Evolution of platinum-based drugs: From cisplatin to oxaliplatin.

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Evolución de los fármacos a base de platino: del cisplatino al oxaliplatino

Evolució dels fàrmacs basats en platí: del cisplatí a l'oxaliplatí

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ABSTRACT

Platinum-based drugs, such as cisplatin, carboplatin, and oxaliplatin, have revolutionized chemotherapy and are widely used worldwide in the treatment of various types of cancer. These organometallic compounds have demonstrated high antitumor efficacy, which has driven their development and optimization over the decades. This review provides a historical overview of the discovery of platinum, the evolution of its organometallic compounds with pharmacological applications, and a current perspective on the use of nanomaterials as controlled drug delivery systems aimed at improving efficacy while reducing the adverse effects of these agents.

Keywords: platinum-based drugs, cisplatin, nanomaterials, drug delivery.

RESUMEN

Los fármacos a base de platino, como el cisplatino, el carboplatino y el oxaliplatino, han revolucionado la quimioterapia y se utilizan ampliamente en todo el mundo para el tratamiento de diversos tipos de cáncer. Estos compuestos organometálicos han demostrado una alta eficacia antitumoral, lo que ha impulsado su desarrollo y optimización a lo largo de las décadas. Esta revisión ofrece una visión histórica del descubrimiento del platino, la evolución de sus compuestos organometálicos con aplicaciones farmacológicas y una perspectiva actual sobre el uso de nanomateriales como sistemas de administración controlada de fármacos, con el objetivo de mejorar la eficacia y, al mismo tiempo, reducir los efectos adversos de estos agentes.

Palabra clave*:* Fármacos a base de platino, cisplatino, nanomateriales, administración de fármacos.

RESUM

Els fàrmacs basats en platí, com el cisplatí, el carboplatí i l'oxaliplatí, han revolucionat la quimioteràpia i s'utilitzen àmpliament a tot el món en el tractament de diversos tipus de càncer. Aquests compostos organometàl·lics han demostrat una alta eficàcia antitumoral, fet que ha impulsat el seu desenvolupament i optimització al llarg de les dècades. Aquesta revisió ofereix una visió històrica del descobriment del platí, l'evolució dels seus compostos organometàl·lics amb aplicacions farmacològiques i una perspectiva actual sobre l'ús de nanomaterials com a sistemes de lliurament de fàrmacs controlats, amb l'objectiu de millorar l'eficàcia alhora que es redueixen els efectes adversos d'aquests agents.

Paraules clau*: F*àrmacs basats en platí, cisplatí, nanomaterials, alliberament de fàrmacs.

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DISCOVERY OF PLATINUM

Platinum is a noble metal with atomic number 78 that plays a fundamental role in modern society due to its exceptional physicochemical properties, such as high corrosion resistance and excellent electrical conductivity [1]. It is widely applied in catalytic converters for reducing automotive emissions, in electrical contacts, and as electrodes in laboratory equipment, including reference electrodes in electrochemistry and gas sensors [2–4].

Additionally, platinum is a key component in dental equipment, in the jewelry industry due to its durability and aesthetic appeal, and in medical devices such as pacemakers and implants [5–7]. It is also essential in fuel cell production for clean energy generation and in the petrochemical industry as a catalyst for various processes [8,9].

The earliest records of platinum use date back to ancient Egypt, around 700 BCE. Archaeologists have found traces of platinum in the gold used for burial artifacts from that period. For example, a small box discovered in the tomb of Princess Shepenupet II was decorated with hieroglyphs made of gold and platinum [10]. However, it remains uncertain how much the Egyptians knew about the metal, as it is likely that they did not recognize platinum as distinct from the gold they worked with.

Pre-Columbian peoples of the La Tolita culture, which flourished between 300 BCE and 500 CE in the Esmeraldas region of present-day Ecuador, were renowned for their advanced goldsmithing techniques [11,12]. These artisans used gold-platinum alloys to craft ceremonial and ornamental objects such as masks, earrings, and figurines.

One of the most emblematic artifacts attributed to the La Tolita culture is the well-known *Tolita Sun of Gold* (Figure 1), currently preserved in the National Museum of Ecuador and adopted as the institutional symbol of the Central Bank of Ecuador. Created between 300 BCE and 100 CE, the piece depicts a stylized human face surrounded by solar motifs and stands out for its elaborate craftsmanship and use of a complex alloy of gold with small amounts of platinum, silver, and copper.

Figure 1. *Golden Sun, developed by the Tolita culture, Ecuador [13].*

Since platinum has a very high melting point (around 1,769 °C), La Tolita artisans developed innovative methods to work with it without melting. One of these was sintering, which involved mixing precious metal powders such as gold and platinum and heating them to temperatures below their melting points. This allowed the particles to fuse into a cohesive solid mass that could then be hammered and shaped. Nevertheless, the precise dating and contextualization of some of these objects remains difficult, as many examples have been recovered outside their original archaeological contexts, often through pre-Columbian trade networks.

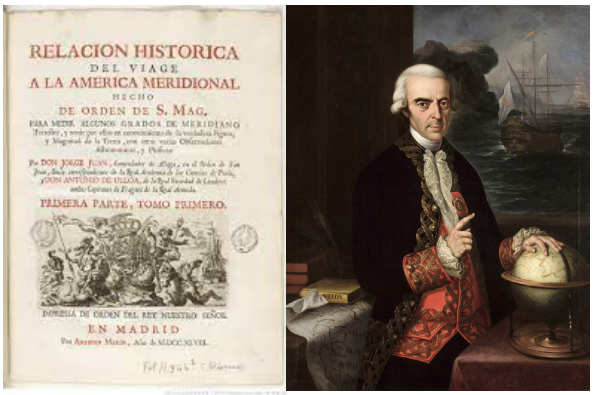

Figure 2. *Cover of "Historical Account of the Voyage to South America" next to the representation of Antonio de Ulloa, 1748.*

The first official written record of platinum appears in the work *Relación histórica del viaje a la América Meridional*, published in 1748 by the Spanish scientist Antonio de Ulloa. The front page of this work, along with a portrait of its author, is shown in Figure 2. In this account, Ulloa describes the collection of the first platinum samples from the gold washings in the Chocó region, in the Viceroyalty of New Granada (modern-day Colombia, Figure 3). Due to its silvery appearance, the metal was initially mistaken for silver. However, miners soon noted that platinum was more difficult to melt with the techniques available at the time, which led to its differentiation and subsequent scientific study [14,15].

Figure 3. *Mapping of the Choco region in the former Viceroyalty of New Granada.*

Later, platinum samples from the Chocó gold washings were taken to Europe, particularly England, where chemists such as William Watson, William Brownrigg, and William Lewis began detailed studies around 1750. They investigated the metal's physicochemical properties, including its corrosion resistance and high density [16,17].

In 1758, French chemists Pierre-Joseph Macquer and Antoine Baumé attempted to melt platinum using a large concave mirror to concentrate heat at a single point. Although they failed to melt it completely due to technological limitations of the time, their experiments marked an important advance in the study of the metal [18,19].

Subsequently, in 1786, the French chemist Pierre-François Chabaneau, under the patronage of the Spanish Crown, succeeded in purifying platinum to obtain a malleable form. Chabaneau removed impurities such as gold, mercury, lead, copper, and iron from crude platinum ore, enabling him to produce the first ingot of pure and malleable platinum [18,19].

Platinum-Derived Compounds

Continuing with the historical perspective, in the 19th century the foundations were laid for later developments in coordination chemistry, medicine, and technology. In 1844, the Italian chemist Michele Peyrone synthesized for the first time the compound cis-diamminedichloroplatinum (II), known as cisplatin or "Peyrone's chloride" [20]. Although at the time it was merely a chemical curiosity, more than a century later, in the 1960s, its potent antitumor activity was discovered, revolutionizing cancer treatment and making it one of the most widely used chemotherapeutic agents in oncology [21].

At the end of the 19th century, the Swiss chemist Alfred Werner developed the theory of coordination chemistry, proposing that transition metals such as platinum form complexes with ligands through specific bonds. In 1893, Werner proposed precise geometric structures for complexes such as $[Pt(NH_3)_4Cl_2]$, laying the foundation of modern inorganic chemistry and earning the Nobel Prize in Chemistry in 1913 [22].

In parallel, during the 19th century, knowledge of the catalytic properties of platinum was consolidated. These properties had been recognized since the beginning of the century, particularly its ability to catalyze the ignition of hydrogen. Such observations were key to its subsequent application in industrial chemical processes, such as hydrocarbon reforming and nitric acid synthesis [14,23].

Furthermore, the study of platinum ores led to the discovery of new elements of the platinum group. Between 1802 and 1804, William Hyde Wollaston succeeded in isolating palladium and rhodium, elements present in small proportions in platinum ores, which broadened knowledge about this group of noble metals and their usefulness in jewelry, fine chemistry, and catalysis [24].

Finally, in 1868, the French chemist Paul Schützenberger synthesized one of the first organometallic platinum complexes, dicarbonyldi-μ-chlorodichlorodiplatinum, thereby paving the way for the systematic study of the organometallic chemistry of transition metals. This field would expand widely in the 20th century, with important implications for homogeneous catalysis and the design of new drugs [25].

Development of Platinum-Based Drugs

In the mid-20th century, interest in metal compounds in molecular biology led to a series of innovative experiments that would forever change the history of chemotherapy. In 1965, biophysicist Barnett Rosenberg, along with Loretta Van Camp and Thomas Krigas, conducted studies on the effects of electric fields on the cell division of *Escherichia coli*. For this purpose, they used platinum electrodes immersed in the culture medium. Unexpectedly, they observed that the bacteria did not divide normally but instead adopted a filamentous and elongated morphology (Figure 4), obtained by electron microscopy: on the left, *E. coli* treated with the platinum complex; on the right, untreated cells maintaining their typical bacillary shape [26,27].

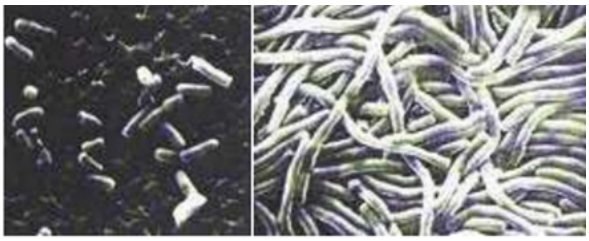

Figure 4. *Effect of cisplatin on the morphology of Escherichia coli bacteria* [28].

These observations were initially attributed to the electrical effect, but subsequent analyses demonstrated that the true cause was a platinum complex released by the electrodes: cis-diamminodichloroplatinum (II), or cisplatin. Intrigued by its inhibitory effect on bacterial mitosis, the researchers tested the compound in mammalian cell lines and later in animal models with induced tumors.

One of the most renowned and decisive experiments for the clinical advancement of cisplatin was performed in mice bearing sarcoma 180. A clear comparison between untreated animals (top row) and those treated with a single intraperitoneal injection of cisplatin at 8 mg/kg (bottom row) (Figure 5). The control mice exhibited progressive tumor growth and died around day 21, while the treated mice showed tumor regression and survived at least until day 36, with a significant reduction in tumor volume [29,30].

This pioneering finding was published in 1969 and led to a series of human clinical trials that culminated in the FDA's approval of cisplatin in 1978. Its impact was immediate: it transformed the prognosis of previously lethal cancers such as metastatic testicular cancer, raising cure rates to over 90% in some cases. Furthermore, its mechanism of action, based on the formation of cross-links with DNA that block cellular replication, opened a new paradigm in the development of metal-based alkylating agents.

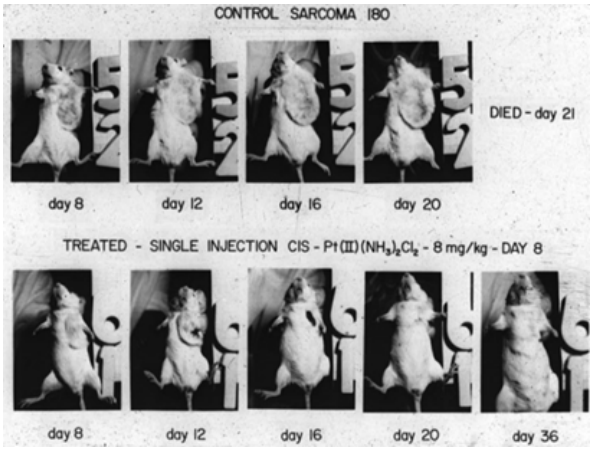

Figure 5. *In vivo assay in mice with sarcoma treated with cisplatin* [31].

The clinical results of cisplatin were not only promising in animal models, but its impact on public health was clearly reflected in cancer epidemiology. One of the most compelling pieces of evidence for the therapeutic value of this compound can be seen in the evolution of testicular cancer mortality from the 1970s to the present day.

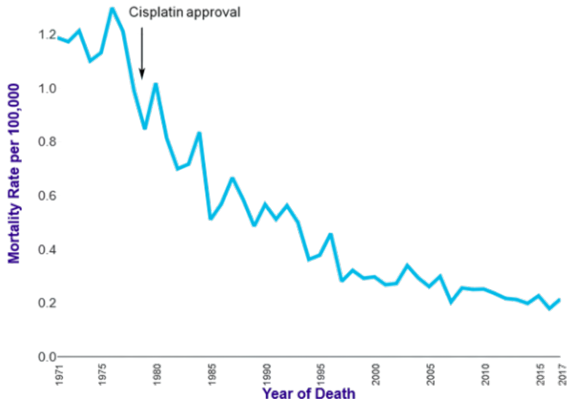

Figure 6. *Decrease in testicular cancer mortality after cisplatin approval* [32].

Figure 6 shows a sustained and significant decline in the mortality rate per 100,000 inhabitants starting in 1978, the year when the clinical use of cisplatin was officially approved. Before this date, metastatic testicular cancer was a disease with a poor prognosis, with cure rates below 10%. However, following the introduction of cisplatin-based therapeutic regimens (such as BEP: bleomycin, etoposide, and cisplatin), mortality began to drop abruptly, stabilizing at minimal levels over the following decades [33].

This effect not only illustrates the success of a chemical compound but also represents one of the greatest achievements of modern chemotherapy: transforming a lethal neoplasm into a curable disease in most cases. Today, more than 95% of patients with germ cell testicular cancer achieve complete remission, and many of them can live normal lives with preserved reproductive function [34].

However, the clinical use of cisplatin also presented significant limitations, such as nephrotoxicity, neurotoxicity, and acquired resistance. This motivated the design of new analogues with improved therapeutic profiles. Figure 7 presents the timeline of approval and/or development of platinum-based drugs along with their chemical structures. One of the first derivatives was carboplatin, approved in 1989, which retains the central structure of cisplatin but incorporates a bidentate cyclobutane dicarboxylic acid ring as a ligand. This structural change significantly reduced renal toxicity and enabled more tolerable treatments, especially in patients with impaired renal function [35].

Subsequently, oxaliplatin, a platinum (II) complex with a cyclic diamine ligand, was developed and approved in 1996 in Europe and in 2002 by the FDA. Its main indication is the treatment of metastatic colorectal cancer, in combination with other agents such as 5-fluorouracil and leucovorin [36]. Unlike cisplatin and carboplatin, oxaliplatin induces acute and chronic neurotoxicity but exhibits a distinct antitumor activity, effective even in cell lines resistant to cisplatin [37].

From these first generations, other compounds were developed, many of which have not been globally approved but have shown promising activity in clinical or preclinical studies. Nedaplatin, developed in Japan in 1983 by Shionogi Pharmaceutical Company, is a water-soluble analogue of cisplatin with lower gastrointestinal and hematological toxicity, used mainly in head and neck and gynecological cancers. Its approval in Japan was granted in 1995, and it has since been applied primarily in the treatment of head and neck neoplasms as well as gynecological cancers [38]

Lobaplatin, initially developed by ASTA Medica in Germany and later marketed by Zentaris AG in collaboration with Chinese companies, was approved in China in 2005 by the regulatory authority (NMPA). It is currently used in the treatment of solid tumors and leukemias and is characterized by lower nephrotoxicity, although with notable myelosuppression [39].

Heptaplatin, developed in South Korea, has a structure that improves its water solubility and has demonstrated efficacy against gastric tumors resistant to cisplatin. Although it has shown promising results in these studies (*in vitro*, in resistant cell lines, and in clinical trials), it has only been approved for clinical use in South Korea, without achieving international approval [40].

In contrast, satraplatin was one of the first platinum (IV) compounds designed for oral administration. Although it showed antitumor activity in preclinical models and some efficacy in phase II clinical trials, particularly in hormone-refractory prostate cancer in combination with prednisone, the FDA did not approve it after the application was withdrawn in 2007 following a negative advisory committee recommendation [41].

Another interesting derivative is picoplatin (also known as AMD473 or ZD0473), specifically designed to overcome resistance to other platinum compounds. Its structure includes a 2-methylpyridine ligand that provides steric hindrance, thus preventing inactivation

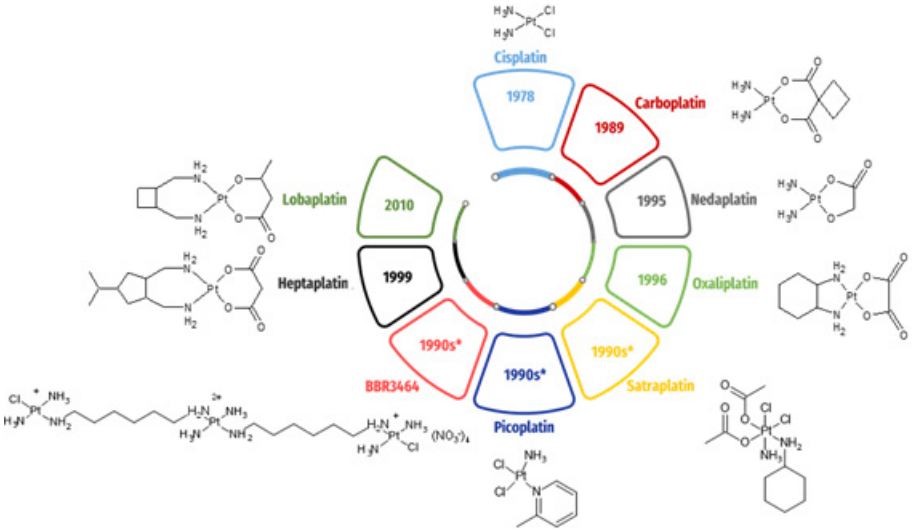

Figure 7. *Chronology and approval of platinum-based drugs.*

by glutathione, one of the cellular mechanisms that neutralize cisplatin. In preclinical studies, picoplatin maintained its antitumor activity even in cisplatin- and carboplatin-resistant cell lines, with more efficient intracellular accumulation and reduced susceptibility to high glutathione levels [42]. However, despite promising results, its clinical development is currently halted, as trials did not show significant improvements in overall survival compared with standard treatments [43]

Finally, BBR3464 represents a completely different approach. It is a polynuclear platinum (II) complex with three metal centers linked by polyamine ligands. This design allows it to interact with DNA in a cross-linking fashion, forming more extensive adducts than mononuclear compounds. Although it generated high expectations due to its novel mechanism of action, it was discontinued after phase II clinical trials because of its toxicity and limited superiority over conventional therapies [44].

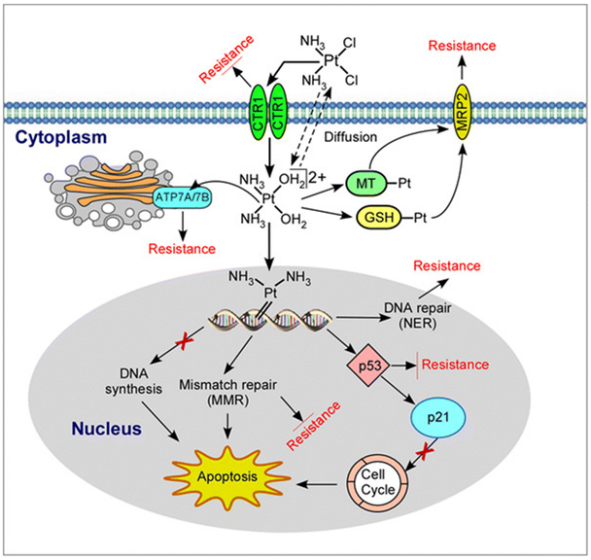

Figure 8. *Molecular mechanism of action of cisplatin in tumor cells [47].*

How Does Cisplatin Work?

Cisplatin acts through a complex mechanism that begins with its entry into the cell (Figure 8). This process can occur via passive diffusion across the plasma membrane, although more recent studies have shown that copper transporters (CTR1) play a fundamental role in its intracellular accumulation. At the same time, resistance mechanisms exist that reduce its efficacy, such as the active efflux of the drug through transporter proteins of the MRP2 family or its inactivation through binding to molecules such as glutathione (GSH) and metallothioneins [45,46]

Once inside the cytoplasm, cisplatin undergoes an essential chemical activation for its action. This process consists of hydrolysis, in which chloride ions are replaced by water molecules, forming positively charged aqueous complexes. These reactive species have a high affinity for nucleophilic groups, particularly nitrogen atoms present in purine bases of DNA [48]

The primary molecular target of cisplatin is nuclear DNA (Figure 9). Once activated, the drug covalently binds to guanine residues and, to a lesser extent, adenine residues, generating adducts that distort the double helix. Approximately 90–95% of these bonds correspond to intrastrand cross-links, that is, between adjacent bases on the same DNA strand, while a small percentage (about 1%) correspond to interstrand cross-links. These bonds alter DNA geometry, interfere with replication and transcription, and constitute the main trigger of its antitumor action [49]

The presence of these adducts activates various cellular DNA damage response pathways. Among them are nucleotide excision repair (NER) and mismatch repair (MMR) systems, which attempt to correct the structural distortion. However, when repair fails, signaling pathways mediated by proteins such as p53 are activated, inducing cell cycle arrest through p21 activation, or directly triggering apoptosis as a defense mechanism against irreparable damage [46,50]

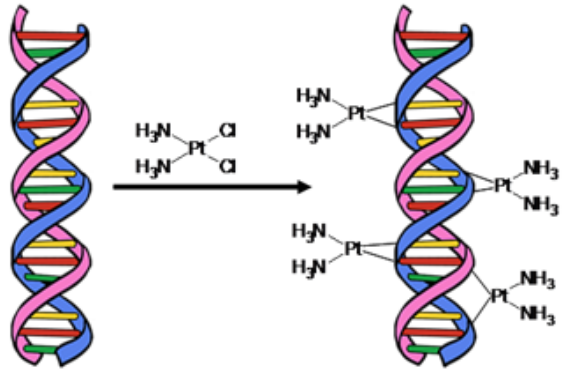

Figure 9. *Types of cisplatin binding to DNA: intra-strand and inter-strand.*

The same mechanism that confers therapeutic efficacy is linked to its clinical toxicity. DNA adducts are not exclusive to tumor cells, and tissues with high proliferative rates, such as renal and gastrointestinal epithelium and the hematopoietic system, are also affected. This explains the nephrotoxicity, neurotoxicity, ototoxicity, and myelosuppression that limit cisplatin use. Despite these adverse effects, its ability to induce tumor regression in multiple cancer types makes it one of the most successful drugs in modern oncology [47,48]

How Does Carboplatin Work?

Carboplatin, like cisplatin, exerts its antitumor action through the formation of DNA adducts that block replication and transcription, ultimately triggering apoptosis (Figure 10). However, its intracellular activation mechanism differs in kinetics: while cisplatin undergoes rapid hydrolysis of its chloride ligands, carboplatin contains a cyclobutane dicarboxylic acid (CBDCA) ring as a bidentate ligand, which confers greater stability and a slower release of the Pt^{2+} ion. This characteristic reduces its initial reactivity and explains its lower renal toxicity compared with cisplatin.

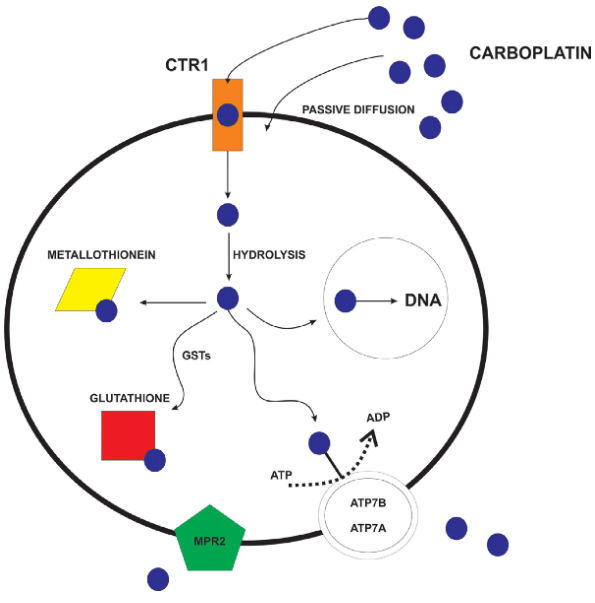

Figure 10. *Cellular mechanism of action of carboplatin* [51].

Carboplatin enters the cell both by passive diffusion and through specific transporters, such as CTR1. Once inside, it can be inactivated by biomolecules such as glutathione or metallothioneins or expelled by ATP-dependent transport pumps (ATP7A, ATP7B, MRP2), phenomena that also contribute to cellular resistance mechanisms. Despite these kinetic and toxicity differences, the molecular target is the same: binding to DNA at guanine and adenine positions, predominantly forming intrastrand adducts (GpG and ApG), which distort the double helix and interfere with cellular replication [45,48,52].

Clinically, carboplatin was introduced as a safer alternative for patients with impaired renal function, being widely used in ovarian and lung cancer, although its main adverse effect is myelosuppression [53,54].

How Does Oxaliplatin Work?

Oxaliplatin (L-OHP) presents a mechanism of action like cisplatin and carboplatin in terms of the formation of adducts with DNA, but with particularities that explain its distinctive clinical profile (Figure 11). After entering the cell via transporters such as *SLC31A1* (CTR1), oxaliplatin undergoes activation and generates covalent bonds with guanine residues in DNA, producing intrastrand cross-links that distort the double helix and block replication and transcription. However, unlike cisplatin and carboplatin, oxaliplatin-induced adducts are recognized and repaired with lower efficiency by nucleotide excision repair (NER) and base excision repair (BER) systems, which enhances its efficacy even in cells resistant to other platinum drugs. Moreover, the figure highlights the role of key genes in repair such as *ERCC1*, *ERCC2*, *XPG*, *XPF*, and *XRCC1*, whose polymorphisms may modulate the clinical response to the drug, as well as the participation of *GSTP1* in its conjugation with glutathione, a mechanism that contributes to detoxification and resistance [37,55].

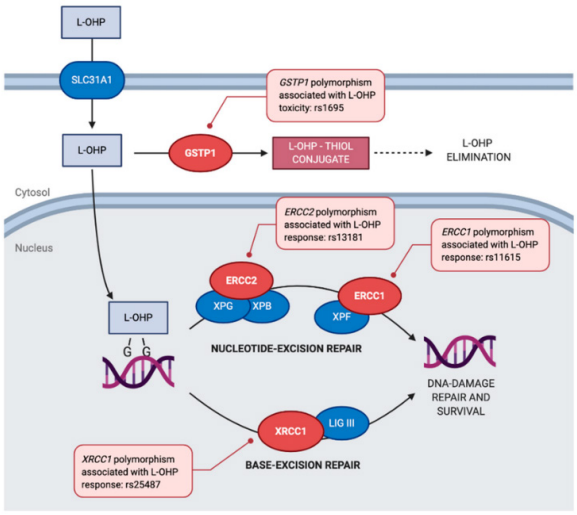

Figure 11. *Cellular mechanism of action of oxaliplatin* [56].

In comparison, cisplatin is rapidly activated in the cytoplasm after hydrolysis and forms DNA adducts that trigger apoptosis mainly through p53 activation,

whereas carboplatin, with slower activation kinetics due to its cyclobutane dicarboxylate group, produces the same type of DNA lesions but with lower renal and gastrointestinal toxicity. Oxaliplatin, on the other hand, generates adducts with a distinct conformation that more strongly affect protein synthesis and trigger apoptosis through complementary mechanisms, although with the drawback of inducing peripheral neurotoxicity, a characteristic adverse effect different from the toxicological profile of cisplatin and carboplatin [45,49,52,55].

Cisplatin, carboplatin, and oxaliplatin share a common anticancer mechanism based on the formation of DNA adducts but they differ markedly in their chemical reactivity. Cisplatin undergoes rapid chloride hydrolysis inside the cell, generating highly reactive aquated species that readily bind DNA. In contrast, carboplatin requires the slow hydrolysis of its bidentate cyclobutane-dicarboxylate ligand, resulting in a delayed release of Pt^{2+} and therefore reduced initial reactivity and lower nephrotoxicity. Oxaliplatin forms adducts through a distinct process involving its bulky diaminocyclohexane (DACH) ligand, producing sterically hindered DNA lesions that are poorly recognized by the nucleotide excision repair (NER) machinery an effect that underlies its activity in cisplatin-resistant tumors [45,57,58].

How do other platinum derivates work?

The development of new cisplatin derivatives sought not only to reduce toxicities but also to diversify the mechanisms of interaction with DNA. Nedaplatin, being more water-soluble, penetrates cells more easily and forms intrastrand bonds with DNA like those of cisplatin, but with lower generation of free radicals, resulting in reduced toxicity [45,59]

In contrast, Satraplatin, a platinum (IV) complex, was designed for oral administration and requires intracellular reduction to active platinum (II) species, which gives it a distinct pharmacokinetic profile and potentially better tolerance [54,60]

Even more innovative was BBR3464, a polynuclear platinum (II) complex capable of cross-linking multiple DNA strands simultaneously, generating more extensive bonds resistant to classical repair mechanisms, although its toxicity limited its clinical development [61,62]

On the other hand, Heptaplatin incorporates ligands that improve its solubility and facilitate the formation of DNA–platinum adducts in gastric tumors resistant to cisplatin, which gave it regional clinical interest in South Korea [63]

Finally, Lobaplatin, approved in China in 2010, combines greater chemical stability with a broad cytotoxic profile, forming both intrastrand and interstrand bonds with DNA, although with lower nephrotoxicity and a higher incidence of myelosuppression as an adverse effect [64,65]

Taken together, these derivatives demonstrate how relatively small structural modifications can significantly alter the way platinum interacts with DNA and the cellular resistance mechanisms.

Platinum-Based Drugs against different types of cancer

Since their clinical approval, platinum compounds have proven to be fundamental tools in the fight against various types of cancer. The main types of cancer treated with the conventional drugs cisplatin, carboplatin, and oxaliplatin, while Table 1 provides additional information such as toxicity (Figure 12). Cisplatin was the first to become established as a therapeutic standard, particularly in the treatment of metastatic testicular cancer, where it transformed a disease with poor prognosis into one curable in most cases [66,67]. In addition, it is used in ovarian, bladder, lung, esophageal, head and neck tumors, as well as in certain lymphomas and myelomas [52,68]. However, prolonged use is associated with significant adverse effects, such as cumulative nephrotoxicity, peripheral neurotoxicity, and irreversible ototoxicity [69,70].

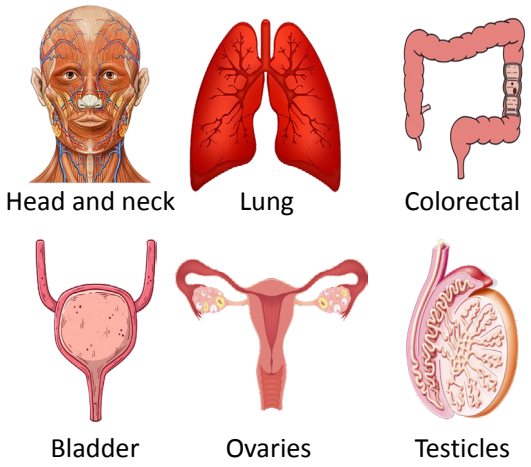

Figure 12. *Main types of cancer treated with platinum-derived drugs.*

Carboplatin, introduced as a less nephrotoxic alternative, became a therapeutic pillar in ovarian cancer, in addition to being applied in bladder, small-cell lung cancer, and head and neck tumors [71,72]. Its safety profile is more favorable, although it has a higher incidence of myelosuppression and peripheral neuropathy [66,73].

For its part, oxaliplatin revolutionized the treatment of metastatic colorectal cancer, becoming an essential component of combined regimens such as FOLFOX (oxaliplatin, 5-fluorouracil, and leucovorin) [74,75]. It has also shown efficacy in tumors of the pancreas, stomach, ovary, and liver. Nevertheless, its characteristic toxicity is peripheral sensory neuropathy, both acute and chronic, which can affect patients' quality of life [76,77].

Table 1. *Types of cancer treated and characteristic side effects.*

Drug	Types of cancer treated	Characteristic side effects	References
Cisplatin	Testicular, ovarian, bladder, lung, esophagus, head and neck, lymphomas, myelomas	Cumulative nephrotoxicity, peripheral neurotoxicity, irreversible ototoxicity, hearing loss, nausea, vomiting, alopecia	[52,66–70]

Drug	Types of cancer treated	Characteristic side effects	References
Carboplatin	Ovarian, bladder, lung (small-cell), head and neck	Myelosuppression, nausea and vomiting, fatigue, peripheral neuropathy, renal problems, alopecia	66,71–73
Oxaliplatin	Colon, rectum, pancreas, stomach, ovary, liver	Peripheral neuropathy (acute and chronic), fatigue, gastrointestinal problems, thrombocytopenia, leukopenia	74,75

Taken together, these three drugs represent the most successful examples of the clinical application of platinum derivatives, showing how structural modifications can broaden oncological indications but also modify toxicity profiles.

Nanomaterials as drug delivery support for Platinum compounds

One of the main challenges in current oncological research is optimizing the administration of platinum-derived drugs, improving their efficacy, and reducing associated toxicity. In this context, nanomaterials have emerged as innovative delivery systems, defined as materials with at least one dimension smaller than 100 nanometers (Figure 13), which grants them special properties such as greater surface area, improved stability, and the ability to target specific tissues [78].

Among the most studied nanomaterials are dendrimers, polymeric nanoparticles, micelles, nanospheres, inorganic nanoparticles (e.g., gold, silica), and lipid nanoparticles, with liposomes standing out among the latter. Liposomes are spherical vesicles composed of phospholipid bilayers capable of encapsulating both hydrophilic and hydrophobic molecules, making them ideal candidates for transporting drugs such as cisplatin [79]

Liposomal cisplatin has shown significant advantages over its conventional form. Encapsulation of cisplatin in liposomes allows the drug to be preferentially directed toward the tumor, prolonging its half-life in circulation and reducing its accumulation in healthy organs such as the kidney, the primary target of its nephrotoxicity [80]. Preclinical and early clinical studies have demonstrated that liposomes loaded with cisplatin exhibit reduced renal and neurological toxicity, while maintaining or even increasing antitumor efficacy [81]

Among the most relevant developments is Lipoplatin®, a liposomal formulation of cisplatin that has advanced to phase III clinical trials. This formulation showed a significant reduction in adverse effects, especially nephrotoxicity, and a more favorable pharmacokinetic profile, with preferential accumulation in lung and pancreatic tumor tissues [82]. This selective accumulation is largely explained by the Enhanced Permeability and Retention (EPR) effect, a phenomenon in which the leaky and poorly organized vasculature of tumor tissues allows nanoscale liposomal carriers to extravasate and remain trapped for prolonged periods. In the case of Lipoplatin®, its nanosized liposomal structure (≈110–130 nm) facilitates passive tumor targeting through the EPR effect, thereby increasing intratumoral cisplatin concentrations while reducing systemic exposure[83]. These results suggest that liposomes not only represent an alternative release vehicle but also a promising strategy to overcome the classical limitations of platinum derivatives, paving the way for safer and more effective treatments.

Thus, liposomes as delivery systems for cisplatin constitute a paradigmatic example of the potential of nanomaterials in oncology, by combining advances in nanotechnology and pharmacology to enhance therapeutic efficacy while minimizing toxicity.

CONCLUSIONS

The history of platinum-based drugs has a fascinating background that begins in the 18th century, when platinum was first described in the mines of Chocó, Colombia. What was initially regarded as a metallurgical curiosity eventually became the foundation for one

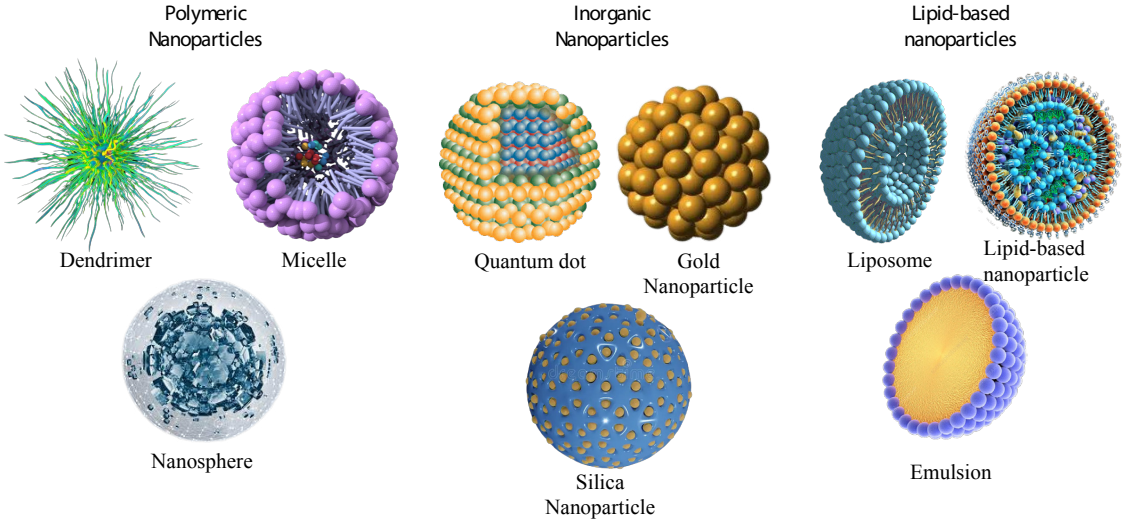

Figure 13. *Different nanomaterials used as drug release carriers.*

of the most important advances in modern medicine: the development of chemotherapeutic agents capable of halting cancer cell proliferation.

From the discovery of cisplatin in the 1960s to the introduction of more recent compounds such as oxaliplatin and lobaplatin, these drugs have transformed oncology and have become pillars in the fight against various types of tumors. However, their remarkable efficacy has been accompanied by significant side effects, which has driven the search for safer and more selective alternatives.

In this context, nanotechnology has opened new possibilities. Nanomaterials used as delivery systems make it possible to target drugs more precisely to cancer cells, improving stability and efficacy while reducing damage to healthy tissues.

The historical journey of platinum, from its discovery in the Chocó region to its role as an essential component of cancer therapies, exemplifies how science can transform a fortuitous finding into hope for millions of people. Today, the union of scientific tradition with nanotechnological innovation projects a future with more effective, less toxic treatments that are better adapted to the needs of patients.

REFERENCES

1. Petrucci, R. H., Herring, F. G., Madura, J. D. & Bissonnette, C. *General Chemistry - Principles and Modern Applications 10e*. vol. 2005 (2007).
2. Sharma, H., Bisht, A., Sethulakshmi, N. & Sharma, S. Catalysis by substituted platinum (ionic Pt) catalysts. *Int J Hydrogen Energy* **51**, 748–768 (2024).
3. Lin, X. *et al.* Robust oxidase mimicking activity of protamine-stabilized platinum nanoparticles units and applied for colorimetric sensor of trypsin and inhibitor. *Sens Actuators B Chem* **284**, 346–353 (2019).
4. Madima, N. & Raphulu, M. Platinum group metals-based electrodes for high-performance lithium-oxygen batteries: A mini-review. *Journal of Electroanalytical Chemistry* **976**, (2025).
5. Bapat, R. A. *et al.* Recent advances of gold nanoparticles as biomaterial in dentistry. *Int J Pharm* **586**, 119596 (2020).
6. Soto, M. A. & MacLachlan, M. J. Responsive macrocyclic and supramolecular structures powered by platinum. *Chem Sci* **15**, 431–441 (2024).
7. Mond, H. G. & Sloman, J. G. The Cardiac Pacemaker Clinic: Memories From a Bygone Era. *Heart Lung Circ* **30**, 216–224 (2021).
8. Mabhulusa, W., Sekhosana, K. E. & Fuku, X. The impact and performance of carbon-supported platinum group metal electrocatalysts for fuel cells. *Int J Electrochem Sci* **19**, 100524 (2024).
9. Wen, J. *et al.* Recovery and value-added utilization of critical metals from spent catalysts for new energy industry. *J Clean Prod* **419**, 138295 (2023).
10. Antiques, L. Platinum. *Antique Jewelry University* https://www.langantiques.com/university/platinum-2/?srsltid=AfmBOooXa8EPUV9-MSTA_vY-BA5ga9welx4Ttt6CLdYsyHqSnrITQA56g (2025).
11. Ecuador, M. de la M. del B. C. del. La Tolita: pioneros en el trabajo del oro y platino. https://museodelamoneda.bce.fin.ec/index.php/colecciones/medallas/item/225-la-tolita-pioneros-en-el-trabajo-del-oro-y-platino.html?utm_source=chatgpt.com (2025).
12. Bustamante, N., Garzón Bonilla, L., Bernal Romero, A. & Hernández Rodríguez, C. Tecnología del platino en la fabricación de piezas de orfebrería precolombina. *Boletin Museo Del Oro* 26–45 (2006).
13. Bruhns, K. O. *Huaquería, Procedencia, y Fantasía: Los Soles de Oro Del Ecuador*. (1998).
14. Aristizábal-Fúquene, A. El platino: contribuciones históricas y científicas desde el Siglo XVIII Parte 1. *Educacion Quimica* **26**, 146–151 (2015).
15. Ulloa, A. de. *Relación Histórica Del Viaje a La América Meridional. Primera Parte, Tomo Primero*. (Madrid, 1748).
16. Watson, W. & Brownrigg, W. Several Papers Concerning a New Semi-Metal, Called Platina; Communicated to the Royal Society by Mr. Wm. Watson F.R.S. *Philosophical Transactions of the Royal Society* **46**, 584–596 (1750).
17. Hunt, L. B. The First Experiments on Platinum. *Platin Met Rev* **29**, 180–184 (1985).
18. Fermin, L. & Vallvey, C. Platina Española Para Europa. *Llull: Revista de la Sociedad Española de Historia de las Ciencias y de las Técnicas* **17**, 289–312 (1994).
19. Cano, P. D. El interés de la corona española por el beneficio del platino y su comercialización a finales del siglo xviii. *De Re Metallica* **26**, 51–60 (2016).
20. Kauffman, G. B., Pentimalli, R., Doldi, S. & Hall, M. D. Michele Peyrone (1813-1883), discoverer of Cisplatin. *Platin Met Rev* **54**, 250–256 (2010).
21. Dasari, S. & Bernard Tchounwou, P. Cisplatin in cancer therapy: Molecular mechanisms of action. *Eur J Pharmacol* **740**, 364–378 (2014).
22. Werner, A. Beitrag zur Konstitution anorganischer Verbindungen. *Zeitschrift für anorganische Chemie* **3**, 267–330 (1893).
23. Wisniak, J. The History of Catalysis. From the Beginning to Nobel Prizes. *Educacion Quimica* **21**, 60–69 (2010).
24. Griffith, W. P. Bicentenary of four platinum group metals: Part II: Osmium and iridium - Events surrounding their discoveries. *Platin Met Rev* **48**, 182–189 (2004).
25. Wisniak, J. Paul Schützenberger. **26**, 57–65 (2015).
26. Rosenberg, B., Van Camp, L. & Krigas, T. Inhibition of Cell Division in Escherichia coli by Electrolysis Products from a Platinum Electrode. *Nature Publishing Group* **205**, 698–699 (1965).
27. Rosenberg, B., Renshaw, E., Vancamp, L., Hartwick, J. & Drobnik, J. Platinum-induced filamentous growth in Escherichia coli. *J Bacteriol* **93**, 716–721 (1967).
28. Rosenberg, B., Van Camp, L. & Krigas, T. Inhibition of Cell Division in Escherichia coli by Electrolysis

Products from a Platinum Electrode. *Nature Publishing Group* **205**, 698–699 (1965).
29. Rosenberg, B., Van Camp, L., Trosko, J. E. & Mansour, V. H. Platinum compounds: a new class of potent antitumour agents. *Nature* **222**, 385–386 (1969).
30. Rosenberg, B. & Van Camp, L. The successful regression of large solid sarcoma 180 tumors by platinum compounds. *Cancer Res* **30**, 1799–1802 (1970).
31. Lippert, Bernhard. *Cisplatin : Chemistry and Biochemistry of a Leading Anticancer Drug.* (Verlag Helvetica Chimica Acta ; Wiley-VCH, 1999).
32. Prüfungsarbeit, W. & Des Titels, E. *History of Platinum-Based Drugs from a Regulatory Perspective*. (2020).
33. Einhorn, L. H. Curing metastatic testicular cancer. *Proc Natl Acad Sci U S A* **99**, 4592–4595 (2002).
34. Oliver, T. Conservative management of testicular germ-cell tumors. *Nature Clinical Practice Urology* vol. 4 550–560 Preprint at https://doi.org/10.1038/ncpuro0905 (2007).
35. Wagstaff, A. J., Ward, A., Benfield, P. & Heel, R. C. Carboplatin: A preliminary review of its pharmacodynamic and pharmacokinetic properties and therapeutic efficacy in the treatment of cancer. *Toxicology* vol. 168 (1989).
36. Chau, I. & Cunningham, D. Oxaliplatin for colorectal cancer in the United States: Better late than never. *Journal of Clinical Oncology* vol. 21 2049–2051 Preprint at https://doi.org/10.1200/JCO.2003.03.074 (2003).
37. Stordal, B., Pavlakis, N. & Davey, R. Oxaliplatin for the treatment of cisplatin-resistant cancer: A systematic review. *Cancer Treatment Reviews* vol. 33 347–357 Preprint at https://doi.org/10.1016/j.ctrv.2007.01.009 (2007).
38. Mabuchi, S. & Kimura, T. Nedaplatin: A Radiosensitizing Agent for Patients with Cervical Cancer. *Chemother Res Pract* **2011**, 1–10 (2011).
39. Lobaplatin D 19466. *ADIS R&D PROFILE* **4**, 369–372 (2003).
40. Lee, J.-W. *et al. Anti-Tumor Activity of Heptaplatin in Combination with 5-Fluorouracil or Paclitaxel against Human Head and Neck Cancer Cells in Vitro*. (2006) doi:10.1097/01.cad.0000205033.08838.c7.
41. Bhargava, A. & Vaishampayan, U. N. Satraplatin: Leading the new generation of oral platinum agents. *Expert Opinion on Investigational Drugs* vol. 18 1787–1797 Preprint at https://doi.org/10.1517/13543780903362437 (2009).
42. Dijkstra, M. *et al.* Exploring the Structure-Activity Relationships of Albumin-Targeted Picoplatin-Based Platinum(IV) Prodrugs. *Inorg Chem* **64**, 2554–2566 (2025).
43. Hamilton, G. & Olszewski, U. Picoplatin pharmacokinetics and chemotherapy of non-small cell lung cancer. *Expert Opin Drug Metab Toxicol* **9**, 1381–1390 (2013).
44. Jodrell, D. I. *et al.* Phase II studies of BBR3464, a novel tri-nuclear platinum complex, in patients with gastric or gastro-oesophageal adenocarcinoma. *Eur J Cancer* **40**, 1872–1877 (2004).
45. Kelland, L. The resurgence of platinum-based cancer chemotherapy. *Nature Reviews Cancer* vol. 7 573–584 Preprint at https://doi.org/10.1038/nrc2167 (2007).
46. Galluzzi, L. *et al.* Molecular mechanisms of cisplatin resistance. *Oncogene* vol. 31 1869–1883 Preprint at https://doi.org/10.1038/onc.2011.384 (2012).
47. Dilruba, S. & Kalayda, G. V. Platinum-based drugs: past, present and future. *Cancer Chemotherapy and Pharmacology* vol. 77 1103–1124 Preprint at https://doi.org/10.1007/s00280-016-2976-z (2016).
48. Dasari, S. & Bernard Tchounwou, P. Cisplatin in cancer therapy: Molecular mechanisms of action. *Eur J Pharmacol* **740**, 364–378 (2014).
49. Wang, D. & Lippard, S. J. Cellular processing of platinum anticancer drugs. *Nature Reviews Drug Discovery* vol. 4 307–320 Preprint at https://doi.org/10.1038/nrd1691 (2005).
50. Siddik, Z. H. Cisplatin: Mode of cytotoxic action and molecular basis of resistance. *Oncogene* vol. 22 7265–7279 Preprint at https://doi.org/10.1038/sj.onc.1206933 (2003).
51. de Sousa, G. F., Wlodarczyk, S. R. & Monteiro, G. Carboplatin: Molecular mechanisms of action associated with chemoresistance. *Brazilian Journal of Pharmaceutical Sciences* vol. 50 693–702 Preprint at https://doi.org/10.1590/S1984-82502014000400004 (2014).
52. Florea, A. M. & Büsselberg, D. Cisplatin as an antitumor drug: Cellular mechanisms of activity, drug resistance and induced side effects. *Cancers* vol. 3 1351–1371 Preprint at https://doi.org/10.3390/cancers3011351 (2011).
53. Hartmann, J. T. & Lipp, H.-P. Toxicity of platinum compounds. *Expert Opin. Pharmacother* **4**, 889–901 (2003).
54. Wheate, N. J., Walker, S., Craig, G. E. & Oun, R. The status of platinum anticancer drugs in the clinic and in clinical trials. *Dalton Transactions* **39**, 8113–8127 (2010).
55. Raymond, E., Chaney, S. G., Taamma, A. & Cvitkovic, E. *Oxaliplatin: A Review of Preclinical and Clinical Studies. Annals of Oncology* vol. 9 (1998).
56. Escalante, P. I., Quiñones, L. A. & Contreras, H. R. Epithelial-Mesenchymal Transition and MicroRNAs in Colorectal Cancer Chemoresistance to FOLFOX. https://doi.org/10.3390/pharmaceutics (2021) doi:10.3390/pharmaceutics.
57. Woynarowski, J. M. *et al. Oxaliplatin-Induced Damage of Cellular DNA*. http://www.molpharm.org (2000).
58. Jamieson, E. R. & Lippard, S. J. Structure, recognition, and processing of cisplatin-DNA adducts. *Chem Rev* **99**, 2467–2498 (1999).
59. Naito, Y. *et al.* Phase II study of nedaplatin and docetaxel in patients with advanced squamous cell carcinoma of the lung. *Annals of Oncology* **22**, 2471–2475 (2011).
60. Akshintala, S. *et al.* Phase 1 trial and pharmacokinetic study of the oral platinum analog satraplatin

in children and young adults with refractory solid tumors including brain tumors. *Pediatr Blood Cancer* **62**, 603–610 (2015).
61. Wheate, N. J. & Collins, J. G. *Multi-Nuclear Platinum Drugs: A New Paradigm in Chemotherapy. Curr. Med. Chem.-Anti-Cancer Agents* vol. 5 (2005).
62. Johnstone, T. C., Suntharalingam, K. & Lippard, S. J. The Next Generation of Platinum Drugs: Targeted Pt(II) Agents, Nanoparticle Delivery, and Pt(IV) Prodrugs. *Chemical Reviews* vol. 116 3436–3486 Preprint at https://doi.org/10.1021/acs.chemrev.5b00597 (2016).
63. Choi, C. H. *et al.* Molecular mechanisms of heptaplatin effective against cisplatin-resistant cancer cell lines: Less involvement of metallothfionein. *Cancer Cell Int* **4**, (2004).
64. Mckeage, M. J. *Lobaplatin: A New Antitumour Platinum Drug*. http://www.ashley-pub.com (2001).
65. Peng, Y. *et al.* A phase I clinical trial of dose escalation of lobaplatin in combination with fixed-dose docetaxel for the treatment of human solid tumours that had progressed following chemotherapy. *Oncol Lett* **9**, 67–74 (2015).
66. Kelland, L. R. *New Platinum Antitumor Complexes. Critical Reviews in Oncology/Hematology* vol. 5 (1993).
67. Einhorn, L. H. Curing metastatic testicular cancer. *Proc Natl Acad Sci U S A* **99**, 4592–4595 (2002).
68. Vougiouka, M. *Cisplatin and Platinum Drugs at the Molecular Level (Review). ONCOLOGY REPORTS* vol. 10 (2003).
69. Arany, I. & Safirstein, R. L. Cisplatin nephrotoxicity. *Semin Nephrol* **23**, 460–464 (2003).
70. Rybak, L. P., Whitworth, C. A., Mukherjea, D. & Ramkumar, V. Mechanisms of cisplatin-induced ototoxicity and prevention. *Hearing Research* vol. 226 157–167 Preprint at https://doi.org/10.1016/j.heares.2006.09.015 (2007).
71. Ozols, R. F. Treatment goals in ovarian cancer. *Int J Gynecol Cancer* vol. 15 3–11 (2005).
72. Calvert, A. H. *et al. Carboplatin Dosage: Prospective Evaluation of a Simple Formula Based on Renal Function*. (1989).
73. Harrap, K. R. *Preclinical Studies Identifying Carboplatin as a Viable Cisplatin Alternative. Cancer Treaeatment Reviews* vol. 2 (1985).
74. André, T. *et al. Oxaliplatin, Fluorouracil, and Leucovorin as Adjuvant Treatment for Colon Cancer for the Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) Investigators. n engl j med* vol. 23 www.nejm.org (2004).
75. A. de Gramont *et al.* Leucovorin and Fluorouracil With or Without Oxaliplatin. *Journal of Clinical Oncology* **18**, 2938–2947 (2000).
76. Wilson, R. H. *et al.* Acute oxaliplatin-induced peripheral nerve hyperexcitability. *Journal of Clinical Oncology* **20**, 1767–1774 (2002).
77. Grothey, A. Clinical management of oxaliplatin-associated neurotoxicity. *Clin Colorectal Cancer* **5**, (2005).
78. Wagner, V., Dullaart, A., Bock, A.-K. & Zweck, A. *The Emerging Nanomedicine Landscape. NATURE BIOTECHNOLOGY VOLUME* vol. 24 http://scientific.thomson.com/products/sci/ (2006).
79. Torchilin, V. P. Recent advances with liposomes as pharmaceutical carriers. *Nature Reviews Drug Discovery* vol. 4 145–160 Preprint at https://doi.org/10.1038/nrd1632 (2005).
80. Stathopoulos, G. P. *et al.* Pharmacokinetics and adverse reactions of a new liposomal cisplatin (Lipoplatin): phase I study. *Oncol Rep* **13**, 589–595 (2005).
81. BOULIKAS, T., STATHOPOULOS, P. G., VOLAKAKIS, N. & VOUGIOUKA, M. Systemic Lipoplatin Infusion Results in Preferential Tumor Uptake in Human Studies. *Anticancer Res* 3031–3040 (2005).
82. Stathopoulos, G. P. & Boulikas, T. Lipoplatin Formulation Review Article. *J Drug Deliv* **2012**, 1–10 (2012).
83. Arantseva, D. A. & Vodovozova, E. L. Platinum-Based Antitumor Drugs and Their Liposomal Formulations in Clinical Trials. *Russ J Bioorg Chem* **44**, 619–630 (2018).