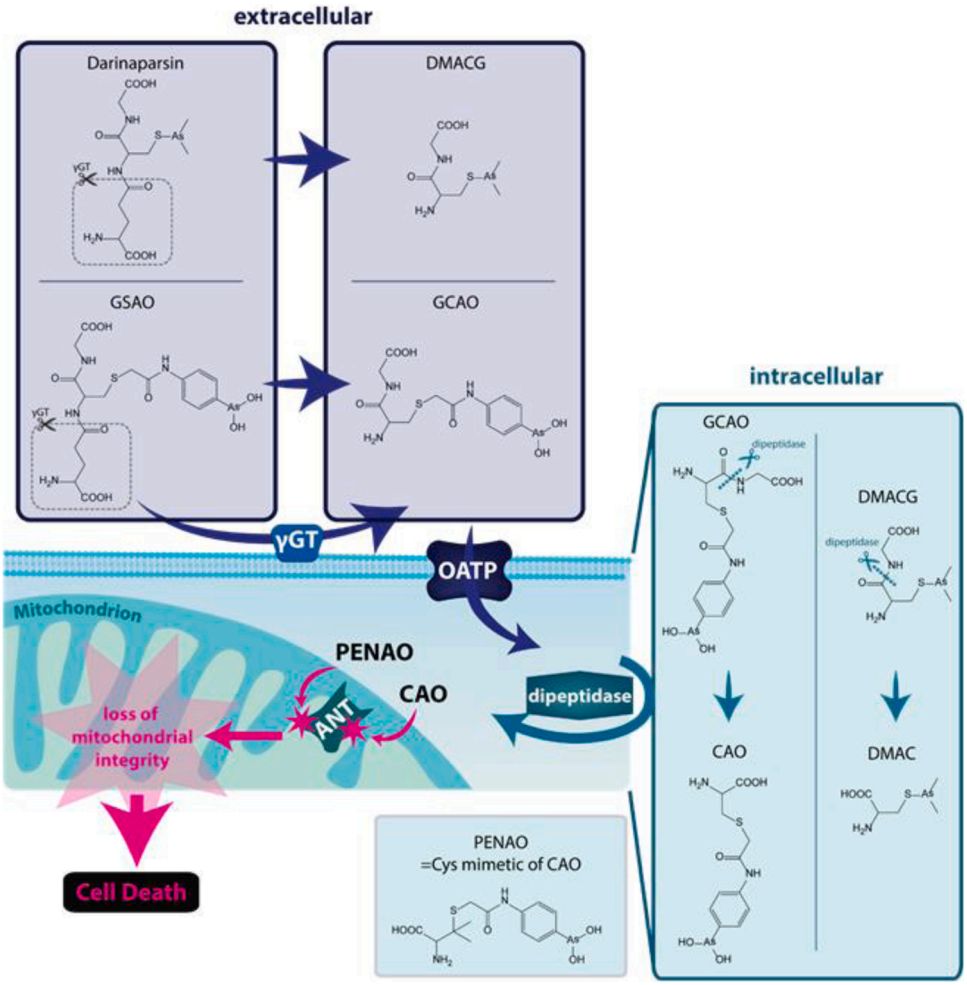


Fig. 11. Mode of action of γGT-targeting arsenicals.

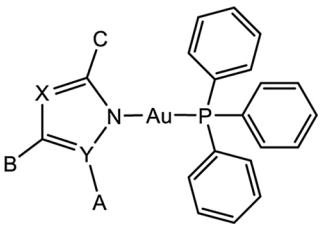
similar apoptosis induction in ATO-resistant (AR2) as well as -sensitive (NB4) cell clones. Moreover, Darinaparsin was not a substrate of ABCC1, which is overexpressed in AR2 cells (Matulis et al., 2009). Darinaparsin was tested for its tolerability and anticancer activity in 14 clinical phase I/II trials. The latest multi-center phase II study in relapsed or refractory patients with peripheral T-cell lymphoma is still ongoing with expected results in 2021 (NCT02653976). It will be interesting to follow, whether Darinaparsin also has activity against drug-resistant cancer cells also in the clinical setting.

3.6.3. *Targeting the TrxR system*

As described in the introduction, drug resistance is frequently associated with increased levels of Trx or TrxR (Cui et al., 2018; Mohammadi et al., 2019; Sasada et al., 1996). Thus, targeting the Trx system might be an attractive approach to overcome cancer drug resistance. As mentioned above, the gold complex auranofin, a specific and well-known inhibitor of TrxR, has already been tested in several clinical phase I and II trials. In this chapter, we provide examples for several other gold complexes that also showed inhibitory activity of the Trx system. Moreover, these complexes were able to overcome platinum resistance in cancer cells. For instance, Gandin and coworkers (Gandin et al., 2010) prepared a series of linear „auranofin-like "gold complexes based on $[Au(PEt_3)]^+$ synthon and additional simple co−ligands (Fig. 12). These compounds were able to circumvent resistance in two cell line pairs resistant to cisplatin (ovarian adenocarcinoma OV2008/C13* and cervix carcinoma A431−Pt) and two tumor cell line pairs resistant to doxorubicin (SCLC U1285dox and colon adenocarcinoma LoVo MDR). All investigated compounds also showed nanomolar activity against rat cytosolic TrxR1 and mitochondrial TrxR2 similar to values obtained for auranofin. On the other hand, the activity of all investigated compounds against GR and GPx was in the micromolar range. In the case of complexes with xanthate and thiocyanate as co−ligands, apoptosis was determined as the mode of cell death (Gandin et al., 2010).

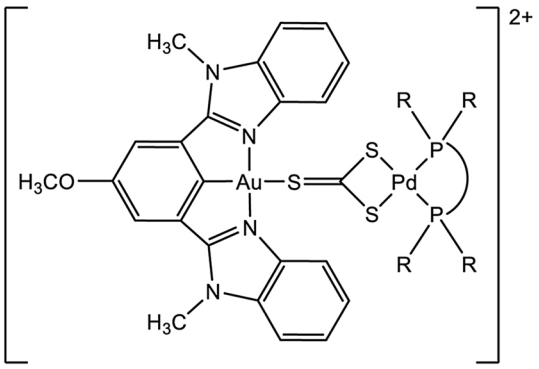
Similar behavior was noticed for a series of heteroleptic, water−soluble gold complexes based on phosphane and thionate co−ligands (Fig. 12) (Vergara et al., 2010). The investigated compounds showed enhanced cytotoxicity in cisplatin-resistant human ovarian carcinoma A2780/cisR cells compared to their sensitive counterparts. These compounds were excellent inhibitors of both TrxR1 and TrxR2 with IC_{50} values in the nanomolar range, while in the case of GR the IC_{50} values were in the micromolar range. Based on a biotin-conjugate iodoacetamide (BIAM) assay, the reported compounds were able to bind selenocysteine in the active site of the TrxR enzyme (Vergara et al., 2010).

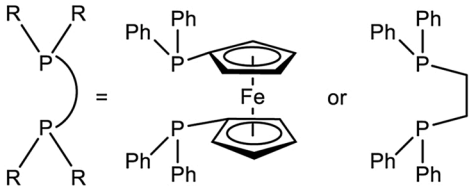
In a study by Galassi et al., the effect of azolate gold(I) phosphane complexes on TrxR was determined, as well as their cytotoxic activity against the cisplatin-sensitive and cisplatin-resistant ovarian adenocarcinoma cell line pair OV2008 and OV2008/C13* (Galassi et al., 2012). Both tumor cell lines demonstrated similar sensitivity to the applied complexes, thus showing the absence of cross-resistance. Heteroleptic complexes (1), (2) and (7) based on 1H-pyrazolate/1H-imidazolate and triphenylphosphane ligands (Fig. 12) showed even higher cytotoxicity against cisplatin-resistant ovarian adenocarcinoma OV2008/C13* cells and were able to inhibit TrxR1 and TrxR2 at the nanomolar range.



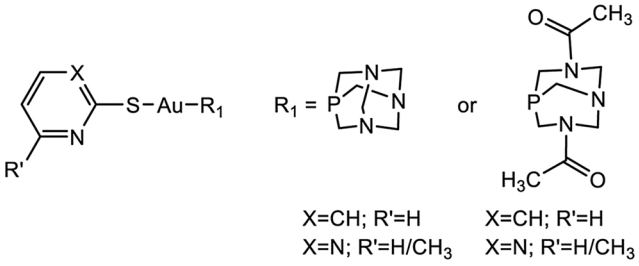
1: X=CH; Y=N; A=/; B=C=CF_3
2: X=CH; Y=N; A=/; B=C=NO_2
7: X=N; Y=C; A=B=Cl; C=H

Heteroleptic complexes (1), (2) and (7) based on triphenylphosphane and 1H-pyrazolate-based (Galassi et al., 2012)



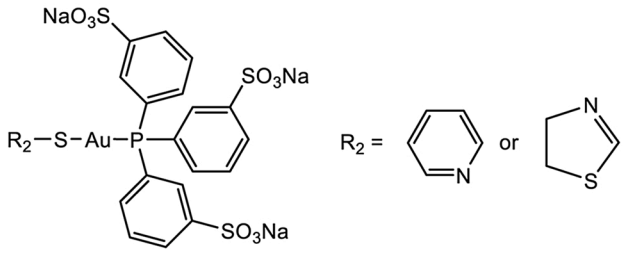


Multinuclear gold(III)/palladium(II) pincer complexes (Tabrizi and Chiniforoshan, 2017)

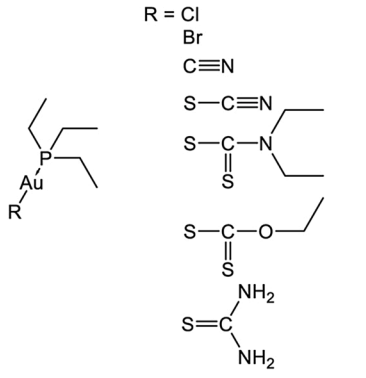


X=CH; R'=H
X=N; R'=H/CH_3

X=CH; R'=H
X=N; R'=H/CH_3



Heteroleptic, water–soluble gold complexes based on phosphine and thionate co–ligands (Vergara et al., 2010)



Linear „auranofin–like" gold complexes (Gandin et al., 2010)

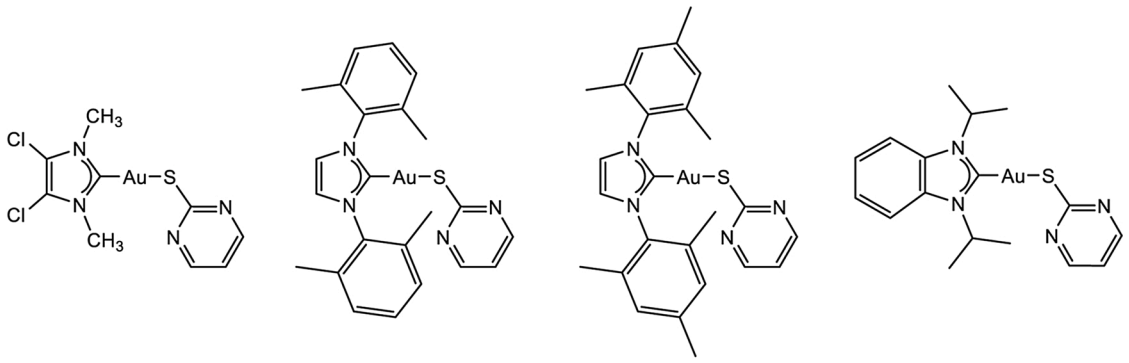
Fig. 12. Metal drugs inhibiting the Trx system (I).

Furthermore, complex (7) also significantly inhibited GR (Galassi et al., 2012).

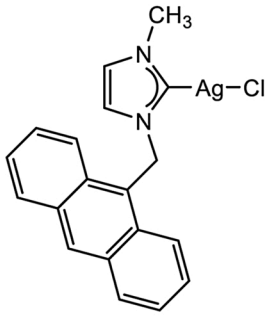
Tabrizi and Chiniforoshan prepared two multinuclear gold(III)/palladium(II) pincer complexes with bis(diphenylphosphino) ferrocene/non-ferrocene ligands (Fig. 12) which showed the same level of activity in sensitive and cisplatin-resistant ovarian adenocarcinoma cancers cells (OV2008 vs. OV2008/C13*). These compounds showed nanomolar inhibition of TrxR1 at a concentration that was comparable or even lower than auranofin, while TrxR2 appeared to be less sensitive. Both complexes displayed micromolar inhibition of GR. Since these complexes are not likely to be involved in ligand exchange reactions, the authors speculated that their activity might be related to their ability to inflict oxidative damage to proteins (Tabrizi and Chiniforoshan, 2017).

Schuh and coworkers tested a series of gold(I) complexes with *N*-heterocyclic carbene (NHC) 1,3-substituted imidazole-2-ylidene and benzimidazole-2-ylidene ligands (Fig. 13) against ovarian carcinoma A2780S/ A2780R cell line pairs (Schuh et al., 2012). All investigated compounds showed an ability to surmount cisplatin resistance. The compounds showed potent and selective TrxR inhibition, particularly in cancer cell lines compared to normal cell lines. Based on the BIAM assay, these compounds bind to the selenocysteine at the redox-active motif of TrxR1. 1,3-Dimethyl-4,5-dichloroimidazole-2-ylidene-gold(I)-pyrimidine-2-thiolate (3b, Fig. 13), one of the most cytotoxic compounds, showed similar behavior as auranofin regarding oxidation of Trx. Namely, oxidation of cytosolic Trx1 and mitochondrial Trx2 was detected, implying its capacity to target both intracellular compartments. The oxidation was more pronounced in the cisplatin-resistant cell line. Moreover, this compound was able to increase the level of

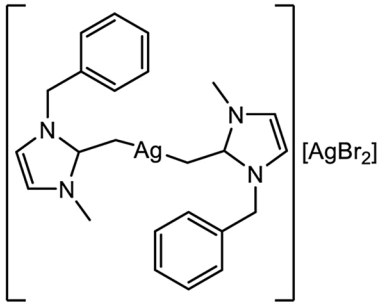
hydrogen peroxide only in A2780R cells (Schuh et al., 2012). Furthermore, Citta and coworkers showed that a silver(I) NHC complex bearing a fluorescent anthracenyl ligand (Fig. 13) was even more potent in inhibiting TrxR1 and TrxR2 than its gold(I) analogue (Citta et al., 2013). Moreover, the silver(I) complex exhibited greater cytotoxicity in the A2780S/A2780R cell pair than in normal HEK-293 T cells. This complex was also able to overcome cisplatin resistance in the A2780/R cell line. In tumor cell extracts, the silver complex efficiently inhibited TrxR activity, while in normal cell extracts, the complex was practically ineffective. Notably, at a higher concentration, this complex showed more pronounced inhibition of TrxR in A2780R cells. Silver(I) NHC complexes also led to oxidation of the Trx1 and Trx2. In particular, the silver complex was more efficient in oxidizing Trx1 in cancer cells than in normal cells. In addition, the oxidation of mitochondrial Prx3 was also observed, demonstrating the ability of these compounds to reach their mitochondrial target. Moreover, in accordance with the



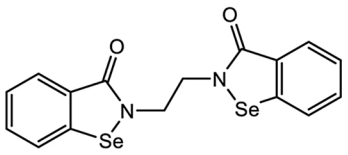
Au(I) complexes with N-heterocyclic carbene (NHC) 1,3-substituted imidazole-2-ylidene and benzimidazole-2-ylidene ligands (Schuh et al., 2012)



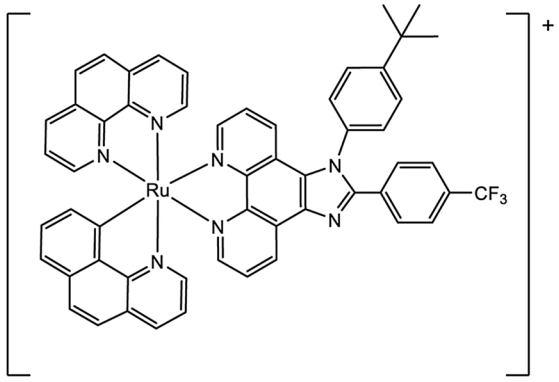
Ag(I) NHC complex (Citta et al., 2013)



Silver-bis(NHC) complex (Ag8) (Allison et al., 2017)



Ethaselen (Ye et al., 2017)



Heteroleptic Ru(II) complex (4) (Zeng et al., 2016)

Fig. 13. Metal drugs inhibiting the Trx system (II).

above-mentioned trends of TrxR1 inhibition and Trxs oxidation, the silver complex caused a more pronounced oxidation of Prx3 in cancer cell lines compared to normal cells. This complex also induced ROS formation in cancer cells, while its effect on ROS production in normal cells was negligible.

Another silver-bis(NHC) complex also showed TrxR inhibition and overcame cisplatin resistance in cancer cells (Fig. 13) (Allison et al., 2017). In detail, the silver-bis(NHC) complex (Ag8) was significantly more active against cisplatin-resistant A2780/CP70 cells compared to cisplatin-sensitive A2780 cells. Ag8 was a potent inhibitor of purified rat TrxR with IC_{50} values in the nanomolar range. Inhibition of TrxR led to induction of apoptosis via the JNK and p38 pathways in A2780 and A2780/CP70 cells. Ag8 induced DNA single- and double-strand breaks in both cell lines. Importantly, more extensive double-strand breaks were observed in A2780/CP70 cells. In contrast to cisplatin, no DNA crosslinking was detected in either cell line. Ag8 proved to be a potent inhibitor of both human topoisomerase I and II in cell-free assays. This silver complex was also a very potent inhibitor of purified human PARP-1 with nanomolar IC_{50} values. Therefore, by targeting multiple pathways, Ag8 is likely to account for its ability to overcome cisplatin resistance in A2780/CP70 cells.

Apart from these examples for gold and silver complexes, the heteroleptic ruthenium(II) organometallic complex with three bidentate ligands (complex 4, Fig. 13) also exhibited the potential to circumvent cisplatin resistance by inhibiting TrxR activity (Zeng et al., 2016). Complex 4 was highly active against cisplatin-resistant NSCLC A549R cells. This complex exhibited 178-fold better activity than cisplatin in A549R cells. 3D multicellular A549R tumor spheroids were also used to confirm the high proliferative and cytotoxic activity of complex 4. Notably, complex 4 was less cytotoxic in a normal human hepatocyte cell line (LO2) compared to cancer cells. A possible explanation for the selectivity towards cancer cells is the lower accumulation of complex 4 in normal cells. This complex also showed a tendency to accumulate in mitochondria of A549R cells. Complex 4 exhibited strong inhibition of TrxR by decreasing its enzymatic activity and protein levels in A549R cells. Inhibition of TrxR led to an increase in intracellular ROS, mitochondrial dysfunction, cell cycle arrest and apoptosis.

Ethaselen (1,2-[bis(1,2-benzisoselenazolone 3(2*H*)-ketone)] ethane or BBSKE, Fig. 13), a symmetrical selenoheterocycle, is the best-studied organoselenium compound regarding anticancer properties. In fact, this compound was tested in a clinical phase I trial (NCT02166242) and the preparation of phase II in clinical trials (gastric, lung and colon cancer) was mentioned but not yet published (Ye et al., 2017). Ethaselen was found to be a promising antitumor agent, both *in vitro* and in mouse models, against various cancers of the lung, cervix, stomach, leukemia, colon, epithelial hepatoma and tongue (Ye et al., 2017). With regard to its mode of action, ethaselen is a strong mixed inhibitor of TrxR1 (at the submicromolar concentrations) by binding to the redox pair Sec498/Cys497 at the C-terminal end of the enzyme. Accordingly, a good correlation between anti-proliferative activity and inhibition of TrxR1 was found It was postulated that the more nucleophilic Sec498 could initiate attack on ethaselen, leading to opening of one of the benzisoselenazol rings, and the formation of a disulfide bond (S–S); then, the resulting intermediate might approach Cys497 that could in turn, attack the second heterocyclic unit, yielding a selenylsulfide bond (Se–S) and provoking the inactivation of the enzyme (Wang et al., 2012). Interestingly, the anticancer activity of cisplatin in certain cancer cells was shown to be enhanced upon co-administration with ethaselen, suggesting a potential to reverse cisplatin chemoresistance (Tan et al., 2010; Ye et al., 2017b). Moreover, there are indications that certain cisplatin-resistant cancer cells might exhibit CS towards the selenium drug (Ye et al., 2017b). In more detail, erythroleukemia K562/CDDP cells were about 4-fold more sensitive to a 72 h ethaselen treatment than their chemosensitive parental counterpart. However, assessment of the mechanisms underlying these effects are still vacant, as the subsequent investigations were solely performed in combination with cisplatin.

3.7. Metal drugs overcoming apoptosis resistance and inducing novel forms of cell death

Ang and Gaiddon developed a family of compounds with the aim to overcome MDR by inducing alternative modes of cell death rather than apoptosis (Chow et al., 2016). Thus, two compounds of the general formula [Ru(η^6-arene)(4-methoxy-N-(2-quinolinylmethylene)aniline] Cl, where the arene is a triisopropylbenzene (RAS-1 T) or a hexamethylbenzene (RAS-1 H; Fig. 14), were synthesized and the structural changes introduced correlated with the modes of action. Both compounds induced non-apoptotic cell death through ER stress pathways. Yet, their modes of action were completely different. While RAS-1 T acted through ROS-mediated ER stress, RAS-1H was ROS-independent. To confirm that these complexes could circumvent apoptosis resistance, the authors used the apoptosis-resistant TC7 cell line (Chantret et al., 1994) as a functional cell model, using the colorectal cancer cell lines HCT116 and HT-29 as non-resistant models. The TC7 cell line is characterized by the loss of p53 along with a higher basal expression of anti-apoptotic Bcl-2 and Bcl-xL, as well as downregulation of pro-apoptotic Bax (Chantret et al., 1994). When compared to the chemotherapeutic drugs oxaliplatin, etoposide, 5-fluorouracil and doxorubicin, both ruthenium compounds (especially RAS-1 T) were the least affected by drug resistance of TC7 cells. Although there is still a need to identify the targets for these compounds, important clues on the design of compounds able to overcome apoptosis resistance were unveiled.

The anticancer therapeutic potential of radioactive $^{186/188}$Re compounds has been already recognized for some compounds in clinical use. Yet, the area of non-radioactive Re complexes as anticancer agents is a relatively new field. Most of the compounds with cytotoxic activity are based on the 'Re$(CO)_3$' core and the remaining coordination positions occupied by heteroaromatic ligands, phosphanes, halogens or η^5-cyclopentadienyl derivatized arenes (Leonidova and Gasser, 2014). From the arena of known cytotoxic Re complexes, there are not yet sufficient studies concerning their potential to overcome MDR. Nevertheless, many Re compounds show an intrinsic ability to overcome cisplatin resistance which seems to be related to the different mechanism of cell death observed for many Re compounds (Knopf et al., 2017; Konkankit et al., 2019; Suntharalingam et al., 2015; Ye et al., 2016). For example, Re(I) and Re(V) complexes bearing phenanthroline-based ligands showed cross-resistance with cisplatin for KBCP20, A2780/CP70, A549CisR and/or H460CisR cells causing cell death by paraptosis or necroptosis (Fig. 14) (Knopf et al., 2017; Konkankit et al., 2019; Suntharalingam et al., 2015; Ye et al., 2016). Also, a rhenium(I) tricarbonyl complex bearing a diimine ligand (Fig. 14) was found to be equally active in both sensitive and cisplatin-resistant cancer cells (A2780/CP70), hence inducing cell death by necrosis (Konkankit et al., 2019).

Since platinum complexes that induce cell necrosis are rare, a heterobinuclear iridium(III)-platinum(II) $[(ppy)_2Ir(dpp)PtCl_2]^+$ (Ir-Pt) was constructed as a novel anticancer agent that is able to overcome cisplatin resistance by inducing necrosis (Fig. 14) (Ouyang et al., 2018). The iridium(III) moiety was introduced to increase the cellular accumulation of platinum and specifically target mitochondria. Ir-Pt complex was effective against cisplatin-resistant NSCLC A549R cells. This complex induced loss of mitochondrial membrane potential, a hallmark of mitochondrial dysfunction, resulting in altered metabolism, mitochondrial DNA damage, and mitochondrial superoxide accumulation. Ir-Pt overcame cisplatin resistance in A549R cells via increased accumulation and decreased efflux compared to platinum alone, mitochondrial targeting which resulted in avoiding the nuclear DNA repair mechanism and inducing necrosis. Interestingly, a novel series of cyclometalated iridium(III) complexes with benzothiazole substituted ligands (Fig. 14) circumvented cisplatin-resistance in A549R cells by inducing oncosis, an alternative mode of cell death (Guan et al., 2018). The complexes entered the cells via endocytosis and were localized in mitochondria.

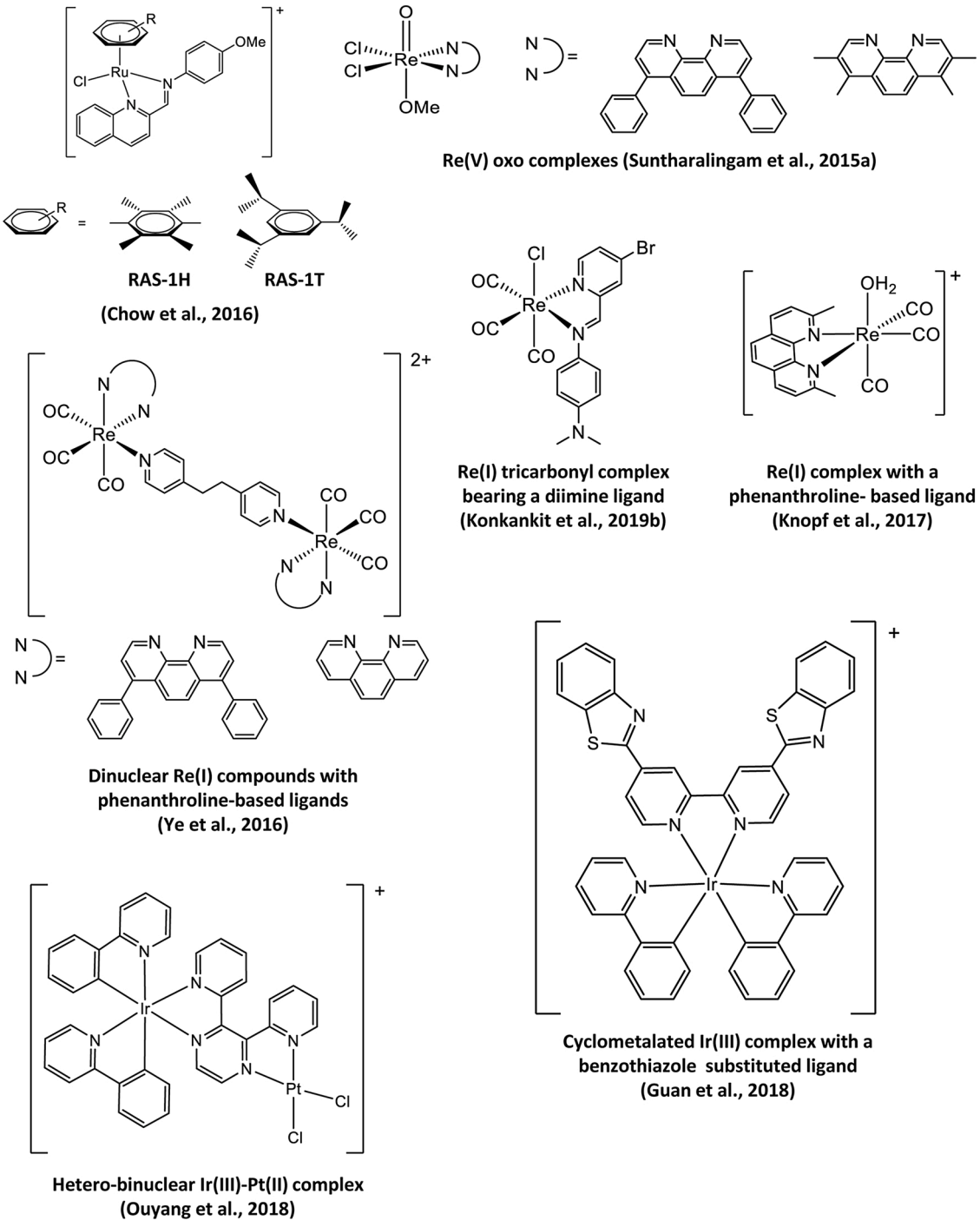


Fig. 14. Metal drugs overcoming apoptosis resistance and inducing new forms of cell death.

This resulted in increased ROS production and loss of mitochondrial membrane potential, followed by ATP depletion and an increased ratio of bcl-2/bax. Activation of protease calpain 1, a marker of oncotic cell death, resulted in cytoskeleton collapse. Increased expression of porimin, another marker of oncosis, led to increased membrane permeability, directly caused the change of the shape and volume of the cell resulting in swelling and rounding of the cells, as well as blebbing of the plasma membrane.

Besides the induction of oncosis, there are several reports on metal drugs inducing paraptotic cell death (cyclometalated iridium(III) complexes (He et al., 2018), phosphorescent rhenium(I) complexes (Ye et al., 2016), (salen)ruthenium(III) complex (Li et al., 2017a), phosphane copper(I) complexes (Marzano et al., 2006), thioxotriazole copper(II) complex A0 (Tardito et al., 2009), copper and zinc 2-(pyridin-2-yl)imidazo[1,2-a]pyridine complexes (Dam et al., 2017), as well as an inokitiol copper complex (Chen et al., 2017)). However, in most cases, the proof that they can overcome apoptosis resistance is still missing.

3.8. *Overcoming p53-mediated resistance*

Inactivating p53 mutations are frequently associated with decreased sensitivity to clinically used platinum drugs (Brabec and Kasparkova, 2005; Lowe et al., 2004; Manic et al., 2003; Martinez-Balibrea et al., 2015; Stewart, 2007). However, in contrast to the prevalent assumption

that mutated p53 confers resistance to all platinum drugs, the activity of neither picoplatin (Pestell et al., 1998; Sharp et al., 2002), satraplatin (Fokkema et al., 2002; Martelli et al., 2007), nor LA-12 (Horvath et al., 2006) or [Pt(BDI^{QQ})]Cl (Suntharalingam et al., 2014) was affected by cellular p53 status. BBR-3464 treatment too did not induce p53, and p53-mutated xenografts were even hypersensitive to this drug (Gatti et al., 2002; Pratesi et al., 1999). In contrast, p53/KO cells displayed resistance to BBR-3464-induced apoptosis (Harris et al., 2006). These findings are in accordance with data indicating that BBR-3464 and cisplatin differentially influence the binding of p53 to modified DNA (Kasparkova et al., 2004). In the case of the new oxaliplatin derivatives KP1537 and KP1691, a reduced impact of p53 loss on the anticancer activity against human colon cancer cells was described (Jungwirth et al., 2012). Regarding ruthenium compounds, the impact of the p53 status seems largely dependent on the ligand sphere, oxidation state and structure of the ruthenium complex. Thus, for example, downregulation of p53 has been shown to significantly reduce the apoptosis induction of several ruthenium arene compounds (Gaiddon et al., 2005; Hayward et al., 2005; Smalley et al., 2007). In contrast, the p53 status seems to have only a minor impact on ruthenium(II) and osmium(II) iodide complexes of (p-cymene)(azo/imino-pyridine) (Romero-Canelon et al., 2013). Moreover, KP1019 activity was not affected by the loss of p53 (Heffeter et al., 2005).

The abovementioned family of cobalt(II) and cobalt(III) tris(bipyridine) compounds tested by (Law et al., 2017) are also of interest with respect to p53. Here, several drugs, including [Co(4,4'-dimethyl-2,2'-bipyridine)$_3$]$^{3+}$ (compare Fig. 8), had significantly higher anticancer activity in HCT116 cells with p53/KO status than in the wild type counterpart. Finally, the anticancer activities of gallium maltolate (Chitambar et al., 2007), the lanthanum compound KP772 (Heffeter et al., 2006), and titanocene dichloride (Christodoulou et al., 1998) were not significantly influenced by the cellular p53 status suggesting a potential to overcome drug resistance associated with inactivating p53 mutations.

3.9. Overcoming drug resistance based on enhanced DNA damage repair

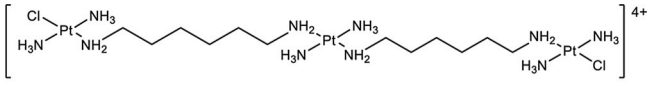
In the 1970's, it was already discovered that certain 1,2-diaminocyclohexane (DACH)-containing platinum drugs were more active in cells with acquired platinum resistance (Jakupec et al., 2003). Subsequently, it was recognized that the bulky DACH ligand has substantial consequences on the processing of the formed DNA lesions resulting enhanced activity in MMR-deficient cancer cells. Thus, the approval of oxaliplatin against colon cancer can be considered a successful attempt to target (platinum) drug resistance based on reduced tolerance of DNA adducts (Jakupec et al., 2003). However, there are also indications that distinct differences in the uptake between cisplatin and oxaliplatin exist (as the latter seems to be primarily accumulated via organic anion transporter (Buß et al., 2018)), which could contribute to the variable activity profile of oxaliplatin.

One drug that has been clinically developed specifically to treat drug-resistant cancer is BBR3464 (Fig. 15). This avenue was stimulated by the discovery that the multinuclear platinum complex exhibits a unique DNA-binding pattern distinct from other platinum drugs such as cisplatin. Consequently, BBR3464 was active in several cell models with acquired (platinum) drug resistance based on enhanced DNA damage tolerance (MMR loss) and repair (enhanced ERCC1/2 levels) such as the human ovarian carcinomas OAW42MER (Colella et al., 2001; Orlandi et al., 2001). BBR3464 was tested in several clinical phase I and II studies, e.g. in sensitive or refractory SCLC (NCT00014547), pancreatic (NCT00024362) and gastric/ gastro-esophageal adenocarcinoma (Hensing et al., 2006; Jodrell et al., 2004). However, the lack of activity based on a relatively small therapeutic window finally resulted in the discontinuation of its development. With the aim to design an improved version of the compound, a few years ago several "picoplatin derivatives" of BBR3464 were synthesized and biologically evaluated. Unfortunately, none of them could circumvent the resistance of A2780/cp70 cells (Brown et al., 2012).

3.10. Overcoming resistance based on altered recognition by immune cells

Based on the somewhat limited knowledge on the role of immune cells in the resistance against chemotherapy in general and metallodrugs in particular, it is not surprising that there are only very few attempts to specifically address this issue for new therapeutic approaches. One of them is the design of novel platinum drugs which are releasing immunomodulatory ligands. The rationale is that cancer cells are known to actively inhibit immune recognition through diverse mechanisms, including loss of the antigen-presenting machinery or expression of inhibitory molecules and enzymes that induce T cell suppression (Thommen and Schumacher, 2018). One such enzyme is indoleamine 2,3-dioxygenase (IDO) which catabolizes the amino acid tryptophan (Trp) to kynurenine (Kyn), a process which activates the aryl hydrocarbon receptor. This, in turn, inhibits T-cell activation and supports regulatory T-cell proliferation (Yentz and Smith, 2018). IDO expression in tumors has been frequently observed, and the interest in this enzyme is also reflected by the clinical development of several IDO inhibitors such as 1-methyltryptophan (1-MT) (Coletti et al., 2017). Concerning platinum drugs, there is strong evidence that the combination with IDO inhibition (e.g. 1-MT) is highly synergistic (Lu et al., 2017; Muller et al., 2005; Wang et al., 2018). There are already some reports on nano-formulations combining platinum-based chemotherapy with IDO inhibitors (Awuah et al., 2015; Lu et al., 2017; Wang et al., 2018). However, two platinum-based prodrug approaches have also been reported (Awuah et al., 2015 and Poetsch et al 2021 in press. Yet, these drugs have not been tested in drug-resistant tumors.

The only compound which has been investigated for its immunoregulatory activity in drug-resistant cancer is CuNG (compare Fig. 7), which has been identified as potent immune modulator (Chakraborty et al., 2014). In more detail, the drug resulted in downregulation of both immune-suppressive Tregs (Mookerjee et al., 2006a) and MDSCs (Chakraborty et al., 2014) in ascites of doxorubicin-resistant EAC/-dox-bearing mice. This effect was tumor-specific as no suppression was detected in the bone marrow or spleen of the treated animals. Subsequent analysis indicated that the downregulation of MDSC is not based on changed differentiation or inhibition of MDSC expansion but on T cell-induced apoptosis via the Fas/FasL axis (Chakraborty et al., 2014). Moreover, CuNG treatment increased the interferon γ-producing T cell population in the ascites of EAC/dox-bearing mice and splenic mononuclear cells from these animals induced apoptotic cell death in resistant cancer cells in cell culture in an interferon γ-dependent manner (Mookerjee et al., 2006a). In a follow-up study, the authors could show that these effects were based on CuNG-induced reprograming of tumor-associated macrophages (Chatterjee et al., 2009). Thus, CuNG treatment stimulated interleukin 12 release from macrophages (together with downregulation of interleukin 10 and tumor growth factor β), which in turn induced a shift from immunosuppressive Tregs towards an active Th1 cell population. Similar effects were also observed in peripheral blood monocytes from patients with drug-resistant metastatic cancer. The CuNG-induced effects on macrophages were based on ROS-induced stimulation of the P38 and ERK signaling pathway (Chakraborty et al., 2012). Although there is no doubt that CuNG has a strong immunological component in its activity, the proof that this is



BBR3464
(Colella et al., 2001; Orlandi et al., 2001)

Fig. 15. Metal drug overcoming resistance to enhanced DNA-damage repair.

especially true for drug-resistant cancer types is missing, as all studies have been performed solely in the resistant subclones without comparison to, e.g. chemosensitive EAC cells.

4. Conclusions and future perspectives

Drug resistance is one of the dominant obstacles for treatment success, especially at the late stage of the disease, resulting in death of numerous cancer patients worldwide. New metal complexes are continuously synthesized with the aim to improve anticancer therapy and surmount drug resistance. However, despite the fact that metal complexes can cover very different chemical properties and display a variety of mechanisms of actions, unlike organic compounds, the investigations of their activity against drug-resistant cancer cells are rare and often at the very early stage of research. Consequently, the majority of metal complexes are only tested based on a "trial and error" approach. Thus, in most cases the data are not connected with the mechanisms underlying drug resistance of the tested cancer cell models. Moreover, the rational design of compounds with the aim to overcome/circumvent a specific form of drug resistance is rare resulting only in a small number of compounds which have been (pre)clinically developed. Finally, even in such cases, the respective cellular alteration(s) are usually not used as a biomarker in clinical trials. This seems surprising, considering that in case of (oncogene)-targeted therapy - like for example small-molecule tyrosine kinase inhibitors of the epithermal growth factor receptor (EGFR), it is state-of-the-art that the drugs are applied only to a specific patient subset that is positive for this biomarker (e.g. activating EGFR mutations) (Juchum et al., 2015; Xu et al., 2017). In contrast, in the case of many cytotoxic drugs including platinum therapeutics, no such clear-cut biomarkers are available. The rational design of (metal) drugs to circumvent or break specific forms of drug resistance might offer the chance to develop new drugs for improved therapy in a personalized manner. However, this will require a more tailored and rational drug evaluation process.

The phenomenon of CS shows that drug resistance can even be exploited for anticancer therapy. This observation, that the acquisition of drug resistance features (such as overexpression of ABC pumps) renders cancer cells more collaterally sensitive to other drugs, has been addressed in diverse studies and inspired the development of multiple new compounds. Noteworthy, the compound classes associated with CS-inducing potential are very different and the mode of action of the observed CS of drug-resistant cancer cells are heavily discussed. This already indicates that the mechanisms underlying CS might be multifacetted just as the mechanisms underlying drug resistance *per se*. As already stated above, in most cases, the term CS is used for targeting ABC transporter (mainly ABCB1)-overexpressing cancer cells. However, it can be expected that resistance to platinum drugs too will result in sensitivity to certain drugs. This needs to be addressed in future studies. Again, the elucidation of the mode of action underlying the specific forms of CS needs to result in a rational and tailored form of drug development resulting in personalized and biomarker-driven forms of anticancer therapy.

In this review, we focused mainly on metal complexes, for which at least some promising details about their mechanism of action are reported. The reviewed data represent the first collection of metal complexes which exhibit an ability to surmount drug resistance. In most cases, this is only based on cell culture data and an *in vivo* confirmation is still missing. By this approach, we want to draw the attention to open research questions in the field. Future investigations are needed to provide more molecular insights into the mechanisms of action of the most potent compounds considering specific forms of drug resistance. This will provide a solid basis for the design of more potent derivatives. As metal drugs are very versatile compounds, they would offer the possibility to develop drugs with enhanced anticancer activity especially for late stage patients which have already developed highly drug-resistant forms of the disease. However, to this end, the individual modalities of drug resistance need to be carefully considered allowing the selection of the most appropriate patient cohort for successful clinical studies. This requires both a better understanding of the mechanisms responsible for drug resistance in the patient as well as a rational design and evaluation of new drugs based on the cumulated biological understanding.

Acknowledgements

This work was financed by the Portuguese Foundation for Science and Technology (Fundação para a Ciência e Tecnologia, FCT) within the scope of Projects UIDB/00100/2020 (Centro de Química Estrutural) and PTDC/QUI-QIN/28662/2017. AV acknowledges the CEECIND 2017 Initiative (CEECIND/01974/2017). IP was financed by the FWF-funded research group FG3 to PH. We also thank Slovenian Research Agency (ARRS) for financial support (P1-0175). NF gratefully acknowledges financial support from the Ministry of Education, Science and Technological Development of Republic of Serbia, Contract number: 451-03-9/2021-14/200116. Ó.L. thanks Spanish MICINN (CTQ2016-78703-P). This article is based upon work from COST Action 17104 STRATAGEM supported by COST (European Cooperation in Science and Technology; www.cost.eu). Many thanks to Christian Kowol and Sonja Hager for their input and helpful scientific discussions as well as Ian Teasdale for proof reading.

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