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Organometallic Osmium Compounds in Cancer Therapy

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Abstract

The exploration of organometallic complexes with osmium as potential anticancer agents was indeed an area of ongoing research. These complexes were being investigated for their unique properties and mechanisms of action against cancer cells. However, it's essential to note that the field of scientific research is dynamic, and new findings may have emerged since then. Organometallic complexes with osmium can be designed to exhibit specific features that make them promising candidates for anticancer applications. These features may include the ability to interact with cellular components, induce DNA damage, or modulate specific pathways crucial for cancer cell survival. To get the most current and accurate information on the latest developments in this field, I recommend checking recent scientific literature, research articles, and updates from reputable sources. Researchers often publish their findings in peer-reviewed journals, and these publications provide valuable insights into the progress of studies involving osmium-based organometallic complexes in cancer research and treatment.KP1339, also known as tetrachloride (dimethyl sulfoxide) (1H-indazole) ruthenate (III), is an osmium (III) compound that has been studied for its potential anticancer properties. It belongs to the class of organometallic compounds and has been investigated for its ability to induce cancer cell death and inhibit tumor growth. Osmium (II) arene complexes are a class of organometallic compounds that involve osmium in the +2-oxidation state coordinated with arene ligands. The structural characteristics and coordination environment of osmium (II) arene complexes make them interesting subjects of study for their potential applications, particularly in the field of medicinal chemistry and cancer research.

Keywords: Osmium (II) arene complexes, Osmium (III) compound, Cellular proteins, Induction of oxidative stress, Cancer cell replication

INTRODUCTION

The introduction of osmium-containing organometallic compounds in cancer treatment was an emerging area of research. Osmium is a transition metal that shares some similarities with platinum, which has been widely used in cancer chemotherapy [1]. Osmium compounds were being investigated for their potential as anticancer agents due to their unique chemical properties and mechanisms of action [2].

Mechanisms of Action: Osmium containing organometallic compounds, like their platinum counterparts, were explored for their ability to form covalent adducts with DNA, leading to DNA damage and interference with cancer cell replication (Figure 1). Additionally, these compounds might exhibit other mechanisms of action, such as interactions with cellular proteins and induction of oxidative stress [3].

Reduced Cross-Resistance: One potential

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advantage of osmium-containing compounds is a reduced cross-resistance with platinum drugs. This means that cancers resistant to platinum-based therapies might still respond to osmium-containing compounds [4-29].

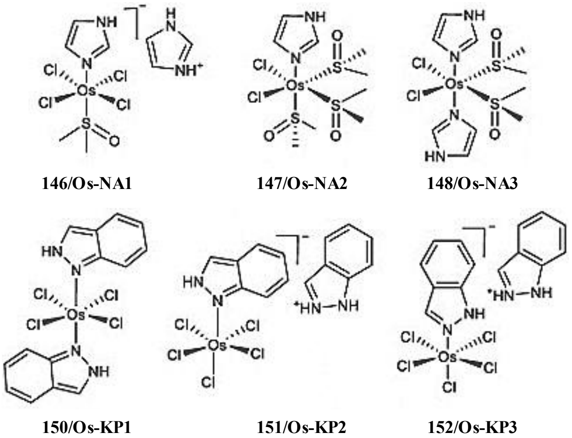

Figure 1. Osmium-containing organometallic compounds, like their platinum counterparts, were explored for their ability to form covalent adducts with DNA, leading to DNA damage and interference with cancer cell replication.

Structural Diversity: Researchers were designing and studying various osmium-containing complexes with different ligands to explore their structural diversity. The modification of ligands allows for the fine-tuning of the compounds' properties, including their stability, reactivity, and specificity for cancer cells [30].

Preclinical Studies: Preclinical studies involving osmium-containing organometallic compounds were ongoing to assess their efficacy, safety, and mechanisms of action. These studies typically involve testing the compounds in laboratory models before advancing to human clinical trials [31].

Clinical Development: The clinical development of osmium-containing compounds for cancer treatment was likely in the early stages, with a focus on safety and initial efficacy assessments. Clinical trials would be necessary to determine their therapeutic potential in humans (Table 1) [32].

Table 1. Clinical development typically follows a well-defined process, involving several phases.

S.N.	Content	Key Functions
1	Preclinical Research	Before entering clinical trials, researchers conduct preclinical studies to assess the safety, pharmacokinetics, and pharmacodynamics of the osmium-containing compounds. This stage involves laboratory experiments and animal testing to understand the compound's biological effects.
2	Phase I Clinical Trials	Phase I trials are the first step in testing new drugs in humans. These trials primarily focus on evaluating the safety, dosage, and side effects of the osmium-containing compounds. A small group of healthy volunteers or patients is usually involved in this phase
3	Phase II Clinical Trials	Phase I trials show promising results regarding safety, the compounds move to Phase II trials. These trials involve a larger group of patients and aim to assess the initial efficacy of the treatment. Researchers gather data on how well the drug works against the targeted cancer, as well as its side effects.
4	Phase III Clinical Trials	Phase II trials demonstrate positive outcomes, the compounds progress to Phase III trials. These trials involve an even larger patient population and compare the new treatment with existing standard treatments. The focus is on confirming efficacy, monitoring side effects, and collecting

		additional safety data.
5	Regulatory Approval	Successful completion of Phase III trials allows researchers to submit a New Drug Application (NDA) to regulatory agencies such as the U.S. Food and Drug Administration (FDA) or the European Medicines Agency (EMA). Regulatory agencies review the data and decide whether to approve the drug for commercial use.
6	Post-Marketing Surveillance	After approval, ongoing monitoring and studies may continue to assess the long-term safety and effectiveness of the osmium-containing compounds. This phase helps identify any rare or long-term side effects that may not have been evident in earlier stages. It's important to note that the development of new cancer treatments is a complex and lengthy process, and many compounds do not progress beyond certain phases due to safety concerns or lack of efficacy. As of my last update, specific information on osmium-containing compounds in clinical trials might not be readily available, and you may need to check more recent sources or clinical trial databases for the latest developments.

The clinical development of osmium-containing compounds for cancer treatment was limited, and specific details may have evolved since then. However, I can provide some general insights into the early stages of drug development and clinical trials.

RESEARCH AND METHODOLOGIES

KP1339 (Osmium (III) compound): The description of KP1339 (Osmium (III) compound) is accurate. KP1339 is an organometallic osmium compound that has shown anticancer properties in preclinical studies [33]. It has been studied for its ability to induce cancer cell death and inhibit tumor growth. KP1339 is indeed an organometallic osmium compound, and it has shown anticancer properties in preclinical studies (Figure 2) [34].

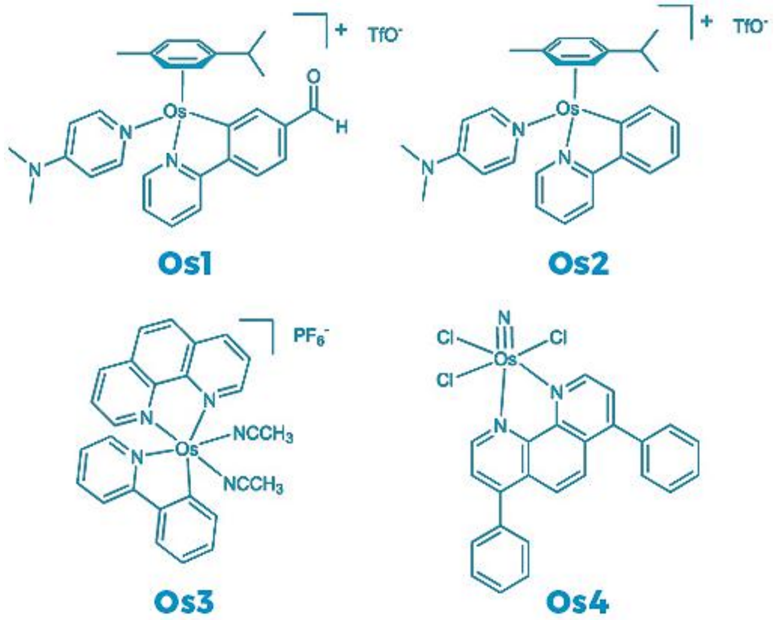

Figure 2. KP1339 is an organometallic osmium compound that has shown anticancer properties in preclinical studies.

Researchers have studied its ability to induce cancer cell death and inhibit tumor growth, making it a subject of interest in cancer research. The investigation of KP1339 and similar organometallic compounds highlights the diverse range of metals being explored for their potential in anticancer treatments [35]. Understanding their mechanisms of action and assessing their efficacy in preclinical studies are critical steps in the development of novel cancer therapies. As always, for the most up-to-date information on KP1339 and its progress in research and clinical development (Table 2) [36].

Table 2. KP1339, also known as tetrachloride (ethylbenzylamine)osmate (IV), is an osmium-containing compound that has been investigated for its potential role in cancer treatment.

S.N.	Content	Key Functions
1	Mechanism of Action	KP1339 is believed to exert its anti-cancer effects through multiple mechanisms, including the induction of cell death (apoptosis), inhibition of cell proliferation, and interference with cellular signaling pathways. The exact molecular targets and mechanisms of action may vary and are subject to ongoing research.
2	Preclinical Studies	Preclinical studies involving laboratory experiments and animal models are typically conducted to assess the efficacy and safety of KP1339. These studies aim to understand how the compound interacts with cancer cells, its potential toxicities, and its overall effectiveness in inhibiting tumor growth.
3	Early Clinical Trials (Phase I/II)	Preclinical studies show promising results, the compound may progress to early-phase clinical trials. Phase I trials focus on establishing the safety profile, determining the maximum tolerated dose, and understanding the pharmacokinetics of the compound in humans. Phase II trials further investigate efficacy in a larger group of patients.
4	Clinical Efficacy and Safety	Data from clinical trials would provide insights into the compound's efficacy in treating specific types of cancer. Researchers assess various parameters, including tumor response rates, progression-free survival, overall survival, and the safety profile of the drug.
5	Challenges and Limitations	Like any experimental cancer treatment, challenges may arise during clinical development. These challenges could include issues related to toxicity, patient tolerability, or the need for combination therapies to enhance effectiveness.
6	Future Directions	Depending on the outcomes of early clinical trials, researchers may explore combination therapies, evaluate the compound in different cancer types, or refine treatment regimens to optimize its therapeutic potential.

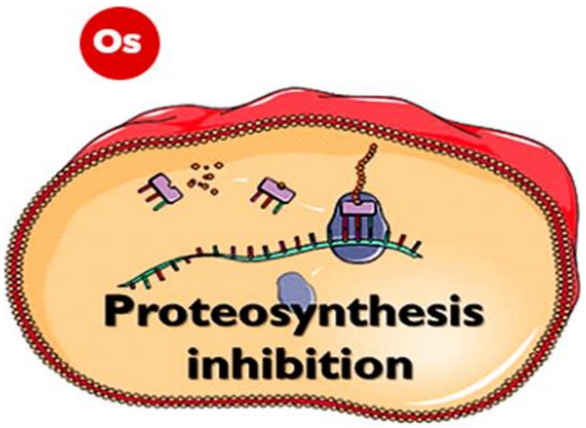

Figure 3. The mechanisms by which KP1339 interacts with cancer cells is a crucial aspect of understanding its potential as an anticancer agent.

KP1339 is an organometallic complex containing osmium in the +3-oxidation state.KP1339 has demonstrated anticancer activity in preclinical studies. The mechanisms of action may involve interactions with cellular targets, induction of cell death, and inhibition of tumor growth. KP1339 is indeed an organometallic complex containing osmium in the +3-oxidation state [37]. This osmium-based compound has demonstrated anticancer activity in preclinical studies. The mechanisms of action associated with KP1339's anticancer effects may involve interactions with cellular targets, induction of cell death (apoptosis), and inhibition of tumor growth [38]. The exploration of the mechanisms by which

KP1339 interacts with cancer cells is a crucial aspect of understanding its potential as an anticancer agent (Figure 3) [39].

These studies help researchers uncover the specific pathways or processes affected by the compound, which is essential for advancing its development and potential clinical applications. As research on KP1339 progresses, further insights into its mechanisms of action, efficacy in different cancer types, and potential applications in clinical settings may emerge.

Research has focused on exploring the potential of KP1339 in combination with other anticancer agents to achieve synergistic effects. Combination therapies are often investigated to enhance the overall efficacy of cancer treatment while minimizing potential resistance [40-50]. Research has indeed focused on exploring the potential of KP1339 in combination with other anticancer agents to achieve synergistic effects. Combination therapies, which involve the use of multiple drugs or treatment modalities, are often investigated in cancer research to enhance the overall efficacy of treatment and address potential issues such as drug resistance [51].

The rationale behind combination therapies includes targeting multiple pathways or mechanisms involved in cancer development and progression, thereby increasing the chances of success and reducing the likelihood of resistance. This approach is particularly relevant in the context of the complex and heterogeneous nature of cancer. By combining KP1339 with other anticancer agents, researchers aim to enhance the therapeutic effects, improve treatment outcomes, and potentially overcome resistance that might occur with single-agent treatments. The exploration of combination therapies is a dynamic area of research that involves careful consideration of drug interactions, safety profiles, and the specific characteristics of the cancer being treated [52-66] (Figure 4).

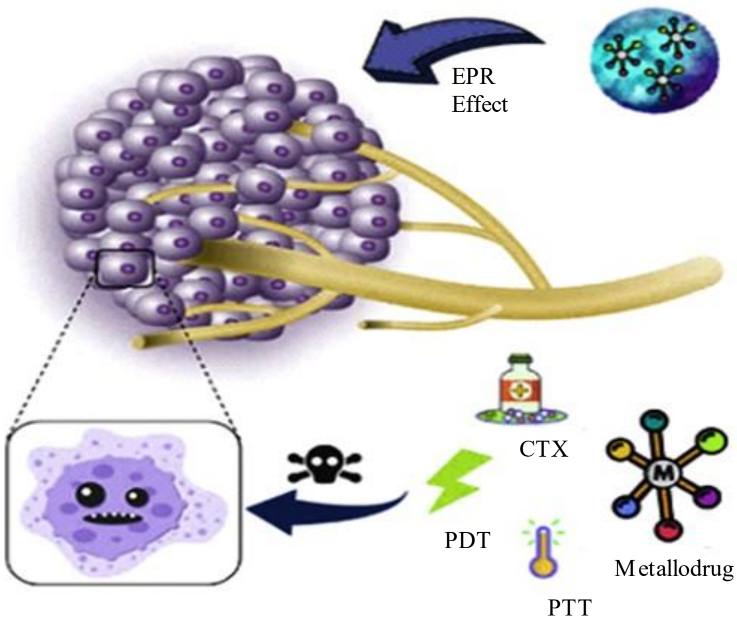

Figure 4. Osmium-based compounds, including KP1339, represent a class of metal-containing complexes that are being investigated for their potential in cancer treatment.

As the field progresses, insights gained from studies on combination therapies involving KP1339 will contribute to the development of more effective and personalized approaches to cancer treatment. Always refer to the latest scientific literature for updates on the progress and findings related to KP1339 and combination therapies in cancer research [67].

KP1339 is an organometallic complex containing osmium in the +3-oxidation state.KP1339 has demonstrated anticancer activity in preclinical studies. The mechanisms of action may involve interactions with cellular targets, induction of cell death, and inhibition of tumor growth. KP1339 is indeed an organometallic complex containing osmium in the +3-oxidation state [37]. This osmium-based compound has demonstrated anticancer activity in preclinical studies. The mechanisms of action associated with KP1339's anticancer effects may involve interactions with cellular targets, induction of cell death (apoptosis), and inhibition of tumor growth [38]. The exploration of the mechanisms by which KP1339 interacts with cancer cells is a crucial aspect of understanding its potential as an anticancer agent (Figure 3) [39].

Before advancing to clinical trials, it is standard practice for a compound like KP1339 to undergo preclinical studies. These studies are designed to assess various aspects of the compound's behavior, including its safety, pharmacokinetics (how the compound is absorbed, distributed, metabolized, and excreted in the body), and anticancer effects [68-75]. Osmium-based compounds, including KP1339, represent a class of metal-containing complexes that researchers are actively investigating for their potential in cancer treatment. The unique properties of osmium and the ability to design specific complexes with tailored characteristics make these compounds attractive candidates for exploration in oncology [76].

Preclinical studies play a crucial role in the drug development process, providing valuable insights into the compound's biological activity and informing decisions about its suitability for testing in human subjects. These studies are typically conducted in laboratory settings using cell cultures and animal models [77-87]. As with any promising anticancer agent, the transition from preclinical studies to clinical trials involves a careful evaluation of safety and efficacy data. Clinical trials are then conducted to assess the compound's performance in human subjects and gather additional information that is essential for regulatory approval and eventual clinical use. Always refer to the latest scientific literature for updates on the progress of research involving KP1339 and its potential in cancer treatment [88].

The unique properties of osmium make these compounds interesting candidates for further exploration in the development of novel anticancer agents. The unique properties of osmium make compounds containing this metal intriguing candidates for further exploration in the development of novel anticancer agents. Osmium-based compounds offer several characteristics that researchers find appealing for their potential applications in cancer treatment [89]:

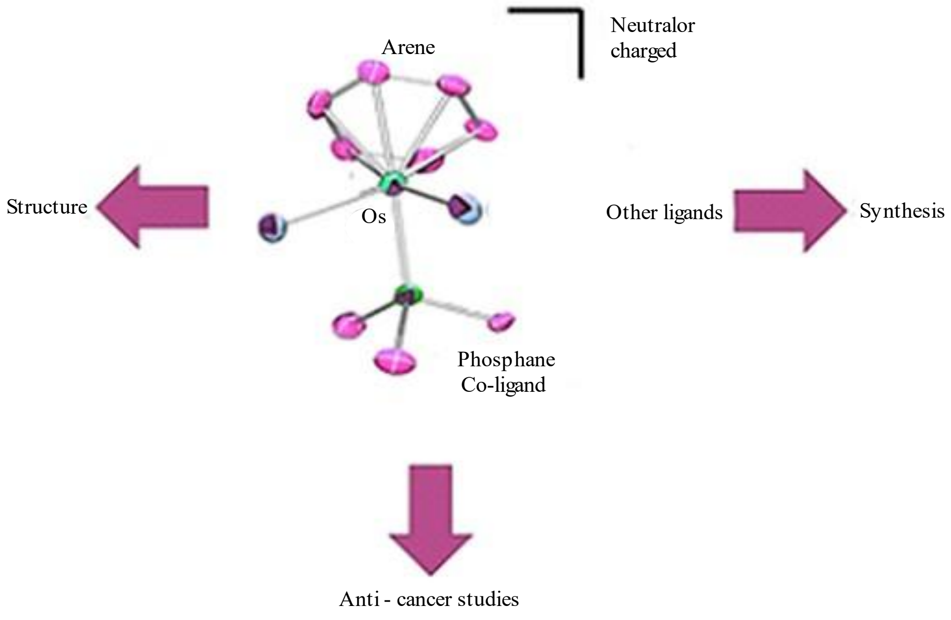

Figure 5. Osmium exhibits diverse coordination chemistry, allowing for the creation of a wide range of complex structures with specific properties.

Diverse Coordination Chemistry: Osmium exhibits diverse coordination chemistry, allowing for the creation of a wide range of complex structures with specific properties (Figure 5).

Osmium is known for its diverse coordination chemistry, and this property has led to the creation of a wide range of complex structures with specific properties. Osmium belongs to the platinum group of metals and shares some similarities with platinum in terms of its coordination behavior (Table 3).

Table 3. Osmium exhibits diverse coordination chemistry, allowing for the creation of a wide range of complex structures with specific properties.

S.N.	Content	Key Functions
1	Variable Oxidation States	Osmium can exist in various oxidation states, including +2, +3, +4, +6, and +8. This ability to adopt multiple oxidation states allows for the formation of a diverse array of coordination complexes with different ligands.
2	Ligand Preferences	Osmium complexes can coordinate with a variety of ligands, ranging from simple monodentate ligands to more complex polydentate ligands. The choice of ligands significantly influences the structure and properties of osmium complexes.
3	Geometry and Stereochemistry	Osmium complexes can adopt various geometries, including octahedral, square pyramidal, and square planar. The stereochemistry of osmium complexes is influenced by factors such as the oxidation state, the nature of ligands, and the coordination number.
4	Catalytic Activity	Osmium compounds have been explored for their catalytic properties in various reactions. For example, osmium tetroxide (OsO_4) is known for its catalytic role in the asymmetric dihydroxylation of alkenes.
5	Coordination Polymers and Clusters	Osmium can form coordination polymers and clusters, where multiple metal atoms are connected by bridging ligands. These structures often exhibit unique properties and are of interest in materials science.
6	Electron-Transfer Reactions	Osmium complexes are involved in electron-transfer reactions due to their ability to undergo changes in oxidation states. This property is relevant in redox processes and electronic applications.
7	Biological Applications	The diverse coordination chemistry of osmium makes it a versatile element for the design of compounds with tailored properties. Researchers leverage these properties for applications in catalysis, materials science, and medicinal chemistry. The exploration of osmium complexes continues to be an active area of research with potential implications in various fields. Some osmium-containing compounds have been investigated for their potential biological applications, including anti-cancer properties. The unique coordination chemistry of osmium can influence its interactions with biomolecules.

This versatility is valuable for tailoring compounds to interact with biological systems in unique ways. Variable Oxidation States: Osmium can exist in different oxidation states, and this flexibility enables the design of compounds with varied electronic configurations, impacting their reactivity and biological activities (90].

Potential Mechanisms of Action: Osmium-based compounds, like KP1339, have shown promise in preclinical studies for their anticancer properties. The investigation of their mechanisms of action involves understanding how they interact with cancer cells, modulate cellular processes, and induce therapeutic effects (Figure 6).

Some osmium compounds have demonstrated anticancer activity with reduced toxicity to healthy tissues compared to certain traditional chemotherapy agents. This is an important consideration for developing agents that minimize side effects [91-118].

Some osmium compounds have shown promise as potential anticancer agents, and their unique properties, including diverse coordination chemistry and lower toxicity to healthy tissues, make them attractive candidates for further research in cancer treatment. Osmium-containing compounds, particularly those with organometallic structures, have been explored for their ability to selectively target cancer cells while minimizing damage to normal tissues (Table 4).

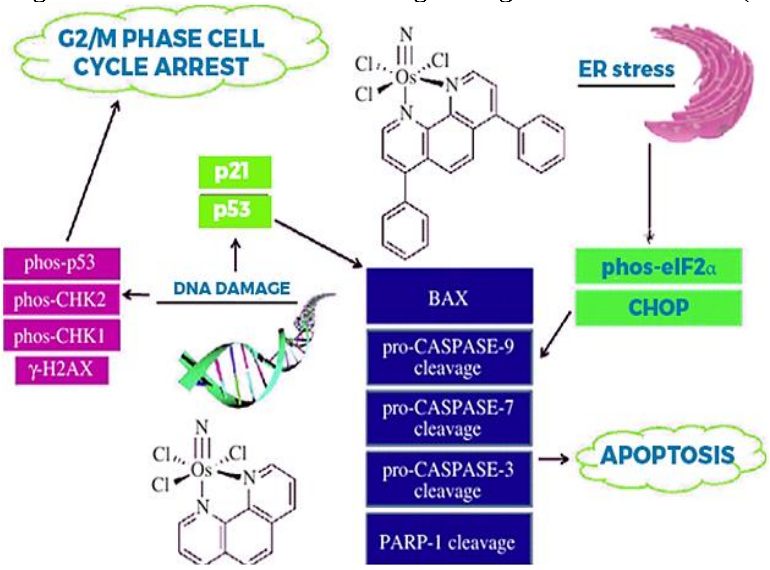

Figure 6. The investigation of their mechanisms of action involves understanding how they interact with cancer cells, modulate cellular processes, and induce therapeutic effects.

Table 4. Osmium compounds have shown promise as potential anticancer agents, and their unique properties, including diverse coordination chemistry and lower toxicity to healthy tissues, make them attractive candidates for further research in cancer treatment.

S.N.	Content	Key Functions
1	Selective Targeting	Osmium compounds can be designed to selectively target cancer cells. The unique coordination chemistry and reactivity of these compounds can be tailored to interact with specific biomolecules or cellular processes that are more prevalent in cancer cells.
2	Reduced Toxicity	The development of anticancer agents with reduced toxicity to healthy tissues is a crucial goal in cancer research. Osmium compounds have been investigated for their potential to achieve this by exploiting differences in the biochemical characteristics of cancer cells compared to normal cells.
3	Mechanisms of Action	Osmium compounds may exert their anticancer effects through various mechanisms, including induction of apoptosis (programmed cell death), interference with DNA repair mechanisms, inhibition of cell proliferation, and disruption of key signaling pathways. These mechanisms can contribute to the selective targeting of cancer cells.
4	Combination Therapies	Osmium compounds may be used in combination with other therapeutic agents to enhance their efficacy or reduce the risk of resistance development. Combination therapies can be designed to target multiple pathways involved in cancer progression.
5	Preclinical and Clinical Studies	The evaluation of osmium compounds in preclinical studies involves testing their efficacy and safety in laboratory settings and animal models. Positive results from preclinical studies may lead to the initiation of clinical trials to assess the compounds' performance in human patients.
6	Ongoing Research	Osmium-containing compounds are still an area of active research in the field of cancer treatment. Researchers continue to explore new osmium complexes, optimize their properties, and investigate their potential in various cancer types.While the development of osmium-containing compounds for cancer treatment is promising, it's important to note that the clinical translation of these compounds is a complex process, and not all experimental agents progress to the clinic. Additionally, the specific properties and mechanisms of individual

		osmium compounds may vary, so each compound needs to be evaluated independently.

For the latest information on specific osmium-containing compounds and their progress in clinical development, it's advisable to consult recent scientific literature, clinical trial databases, and updates from relevant conferences in the field of oncology.

The ongoing exploration of osmium-based compounds in cancer research contributes to the broader effort to identify and develop innovative therapies. As research progresses, the hope is to better understand the specific mechanisms by which these compounds interact with cancer cells and to optimize their therapeutic potential while minimizing adverse effects. Always refer to the latest scientific literature for updates on the progress of research involving osmium-based compounds in cancer treatment [119].

As research in this field is dynamic, it's recommended to consult the latest scientific literature, research articles, and updates from clinical trials for the most current information on KP1339 and its potential applications in cancer therapy. Given the dynamic nature of research, staying informed by consulting the latest scientific literature, research articles, and updates from clinical trials is crucial for obtaining the most current and accurate information on KP1339 and its potential applications in cancer therapy.

Scientific understanding and advancements in the field of cancer research can evolve rapidly, and new findings may influence the assessment of KP1339's efficacy, safety, and clinical utility. Regularly checking reputable sources, such as peer-reviewed journals and official clinical trial databases, ensures access to the latest insights and developments in the ongoing research on KP1339 and related compounds [120].

For individuals interested in the progress of KP1339 or healthcare professionals seeking the most up-to-date information, staying connected to the latest scientific literature is a key practice. Always refer to authoritative sources and publications to obtain the most reliable and current information on the status of KP1339 in cancer therapy research.

Osmium (II) Arene Complexes: The description of osmium (II) arene complexes is accurate. Osmium (II) arene complexes, akin to their ruthenium analogs, have been subjects of exploration in cancer research due to their potential cytotoxic effects against cancer cells. Osmium (II) arene complexes, similar to their ruthenium analogs, have indeed been subjects of exploration in cancer research (Figure 7).

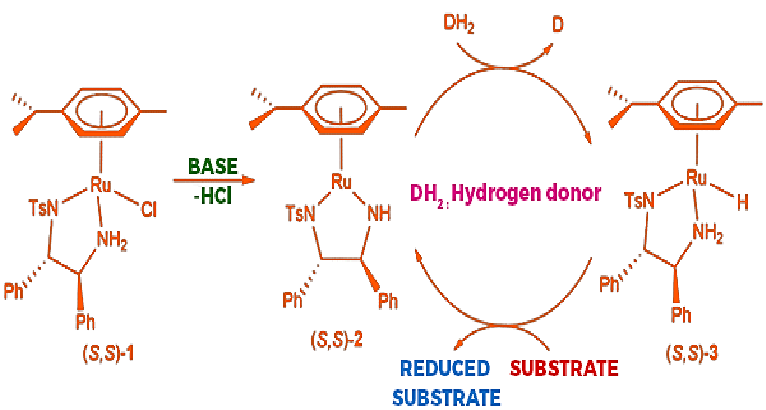

Figure 7. Osmium (II) arene complexes, akin to their ruthenium analogs, have been subjects of exploration in cancer research due to their potential cytotoxic effects against cancer cells.

These complexes are of interest due to their potential cytotoxic effects against cancer cells. The field of metal-based anticancer compounds encompasses a variety of metal ions and ligands, and osmium complexes are among those actively investigated for their therapeutic potential [121].

The properties and coordination chemistry of osmium (II) arene complexes, like those of ruthenium, contribute to their potential cytotoxicity. Researchers aim to understand the mechanisms of action by which these complexes interact with cancer cells, induce cell death, and inhibit tumor growth. This exploration is part of ongoing efforts to develop new and effective strategies for cancer treatment [122].

These complexes typically involve osmium in the +2-oxidation state coordinated with arene ligands, and they can be designed to target specific cellular processes. Osmium in the +2-oxidation state coordinated with arene ligands is a common component of osmium (II) arene complexes. The coordination of osmium with arene ligands allows for the design of complexes that can be tailored to target specific cellular processes. This design flexibility is valuable in the development of metal-based compounds for cancer research and treatment [123].

The +2-oxidation state of osmium is a key feature in these complexes, and it influences their chemical reactivity and interactions with biological systems. Researchers can fine-tune the structure of these complexes to enhance their efficacy against cancer cells while minimizing effects on normal, healthy cells.

The ability to target specific cellular processes is crucial in the development of anticancer agents, as it allows for a more selective approach in disrupting the aberrant pathways associated with cancer. Ongoing research aims to elucidate the mechanisms of action of osmium (II) arene complexes and optimize their therapeutic potential [124].

This oxidation state can influence the reactivity and biological properties of the complex. The complexes often include arene ligands, which are aromatic hydrocarbons like benzene or substituted benzene rings. The choice of arene ligands can impact the stability and properties of the complex. The oxidation state of osmium in osmium (II) arene complexes indeed plays a crucial role in influencing the reactivity and biological properties of the complex. The +2-oxidation state determines the electronic configuration of osmium, affecting its ability to interact with other molecules, including those found in biological systems.

The inclusion of arene ligands, which are often aromatic hydrocarbons like benzene or substituted benzene rings, further contributes to the overall properties of the complex. The choice of arene ligands is a critical aspect of designing these complexes, and it can impact several key factors [125]:

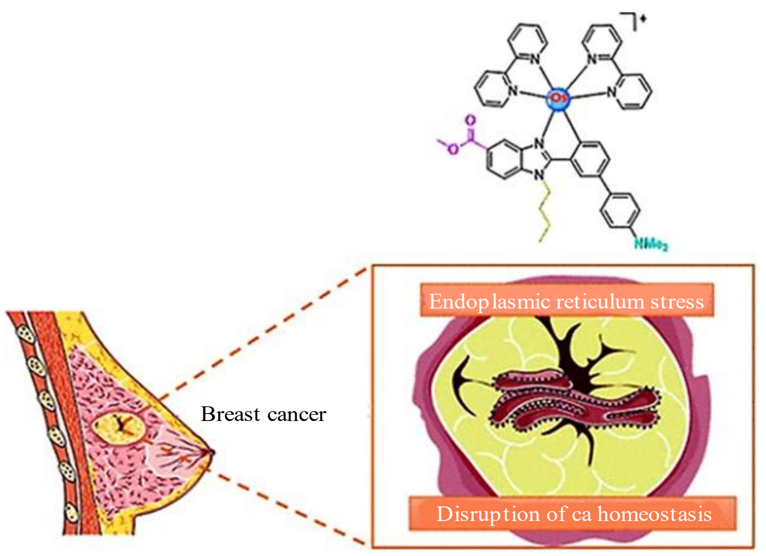

Figure 8. The design of osmium (II) arene complexes with specific arene ligands allows researchers to tailor the complexes to target particular cellular processes or molecular targets associated with cancer.

Stability: The specific arene ligands selected can influence the stability of the osmium (II) arene complex. Stability is important for ensuring that the complex remains intact under physiological conditions.

Reactivity: Different arene ligands can confer distinct reactivity to the complex, influencing how it interacts with cellular components and the mechanisms by which it exerts its cytotoxic effects on cancer cells.

Targeting: The design of osmium (II) arene complexes with specific arene ligands allows researchers to tailor the complexes to target particular cellular processes or molecular targets associated with cancer (Figure 8).

By carefully selecting and modifying the arene ligands, researchers can fine-tune the properties of osmium (II) arene complexes to optimize their therapeutic potential while minimizing potential side effects. This design approach is a key consideration in the development of metal-based compounds for cancer research and treatment.

Osmium (II) arene complexes have been explored for their cytotoxic effects against cancer cells. These effects can be attributed to interactions with cellular components, including DNA, proteins, or enzymes critical for cell survival. Osmium (II) arene complexes have indeed been explored for their cytotoxic effects against cancer cells. These effects can be attributed to interactions with various cellular components, including DNA, proteins, or enzymes that are critical for cell survival [126].

The mechanisms by which osmium (II) arene complexes induce cytotoxicity are multifaceted. Some of the interactions that contribute to their anticancer effects include:

DNA Interactions: Osmium (II) arene complexes can interact with DNA, leading to the formation of adducts or cross-links. These interactions may interfere with DNA replication and transcription, ultimately inducing DNA damage and cell death.

Protein Binding: The complexes may interact with specific proteins within the cell, disrupting normal cellular functions. Targeting proteins involved in essential pathways can lead to the inhibition of cell survival mechanisms.

Enzyme Inhibition: Osmium (II) arene complexes may inhibit crucial enzymes involved in cellular processes. This interference with enzymatic activity can disrupt metabolic pathways or signaling cascades, contributing to the cytotoxic effects (Figure 9).

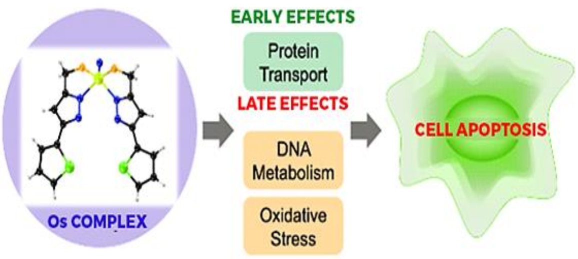

Figure 9. This interference with enzymatic activity can disrupt metabolic pathways or signaling cascades, contributing to the cytotoxic effects.

Understanding the specific interactions of osmium (II) arene complexes with cellular components is vital for optimizing their therapeutic potential and minimizing off-target effects. Ongoing research in this field aims to uncover the detailed mechanisms of action and further refine the design of osmium-based compounds for cancer treatment.

Researchers can design these complexes to target specific cellular processes or pathways, enhancing their selectivity for cancer cells while minimizing impact on normal cells. One of the advantages of osmium (II) arene complexes, like other metal-based anticancer compounds, lies in the ability to design them with a level of specificity for targeting particular cellular processes or pathways. This design flexibility allows researchers to enhance the selectivity of these complexes for cancer cells while minimizing their impact on normal, healthy cells [127].

By carefully tailoring the structure of osmium (II) arene complexes, researchers can aim to achieve the following:

Targeted Interactions: Designing the complexes to interact with specific cellular components or molecular targets associated with cancer allows for a more targeted and selective approach.

Pathway Modulation: Osmium (II) arene complexes can be engineered to modulate specific cellular pathways that are dysregulated in cancer. This modulation can lead to the inhibition of cancer cell growth and survival.

Reduced Toxicity to Normal Cells: The specificity in design helps minimize the impact on normal, non-cancerous cells, potentially reducing side effects associated with treatment.

The goal is to enhance the therapeutic index of osmium (II) arene complexes, making them more potent against cancer cells while sparing normal cells. This approach aligns with the broader goal of developing precision therapies that target the unique features of cancer cells, leading to more effective and less toxic treatments.

Ongoing research in this field continues to refine the design principles of metal-based anticancer compounds, including osmium (II) arene complexes, with the aim of improving their selectivity and efficacy in cancer treatment.

The exploration of osmium (II) arene complexes is part of ongoing efforts to broaden the range of metal-based compounds with potential anticancer properties. The exploration of osmium (II) arene complexes is indeed part of ongoing efforts to broaden the range of metal-based compounds with potential anticancer properties. Researchers are actively investigating various metal-containing complexes, including those involving osmium, in the quest to discover and develop new agents for cancer treatment [128].

Metal-based compounds offer unique chemical properties and modes of action, and different metals can be incorporated into complexes to create diverse structures. The exploration of osmium (II) arene complexes contributes to the diversification of metal-based anticancer agents, allowing scientists to examine their specific mechanisms of action, efficacy, and potential clinical applications [129].

As research progresses, the hope is to identify compounds that exhibit potent anticancer activity with reduced toxicity to normal cells, ultimately improving the therapeutic options available for cancer patients. The dynamic nature of this field means that ongoing investigations will likely reveal new insights into the potential of osmium (II) arene complexes and other metal-based compounds in cancer research and treatment [130].

As with other metal-containing complexes, the design, synthesis, and evaluation of osmium (II) arene complexes involve considerations of their stability, reactivity, and biological activity. The design, synthesis, and evaluation of osmium (II) arene complexes, like other metal-containing complexes, involve careful considerations of their stability, reactivity, and biological activity. These aspects are crucial for developing metal-based compounds with potential applications in various fields, including cancer research. Here's a breakdown of these considerations [131]:

Stability: The stability of osmium (II) arene complexes is a key factor in ensuring their effectiveness as therapeutic agents. Stability studies assess how well the complex holds its structure under different conditions, including physiological conditions in the human body [132].

Reactivity: Understanding the reactivity of the complex is essential for predicting its behavior in biological systems. This includes how it interacts with cellular components, such as DNA, proteins, and enzymes, which can influence its cytotoxic effects on cancer cells [133].

Biological Activity: Researchers aim to evaluate the biological activity of osmium (II) arene complexes in preclinical studies. This involves assessing their effects on cancer cells, studying mechanisms of action, and determining their potential for inducing cell death or inhibiting tumor growth [134].

Toxicity Profiles: Assessing the toxicity of the complexes is crucial for understanding their safety profile. Researchers aim to minimize off-target effects on normal cells to develop compounds with favorable therapeutic indices. The design and optimization of osmium (II) arene complexes require a multidisciplinary approach, involving expertise in inorganic chemistry, biochemistry, and pharmacology. Ongoing research in this field continues to refine the understanding of structure-activity relationships and guide the development of metal-based compounds for various applications, including cancer treatment [135-144].

RESULTS AND DISCUSSIONS

The research on osmium-containing organometallic compounds in cancer treatment has been a growing area of interest in the field of medicinal chemistry and oncology. Osmium compounds, like those of platinum and ruthenium, have shown potential for their anticancer properties. However, it's important to note that the field may have seen new developments or findings since then. Here's a general overview of the results and discussions related to osmium-containing organometallic compounds in cancer treatment [145]:

Mechanisms of Action

Osmium compounds exhibit various mechanisms of action, including interactions with DNA, proteins, and cellular signaling pathways. Some osmium compounds may induce apoptosis or inhibit cancer cell proliferation through unique modes of action [146].

Osmium Compounds in Preclinical Studies

Preclinical studies have demonstrated the anticancer efficacy of certain osmium-containing compounds against a range of cancer types. Investigations often focus on understanding the compound's selectivity for cancer cells and its impact on tumor growth [147].

DNA Binding and Cellular Effects

Similar to platinum and ruthenium compounds, osmium compounds may form stable complexes with DNA, leading to DNA damage and disruption of cellular processes. Research may delve into the specific DNA-binding properties and structural features that contribute to their anticancer effects (Figure 10).

Protein Targeting and Signaling Pathways

Some osmium-containing compounds may interact with specific proteins or modulate signaling pathways critical for cancer cell survival. Understanding the protein targets helps elucidate the compound's mechanism of action and potential for targeted cancer therapy [148].

Structural Optimization

Efforts to optimize the chemical structure of osmium complexes to enhance their anticancer properties, improve bioavailability, and reduce potential toxicities. Structure-activity relationship studies contribute to designing osmium compounds with improved efficacy and selectivity [149].

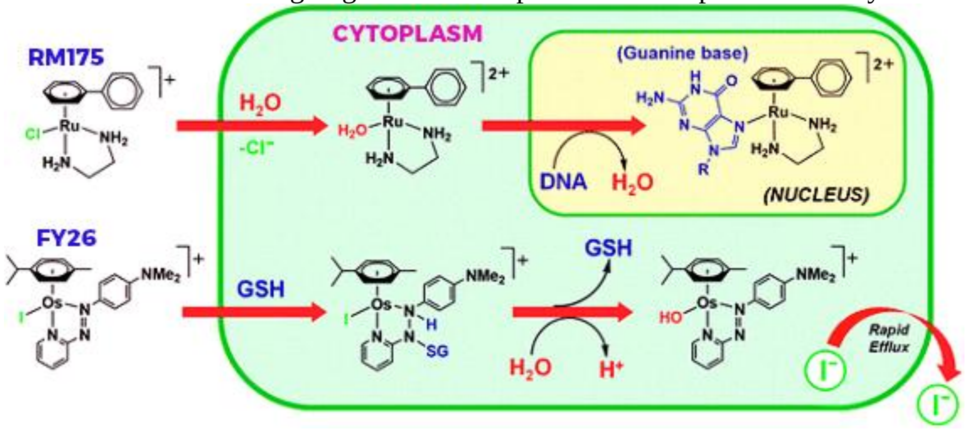

Figure 10. Similar to platinum and ruthenium compounds, osmium compounds may form stable complexes with DNA, leading to DNA damage and disruption of cellular processes.

Synergistic Effects and Combination Therapies

Exploration of combination therapies involving osmium-containing compounds with other chemotherapeutic agents to achieve synergistic effects. Combining osmium compounds with existing treatments may enhance overall therapeutic outcomes [150].

Toxicity Profiles and Safety

Evaluation of the toxicity profiles of osmium-containing compounds to ensure an acceptable safety profile for clinical applications. Researchers aim to minimize off-target effects and systemic toxicities associated with these compounds [151].

Drug Delivery Strategies

Utilization of drug delivery systems, such as nanoparticles, to improve the targeted delivery and bioavailability of osmium-containing compounds. Strategies to enhance selective uptake by cancer cells while sparing normal tissues [152-155].

Clinical Translation

Advancement to early-phase clinical trials to assess the safety, pharmacokinetics, and preliminary efficacy of osmium-containing compounds in human subjects. Challenges in clinical translation, including dose optimization and the identification of patient populations most likely to benefit [156,157].

Future Directions

Continued research to uncover new osmium compounds with enhanced anticancer properties. Investigation of osmium compounds in specific cancer subtypes or in combination with emerging therapeutic modalities [158-164].

CONCLUSIONS

The conclusion aptly captures the current status and trajectory of research on osmium-containing organometallic compounds in cancer treatment. It emphasizes the dynamic and evolving nature of this field, acknowledging the promising results from preclinical studies while underscoring the necessity for continued efforts to overcome challenges and advance towards clinical applications. Recognizing that the translation of promising preclinical findings to clinical applications involves addressing multifaceted challenges, including optimizing compound structures, ensuring safety, and achieving therapeutic efficacy. Emphasizing the importance of collaborative efforts between researchers in chemistry, biology, and clinical disciplines to comprehensively address the complexities associated with osmium-containing compounds in cancer treatment. Highlighting the need for a patient-centric approach in the development of osmium-based therapies, considering factors such as personalized medicine, patient heterogeneity, and the potential for combination therapies tailored to individual cases. Acknowledging the potential for ongoing innovation in the design of osmium compounds and the adaptation of research strategies based on new scientific insights and technological advances. Anticipating advancements in early-phase clinical trials as a critical step towards evaluating the safety and efficacy of osmium-containing compounds in human subjects, providing valuable insights for further development. Stressing the importance of effective communication and dissemination of research findings within the scientific community to foster collaboration, share knowledge, and collectively address challenges hindering clinical translation. Recognizing the ethical considerations associated with the development of novel cancer treatments, including considerations of patient welfare, informed consent, and societal impact. Considering the potential global impact of osmium-containing compounds, taking into account diverse patient populations and ensuring accessibility to innovative cancer therapies on a broader scale.

In conclusion, the journey from promising preclinical studies to successful clinical applications for osmium-containing organometallic compounds in cancer treatment is a complex but essential one. The dedication of researchers, collaboration across disciplines, and a commitment to addressing challenges will play pivotal roles in shaping the future of this dynamic and promising area of cancer research. For the latest updates and specific information, consulting recent scientific literature and ongoing clinical trials is recommended.

REFERENCES

1. Johnstone TC, Suntharalingam K, Lippard SJ. Third row transition metals for the treatment of cancer. Philos Trans A Math Phys Eng Sci. 2015 Mar 13;373(2037):20140185. doi: 10.1098/rsta.2014.0185. PMID: 25666060; PMCID: PMC4342973.
2. Bruijnincx PC, Sadler PJ. Controlling Platinum, Ruthenium and Osmium Reactivity for Anticancer Drug Design. Adv Inorg Chem. 2009 Jul 7;61:1–62. doi: 10.1016/S0898-8838(09)00201–3. PMID: 21258628; PMCID: PMC3024542.
3. van Rijt SH, Romero-Canelón I, Fu Y, Shnyder SD, Sadler PJ. Potent organometallic osmium compounds induce mitochondria-mediated apoptosis and S-phase cell cycle arrest in A549 non-small cell lung cancer cells. Metallomics. 2014 May;6(5):1014–22. doi: 10.1039/c4mt00034j. PMID: 24668459.
4. Florea, A.-M.; Büsselberg, D. Cisplatin as an Anti-Tumor Drug: Cellular Mechanisms of Activity, Drug Resistance and Induced Side Effects. Cancers 2011, 3, 1351–1371. https://doi.org/10.3390/cancers3011351
5. Frezza, M.; Hindo, S.; Chen, D.; Davenport, A.; Schmitt, S.; Tomco, D.; Dou, Q.P. Novel metals and metal complexes as platforms for cancer therapy. Curr. Pharm. Des. 2010, 16, 1813–1825.
6. Aoki K, Murayama K. Nucleic acid-metal ion interactions in the solid state. Met Ions Life Sci. 2012; 10:43–102. doi: 10.1007/978–94–007–2172–2_2. PMID: 22210335.
7. Desoize B, Madoulet C. Particular aspects of platinum compounds used at present in cancer treatment. Crit Rev Oncol Hematol. 2002 Jun;42(3):317–25. doi: 10.1016/s1040–8428(01)00219–0. PMID: 12050023.
8. Che CM, Siu FM. Metal complexes in medicine with a focus on enzyme inhibition. Curr Opin Chem Biol. 2010 Apr;14(2):255–61. doi: 10.1016/j.cbpa.2009.11.015. Epub 2009 Dec 16. PMID: 20018553.
9. Chen D, Milacic V, Frezza M, Dou QP. Metal complexes, their cellular targets and potential for cancer therapy. Curr Pharm Des. 2009;15(7):777–91. doi: 10.2174/138161209787582183. PMID: 19275642.
10. Zhang J, Wang L, Xing Z, Liu D, Sun J, Li X, Zhang Y. Status of bi- and multi-nuclear platinum anticancer drug development. Anticancer Agents Med Chem. 2010 May;10(4):272–82. doi: 10.2174/187152010791162270. PMID: 20184553.
11. Lebwohl D, Canetta R. Clinical development of platinum complexes in cancer therapy: an

historical perspective and an update. Eur J Cancer. 1998 Sep;34(10):1522–34. doi: 10.1016/s0959–8049(98)00224–x. PMID: 9893623.
12. Olszewski U, Hamilton G. A better platinum-based anticancer drug yet to come? Anticancer Agents Med Chem. 2010 May;10(4):293–301. doi: 10.2174/187152010791162306. PMID: 20187870.
13. Shah N, Dizon DS. New-generation platinum agents for solid tumors. Future Oncol. 2009 Feb;5(1):33–42. doi: 10.2217/14796694.5.1.33. PMID: 19243296.
14. Günes DA, Florea AM, Splettstoesser F, Büsselberg D. Co-application of arsenic trioxide (As2O3) and cisplatin (CDDP) on human SY-5Y neuroblastoma cells has differential effects on the intracellular calcium concentration ([Ca2+]i) and cytotoxicity. Neurotoxicology. 2009 Mar;30(2):194–202. doi: 10.1016/j.neuro.2008.12.001. Epub 2008 Dec 11. PMID: 19118571.
15. Tsang RY, Al-Fayea T, Au HJ. Cisplatin overdose: toxicities and management. Drug Saf. 2009;32(12):1109–22. doi: 10.2165/11316640–000000000–00000. PMID: 19916578.
16. Knoll C, Smith RJ, Shores C, Blatt J. Hearing genes and cisplatin deafness: a pilot study. Laryngoscope. 2006 Jan;116(1):72–4. doi: 10.1097/01.mlg.0000185596. 20207.d2. PMID: 16481813.
17. Rademaker-Lakhai JM, Crul M, Zuur L, Baas P, Beijnen JH, Simis YJ, van Zandwijk N, Schellens JH. Relationship between cisplatin administration and the development of ototoxicity. J Clin Oncol. 2006 Feb 20;24(6):918–24. doi: 10.1200/JCO.2006.10.077. PMID: 16484702.
18. Drottar M, Liberman MC, Ratan RR, Roberson DW. The histone deacetylase inhibitor sodium butyrate protects against cisplatin-induced hearing loss in guinea pigs. Laryngoscope. 2006 Feb;116(2):292–6. doi: 10.1097/01.mlg.0000197630.85208.36. PMID: 16467722; PMCID: PMC2570099.
19. Momekov G, Ferdinandov D, Bakalova A, Zaharieva M, Konstantinov S, Karaivanova M. In vitro toxicological evaluation of a dinuclear platinum(II) complex with acetate ligands. Arch Toxicol. 2006 Sep;80(9):555-60. doi: 10.1007/s00204-006-0078-0. Epub 2006 Feb 17. PMID: 16485120.
20. Liu M, Chien CC, Burne-Taney M, Molls RR, Racusen LC, Colvin RB, Rabb H. A pathophysiologic role for T lymphocytes in murine acute cisplatin nephrotoxicity. J Am Soc Nephrol. 2006 Mar;17(3):765–74. doi: 10.1681/ASN.2005010102. Epub 2006 Feb 15. PMID: 16481417.
21. Masubuchi Y, Kawasaki M, Horie T. Down-regulation of hepatic cytochrome P450 enzymes associated with cisplatin-induced acute renal failure in male rats. Arch Toxicol. 2006 Jun;80(6):347–53. doi: 10.1007/s00204–006–0079–z. Epub 2006 Feb 17. PMID: 16485119.
22. Ralph SJ, Neuzil J. Mitochondria as targets for cancer therapy. Mol Nutr Food Res. 2009 Jan;53(1):9–28. doi: 10.1002/mnfr.200800044. PMID: 19123183.
23. Brozovic A, Ambriović-Ristov A, Osmak M. The relationship between cisplatin-induced reactive oxygen species, glutathione, and BCL-2 and resistance to cisplatin. Crit Rev Toxicol. 2010 Apr;40(4):347–59. doi: 10.3109/10408441003601836. PMID: 20163198.
24. Desoize B. Cancer and metals and metal compounds: part I--carcinogenesis. Crit Rev Oncol Hematol. 2002 Apr;42(1):1–3. doi: 10.1016/s1040–8428(02)00017–3. PMID: 11923064.
25. Jordan P, Carmo-Fonseca M. Molecular mechanisms involved in cisplatin cytotoxicity. Cell Mol Life Sci. 2000 Aug;57(8–9):1229–35. doi: 10.1007/pl00000762. PMID: 11028915.
26. Sedletska Y, Giraud-Panis MJ, Malinge JM. Cisplatin is a DNA-damaging antitumour compound triggering multifactorial biochemical responses in cancer cells: importance of apoptotic pathways. Curr Med Chem Anticancer Agents. 2005 May;5(3):251–65. doi: 10.2174/1568011053765967. PMID: 15992353.
27. Chaney SG, Campbell SL, Bassett E, Wu Y. Recognition and processing of cisplatin- and oxaliplatin-DNA adducts. Crit Rev Oncol Hematol. 2005 Jan;53(1):3–11. doi: 10.1016/j.critrevonc.2004.08.008. PMID: 15607931.
28. Schär P, Fäsi M, Jessberger R. SMC1 coordinates DNA double-strand break repair pathways. Nucleic Acids Res. 2004 Jul 27;32(13):3921–9. doi: 10.1093/nar/gkh716. PMID: 15280507; PMCID: PMC506803.
29. Brabec V, Kasparkova J. Modifications of DNA by platinum complexes. Relation to resistance of

tumors to platinum antitumor drugs. Drug Resist Updat. 2005 Jun;8(3):131–46. doi: 10.1016/j.drup.2005.04.006. PMID: 15894512.
30. Kim, J.H., Reeder, E., Parkin, S. et al. Gold(I/III)-Phosphine Complexes as Potent Antiproliferative Agents. Sci Rep 9, 12335 (2019). https://doi.org/10.1038/s41598-019–48584–5
31. Gasser G, Ott I, Metzler-Nolte N. Organometallic anticancer compounds. J Med Chem. 2011 Jan 13;54(1):3–25. doi: 10.1021/jm100020w. Epub 2010 Nov 15. PMID: 21077686; PMCID: PMC3018145.
32. Frei, A., Verderosa, A.D., Elliott, A.G. et al. Metals to combat antimicrobial resistance. Nat Rev Chem 7, 202–224 (2023). https://doi.org/10.1038/s41570–023–00463–4
33. Berndsen RH, Weiss A, Abdul UK, Wong TJ, Meraldi P, Griffioen AW, Dyson PJ, Nowak-Sliwinska P. Combination of ruthenium(II)-arene complex [Ru(η6-p-cymene)Cl2(pta)] (RAPTA-C) and the epidermal growth factor receptor inhibitor erlotinib results in efficient angiostatic and antitumor activity. Sci Rep. 2017 Feb 22;7:43005. doi: 10.1038/srep43005. PMID: 28223694; PMCID: PMC5320450.
34. Christian G. Hartinger, Stefanie Zorbas-Seifried, Michael A. Jakupec, Bernd Kynast, Haralabos Zorbas, Bernhard K. Keppler,From bench to bedside – preclinical and early clinical development of the anticancer agent indazolium trans-[tetrachlorobis(1H-indazole)ruthenate(III)] (KP1019 or FFC14A),Journal of Inorganic Biochemistry,Volume 100, Issues 5–6,2006,Pages 891–904,ISSN 0162–0134, https://doi.org/10.1016/j.jinorgbio.2006.02.013
35. Wernitznig D, Kiakos K, Del Favero G, Harrer N, Machat H, Osswald A, Jakupec MA, Wernitznig A, Sommergruber W, Keppler BK. First-in-class ruthenium anticancer drug (KP1339/IT-139) induces an immunogenic cell death signature in colorectal spheroids in vitro. Metallomics. 2019 Jun 19;11(6):1044–1048. doi: 10.1039/c9mt00051h. PMID: 30942231.
36. Alessio E, Messori L. NAMI-A and KP1019/1339, Two Iconic Ruthenium Anticancer Drug Candidates Face-to-Face: A Case Story in Medicinal Inorganic Chemistry. Molecules. 2019 May 24;24(10):1995. doi: 10.3390/molecules24101995. PMID: 31137659; PMCID: PMC6571951.
37. Heffeter P, Atil B, Kryeziu K, Groza D, Koellensperger G, Körner W, Jungwirth U, Mohr T, Keppler BK, Berger W. The ruthenium compound KP1339 potentiates the anticancer activity of sorafenib in vitro and in vivo. Eur J Cancer. 2013 Oct;49(15):3366–75. doi: 10.1016/j.ejca.2013.05.018. Epub 2013 Jun 18. PMID: 23790465; PMCID: PMC3807657.
38. Flocke, L.S., Trondl, R., Jakupec, M.A. et al. Molecular mode of action of NKP-1339 – a clinically investigated ruthenium-based drug – involves ER- and ROS-related effects in colon carcinoma cell lines. Invest New Drugs 34, 261–268 (2016). https://doi.org/10.1007/s10637–016–0337–8
39. Dhyani, P., Quispe, C., Sharma, E. et al. Anticancer potential of alkaloids: a key emphasis to colchicine, vinblastine, vincristine, vindesine, vinorelbine and vincamine. Cancer Cell Int 22, 206 (2022). https://doi.org/10.1186/s12935–022–02624–9
40. Xu X, Dai F, Mao Y, Zhang K, Qin Y, Zheng J. Metallodrugs in the battle against non-small cell lung cancer: unlocking the potential for improved therapeutic outcomes. Front Pharmacol. 2023 Aug 31;14:1242488. doi: 10.3389/fphar.2023.1242488. PMID: 37727388; PMCID: PMC10506097.
41. Anthony EJ, Bolitho EM, Bridgewater HE, Carter OWL, Donnelly JM, Imberti C, Lant EC, Lermyte F, Needham RJ, Palau M, Sadler PJ, Shi H, Wang FX, Zhang WY, Zhang Z. Metallodrugs are unique: opportunities and challenges of discovery and development. Chem Sci. 2020 Nov 12;11(48):12888-12917. doi: 10.1039/d0sc04082g. PMID: 34123239; PMCID: PMC8163330.
42. Asperti, M., Cantamessa, L., Gryzik, M. et al. The modulation of iron metabolism affects the Rhabdomyosarcoma tumor growth in vitro and in vivo. Clin Exp Med 23, 2487–2502 (2023). https://doi.org/10.1007/s10238–023–01012–5
43. Bergamo A., Sava G. (2011). Ruthenium anticancer compounds: myths and realities of the emerging metal-based drugs. Dalton Trans. 40 (31), 7817–7823. 10.1039/c0dt01816c
44. Cui, X.Y.; Park, S.H.; Park, W.H. Anti-Cancer Effects of Auranofin in Human Lung Cancer Cells by Increasing Intracellular ROS Levels and Depleting GSH Levels. Molecules 2022, 27, 5207. https://doi.org/10.3390/molecules27165207
45. Delgobo M, Gonçalves RM, Delazeri MA, Falchetti M, Zandoná A, Nascimento das Neves R,

Almeida K, Fagundes AC, Gelain DP, Fracasso JI, Macêdo GB, Priori L, Bassani N, Bishop AJR, Forcelini CM, Moreira JCF, Zanotto-Filho A. Thioredoxin reductase-1 levels are associated with NRF2 pathway activation and tumor recurrence in non-small cell lung cancer. Free Radic Biol Med. 2021 Dec;177:58–71. doi: 10.1016/j.freeradbiomed.2021.10.020. Epub 2021 Oct 19. PMID: 34673143.

46. Dwyer BG, Johnson E, Cazares E, McFarlane Holman KL, Kirk SR. Ruthenium anticancer agent KP1019 binds more tightly than NAMI-A to tRNAPhe. J Inorg Biochem. 2018 May;182:177–183. doi: 10.1016/j.jinorgbio.2018.02.019. Epub 2018 Feb 24. PMID: 29501978.
47. Elie BT, Pechenyy Y, Uddin F, Contel M. A heterometallic ruthenium-gold complex displays antiproliferative, antimigratory, and antiangiogenic properties and inhibits metastasis and angiogenesis-associated proteases in renal cancer. J Biol Inorg Chem. 2018 May;23(3):399–411. doi: 10.1007/s00775–018–1546–8. Epub 2018 Mar 5. PMID: 29508136; PMCID: PMC6173830.
48. Figueroa-DePaz, Y.; Pérez-Villanueva, J.; Soria-Arteche, O.; Martínez-Otero, D.; Gómez-Vidales, V.; Ortiz-Frade, L.; Ruiz-Azuara, L. Casiopeinas of Third Generations: Synthesis, Characterization, Cytotoxic Activity and Structure–Activity Relationships of Mixed Chelate Compounds with Bioactive Secondary Ligands. Molecules 2022, 27, 3504. https://doi.org/10.3390/molecules27113504
49. Guzmán-Méndez Ó, González F, Bernès S, Flores-Álamo M, Ordóñez-Hernández J, García-Ortega H, Guerrero J, Qian W, Aliaga-Alcalde N, Gasque L. Coumarin Derivative Directly Coordinated to Lanthanides Acts as an Excellent Antenna for UV-Vis and Near-IR Emission. Inorg Chem. 2018 Feb 5;57(3):908–911. doi: 10.1021/acs.inorgchem.7b02861. Epub 2018 Jan 8. PMID: 29308891.
50. Annaraj J, Srinivasan S, Ponvel KM, Athappan P. Mixed ligand copper(II) complexes of phenanthroline/bipyridyl and curcumin diketimines as DNA intercalators and their electrochemical behavior under Nafion and clay modified electrodes. J Inorg Biochem. 2005 Mar;99(3):669–76. doi: 10.1016/j.jinorgbio.2004.11.018. Epub 2005 Jan 1. PMID: 15708787.
51. Heffeter P, Atil B, Kryeziu K, Groza D, Koellensperger G, Körner W, Jungwirth U, Mohr T, Keppler BK, Berger W. The ruthenium compound KP1339 potentiates the anticancer activity of sorafenib in vitro and in vivo. Eur J Cancer. 2013 Oct;49(15):3366–75. doi: 10.1016/j.ejca.2013.05.018. Epub 2013 Jun 18. PMID: 23790465; PMCID: PMC3807657.
52. Kydd J, Jadia R, Velpurisiva P, Gad A, Paliwal S, Rai P. Targeting Strategies for the Combination Treatment of Cancer Using Drug Delivery Systems. Pharmaceutics. 2017 Oct 14;9(4):46. doi: 10.3390/pharmaceutics9040046. PMID: 29036899; PMCID: PMC5750652.
53. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016 Jan-Feb;66(1):7-30. doi: 10.3322/caac.21332. Epub 2016 Jan 7. PMID: 26742998.
54. Weinstein, I., Joe, A. Mechanisms of Disease: oncogene addiction—a rationale for molecular targeting in cancer therapy. Nat Rev Clin Oncol 3, 448–457 (2006). https://doi.org/10.1038/ncponc0558
55. Ji W, Sun B, Su C. Targeting MicroRNAs in Cancer Gene Therapy. Genes (Basel). 2017 Jan 9;8(1):21. doi: 10.3390/genes8010021. PMID: 28075356; PMCID: PMC5295016.
56. Xu X, Ho W, Zhang X, Bertrand N, Farokhzad O. Cancer nanomedicine: from targeted delivery to combination therapy. Trends Mol Med. 2015 Apr;21(4):223–32. doi: 10.1016/j.molmed.2015.01.001. Epub 2015 Feb 2. PMID: 25656384; PMCID: PMC4385479.
57. Sudhakar A. History of Cancer, Ancient and Modern Treatment Methods. J Cancer Sci Ther. 2009 Dec 1;1(2):1–4. doi: 10.4172/1948–5956.100000e2. PMID: 20740081.
58. Jahanban-Esfahlan R, Seidi K, Banimohamad-Shotorbani B, Jahanban-Esfahlan A, Yousefi B. Combination of nanotechnology with vascular targeting agents for effective cancer therapy. J Cell Physiol. 2018 Apr;233(4):2982–2992. doi: 10.1002/jcp.26051. Epub 2017 Aug 23. PMID: 28608554.
59. Kydd, J.; Jadia, R.; Velpurisiva, P.; Gad, A.; Paliwal, S.; Rai, P. Targeting Strategies for the Combination Treatment of Cancer Using Drug Delivery Systems. Pharmaceutics 2017, 9, 46. https://doi.org/10.3390/pharmaceutics9040046
60. Golombek SK, May JN, Theek B, Appold L, Drude N, Kiessling F, Lammers T. Tumor targeting

via EPR: Strategies to enhance patient responses. Adv Drug Deliv Rev. 2018 May;130:17–38. doi: 10.1016/j.addr.2018.07.007. Epub 2018 Jul 19. PMID: 30009886; PMCID: PMC6130746.

61. Ertas, Y.N.; Abedi Dorcheh, K.; Akbari, A.; Jabbari, E. Nanoparticles for Targeted Drug Delivery to Cancer Stem Cells: A Review of Recent Advances. Nanomaterials 2021, 11, 1755. https://doi.org/10.3390/nano11071755
62. Dai Y, Xu C, Sun X, Chen X. Nanoparticle design strategies for enhanced anticancer therapy by exploiting the tumour microenvironment. Chem Soc Rev. 2017 Jun 21;46(12):3830–3852. doi: 10.1039/c6cs00592f. Epub 2017 May 18. PMID: 28516983; PMCID: PMC5521825.
63. Swain S, Sahu PK, Beg S, Babu SM. Nanoparticles for Cancer Targeting: Current and Future Directions. Curr Drug Deliv. 2016;13(8):1290–1302. doi: 10.2174/1567201813666160713121122. PMID: 27411485.
64. Yuan D, Zhao Y, Banks WA, Bullock KM, Haney M, Batrakova E, Kabanov AV. Macrophage exosomes as natural nanocarriers for protein delivery to inflamed brain. Biomaterials. 2017 Oct;142:1–12. doi: 10.1016/j.biomaterials.2017.07.011. Epub 2017 Jul 10. PMID: 28715655; PMCID: PMC5603188.
65. Luan X, Sansanaphongpricha K, Myers I, Chen H, Yuan H, Sun D. Engineering exosomes as refined biological nanoplatforms for drug delivery. Acta Pharmacol Sin. 2017 Jun;38(6):754–763. doi: 10.1038/aps.2017.12. Epub 2017 Apr 10. PMID: 28392567; PMCID: PMC5520184.
66. Siafaka PI, Üstündağ Okur N, Karavas E, Bikiaris DN. Surface Modified Multifunctional and Stimuli Responsive Nanoparticles for Drug Targeting: Current Status and Uses. Int J Mol Sci. 2016 Aug 31;17(9):1440. doi: 10.3390/ijms17091440. PMID: 27589733; PMCID: PMC5037719.
67. Shiravand Y, Khodadadi F, Kashani SMA, Hosseini-Fard SR, Hosseini S, Sadeghirad H, Ladwa R, O'Byrne K, Kulasinghe A. Immune Checkpoint Inhibitors in Cancer Therapy. Curr Oncol. 2022 Apr 24;29(5):3044–3060. doi: 10.3390/curroncol29050247. PMID: 35621637; PMCID: PMC9139602.
68. Boros E, Dyson PJ, Gasser G. Classification of Metal-based Drugs According to Their Mechanisms of Action. Chem. 2020 Jan;6(1):41–60. DOI: 10.1016/j.chempr.2019.10.013. PMID: 32864503; PMCID: PMC7451962.
69. Hartinger CG, Jakupec MA, Zorbas-Seifried S, Groessl M, Egger A, Berger W, Zorbas H, Dyson PJ, Keppler BK. KP1019, a new redox-active anticancer agent--preclinical development and results of a clinical phase I study in tumor patients. Chem Biodivers. 2008 Oct;5(10):2140–2155. doi: 10.1002/cbdv.200890195. PMID: 18972504.
70. Savic, Maja, Milovanovic, Marija, Stankovic, Vesna, Mihajlovic, Katarina, Turnic, Tamara Nikolic, Simovic, Ana Rilak, Arsenijevic, Nebojsa and Jakovljevic, Vladimir. "The Antitumor and Toxicity Effects of Ruthenium(II) Complexes on Heterotopic Murine Colon Carcinoma Model" Experimental and Applied Biomedical Research (EABR), vol.0, no.0, 2022, pp.-. https://doi.org/10.2478/sjecr-2022–0028
71. Mestroni G, Alessio E, Sava G, Pacor S, Coluccia M, Boccarelli A. Water-Soluble Ruthenium(III)-Dimethyl Sulfoxide Complexes: Chemical Behaviour and Pharmaceutical Properties. Met Based Drugs. 1994;1(1):41-63. doi: 10.1155/MBD.1994.41. PMID: 18476216; PMCID: PMC2364872.
72. Ravera M, Bagni G, Mascini M, Osella D. DNA-metallodrugs interactions signaled by electrochemical biosensors: an overview. Bioinorg Chem Appl. 2007;2007:91078. doi: 10.1155/2007/91078. PMID: 18354727; PMCID: PMC2266972.
73. Qin QP, Wang ZF, Huang XL, Tan MX, Shi BB, Liang H. High in Vitro and in Vivo Tumor-Selective Novel Ruthenium(II) Complexes with 3-(2'-Benzimidazolyl)-7-fluoro-coumarin. ACS Med Chem Lett. 2019 May 22;10(6):936–940. doi: 10.1021/acsmedchemlett.9b00098. PMID: 31223451; PMCID: PMC6580534.
74. Zhang, X., Cheng, L., Lu, Y. et al. A MXene-Based Bionic Cascaded-Enzyme Nanoreactor for Tumor Phototherapy/Enzyme Dynamic Therapy and Hypoxia-Activated Chemotherapy. Nano-Micro Lett. 14, 22 (2022). https://doi.org/10.1007/s40820–021–00761-w
75. Sava G, Bergamo A. Ruthenium-based compounds and tumour growth control (review). Int J Oncol. 2000 Aug;17(2):353–65. doi: 10.3892/ijo.17.2.353. PMID: 10891547.
76. Tomiris Nabiyeva, Christoph Marschner, Burgert Blom,Synthesis, structure and anti-cancer activity of osmium complexes bearing π-bound arene substituents and phosphane Co-Ligands: A

review,European Journal of Medicinal Chemistry,Volume 201,2020,112483,ISSN 0223–5234, https://doi.org/10.1016/j.ejmech.2020.112483

77. Mohs RC, Greig NH. Drug discovery and development: Role of basic biological research. Alzheimers Dement (N Y). 2017 Nov 11;3(4):651–657. doi: 10.1016/j.trci.2017.10.005. PMID: 29255791; PMCID: PMC5725284.
78. DiMasi JA, Feldman L, Seckler A, Wilson A. Trends in risks associated with new drug development: success rates for investigational drugs. Clin Pharmacol Ther. 2010 Mar;87(3):272–7. doi: 10.1038/clpt.2009.295. Epub 2010 Feb 3. PMID: 20130567.
79. Paul SM, Mytelka DS, Dunwiddie CT, Persinger CC, Munos BH, Lindborg SR, Schacht AL. How to improve R&D productivity: the pharmaceutical industry's grand challenge. Nat Rev Drug Discov. 2010 Mar;9(3):203–14. doi: 10.1038/nrd3078. Epub 2010 Feb 19. PMID: 20168317.
80. Cummings, J.L., Morstorf, T. & Zhong, K. Alzheimer’s disease drug-development pipeline: few candidates, frequent failures. Alz Res Therapy 6, 37 (2014). https://doi.org/10.1186/alzrt269
81. Breijyeh, Z.; Karaman, R. Comprehensive Review on Alzheimer’s Disease: Causes and Treatment. Molecules 2020, 25, 5789. https://doi.org/10.3390/molecules25245789
82. Cook D, Brown D, Alexander R, March R, Morgan P, Satterthwaite G, Pangalos MN. Lessons learned from the fate of AstraZeneca's drug pipeline: a five-dimensional framework. Nat Rev Drug Discov. 2014 Jun;13(6):419–31. doi: 10.1038/nrd4309. Epub 2014 May 16. PMID: 24833294.
83. Owens PK, Raddad E, Miller JW, Stille JR, Olovich KG, Smith NV, Jones RS, Scherer JC. A decade of innovation in pharmaceutical R&D: the Chorus model. Nat Rev Drug Discov. 2015 Jan;14(1):17–28. doi: 10.1038/nrd4497. Epub 2014 Dec 15. PMID: 25503514.
84. Drews J. Drug discovery: a historical perspective. Science. 2000 Mar 17;287(5460):1960–4. doi: 10.1126/science.287.5460.1960. PMID: 10720314.
85. Sams-Dodd F. Target-based drug discovery: is something wrong? Drug Discov Today. 2005 Jan 15;10(2):139–47. doi: 10.1016/S1359–6446(04)03316–1. PMID: 15718163.
86. Begley, C., Ellis, L. Raise standards for preclinical cancer research. Nature 483, 531–533 (2012). https://doi.org/10.1038/483531a
87. Prinz F, Schlange T, Asadullah K. Believe it or not: how much can we rely on published data on potential drug targets? Nat Rev Drug Discov. 2011 Aug 31;10(9):712. doi: 10.1038/nrd3439–c1. PMID: 21892149.
88. Chen J, Luo X, Qiu H, Mackey V, Sun L, Ouyang X. Drug discovery and drug marketing with the critical roles of modern administration. Am J Transl Res. 2018 Dec 15;10(12):4302–4312. PMID: 30662672; PMCID: PMC6325519.
89. Hanif M, Babak MV, Hartinger CG. Development of anticancer agents: wizardry with osmium. Drug Discov Today. 2014 Oct;19(10):1640–8. doi: 10.1016/j.drudis.2014.06.016. Epub 2014 Jun 21. PMID: 24955838.
90. Supramolecular Coordination: Self-Assembly of Finite Two- and Three-Dimensional Ensembles,Rajesh Chakrabarty, Partha Sarathi Mukherjee, and Peter J. Stang,Chemical Reviews 2011 111 (11), 6810-6918 DOI: 10.1021/cr200077m
91. Hearn JM, Romero-Canelón I, Munro AF, Fu Y, Pizarro AM, Garnett MJ, McDermott U, Carragher NO, Sadler PJ. Potent organo-osmium compound shifts metabolism in epithelial ovarian cancer cells. Proc Natl Acad Sci U S A. 2015 Jul 21;112(29):E3800–5. doi: 10.1073/pnas.1500925112. Epub 2015 Jul 10. PMID: 26162681; PMCID: PMC4517206.
92. Marzo, T.; La Mendola, D. Strike a Balance: Between Metals and Non-Metals, Metalloids as a Source of Anti-Infective Agents. Inorganics 2021, 9, 46. https://doi.org/10.3390/inorganics9060046
93. Komeda S, Casini A. Next-generation anticancer metallodrugs. Curr Top Med Chem. 2012;12(3):219-35. doi: 10.2174/156802612799078964. PMID: 22236158.
94. Muhammad N, Guo Z. Metal-based anticancer chemotherapeutic agents. Curr Opin Chem Biol. 2014 Apr;19:144–53. doi: 10.1016/j.cbpa.2014.02.003. Epub 2014 Mar 5. PMID: 24608084.
95. Patra M, Gasser G. Organometallic compounds: an opportunity for chemical biology?

Chembiochem. 2012 Jun 18;13(9):1232–52. doi: 10.1002/cbic.201200159. Epub 2012 May 22. PMID: 22619182.
96. Jia S, Wang R, Wu K, Jiang H, Du Z. Elucidation of the Mechanism of Action for Metal Based Anticancer Drugs by Mass Spectrometry-Based Quantitative Proteomics. Molecules. 2019 Feb 6;24(3):581. doi: 10.3390/molecules24030581. PMID: 30736320; PMCID: PMC6384660.
97. Suntharalingam K, Johnstone TC, Bruno PM, Lin W, Hemann MT, Lippard SJ. Bidentate ligands on osmium(VI) nitrido complexes control intracellular targeting and cell death pathways. J Am Chem Soc. 2013 Sep 25;135(38):14060–3. doi: 10.1021/ja4075375. Epub 2013 Sep 16. PMID: 24041161; PMCID: PMC3791136.
98. Maillet A, Yadav S, Loo YL, Sachaphibulkij K, Pervaiz S. A novel Osmium-based compound targets the mitochondria and triggers ROS-dependent apoptosis in colon carcinoma. Cell Death Dis. 2013 Jun 6;4(6):e653. doi: 10.1038/cddis.2013.185. PMID: 23744353; PMCID: PMC3698552.
99. Ni WX, Man WL, Cheung MT, Sun RW, Shu YL, Lam YW, Che CM, Lau TC. Osmium(VI) complexes as a new class of potential anti-cancer agents. Chem Commun (Camb). 2011 Feb 21;47(7):2140–2. doi: 10.1039/c0cc04515b. Epub 2011 Jan 4. PMID: 21203649.
100. Hildebrandt, J.; Häfner, N.; Kritsch, D.; Görls, H.; Dürst, M.; Runnebaum, I.B.; Weigand, W. Highly Cytotoxic Osmium(II) Compounds and Their Ruthenium(II) Analogues Targeting Ovarian Carcinoma Cell Lines and Evading Cisplatin Resistance Mechanisms. Int. J. Mol. Sci. 2022, 23, 4976. https://doi.org/10.3390/ijms23094976
101. Romero-Canelón I, Sadler PJ. Next-generation metal anticancer complexes: multitargeting via redox modulation. Inorg Chem. 2013 Nov 4;52(21):12276–91. doi: 10.1021/ic400835n. Epub 2013 Jul 23. PMID: 23879584.
102. Fu Y, Habtemariam A, Pizarro AM, van Rijt SH, Healey DJ, Cooper PA, Shnyder SD, Clarkson GJ, Sadler PJ. Organometallic osmium arene complexes with potent cancer cell cytotoxicity. J Med Chem. 2010 Nov 25;53(22):8192–6. doi: 10.1021/jm100560f. Epub 2010 Oct 26. PMID: 20977192.
103. Shnyder SD, et al. Anti-colorectal cancer activity of an organometallic osmium arene azopyridine complex. Med Chem Comm. 2011;2(7):666–668.
104. Coverdale JPC, Guy CS, Bridgewater HE, Needham RJ, Fullam E, Sadler PJ. Osmium-arene complexes with high potency towards Mycobacterium tuberculosis. Metallomics. 2021 Apr 8;13(4):mfab007. doi: 10.1093/mtomcs/mfab007. PMID: 33693931; PMCID: PMC8026400.
105. Chatterjee A, Mambo E, Sidransky D. Mitochondrial DNA mutations in human cancer. Oncogene. 2006 Aug 7;25(34):4663–74. doi: 10.1038/sj.onc.1209604. PMID: 16892080.
106. Calvo SE, Tucker EJ, Compton AG, Kirby DM, Crawford G, Burtt NP, Rivas M, Guiducci C, Bruno DL, Goldberger OA, Redman MC, Wiltshire E, Wilson CJ, Altshuler D, Gabriel SB, Daly MJ, Thorburn DR, Mootha VK. High-throughput, pooled sequencing identifies mutations in NUBPL and FOXRED1 in human complex I deficiency. Nat Genet. 2010 Oct;42(10):851–8. doi: 10.1038/ng.659. Epub 2010 Sep 5. PMID: 20818383; PMCID: PMC2977978.
107. Parrella P, Xiao Y, Fliss M, Sanchez-Cespedes M, Mazzarelli P, Rinaldi M, Nicol T, Gabrielson E, Cuomo C, Cohen D, Pandit S, Spencer M, Rabitti C, Fazio VM, Sidransky D. Detection of mitochondrial DNA mutations in primary breast cancer and fine-needle aspirates. Cancer Res. 2001 Oct 15;61(20):7623–6. PMID: 11606403.
108. Larman TC, DePalma SR, Hadjipanayis AG; Cancer Genome Atlas Research Network; Protopopov A, Zhang J, Gabriel SB, Chin L, Seidman CE, Kucherlapati R, Seidman JG. Spectrum of somatic mitochondrial mutations in five cancers. Proc Natl Acad Sci U S A. 2012 Aug 28;109(35):14087–91. doi: 10.1073/pnas.1211502109. Epub 2012 Aug 13. PMID: 22891333; PMCID: PMC3435197.
109. Guerra F, Perrone AM, Kurelac I, Santini D, Ceccarelli C, Cricca M, Zamagni C, De Iaco P, Gasparre G. Mitochondrial DNA mutation in serous ovarian cancer: implications for mitochondria-coded genes in chemoresistance. J Clin Oncol. 2012 Dec 20;30(36):e373–8. doi: 10.1200/JCO.2012.43.5933. Epub 2012 Nov 13. PMID: 23150702.
110. Aikhionbare FO, Mehrabi S, Thompson W, Yao X, Grizzle W, Partridge E. mtDNA sequence variants in subtypes of epithelial ovarian cancer stages in relation to ethnic and age difference.

Diagn Pathol. 2008 Jul 28;3:32. doi: 10.1186/1746–1596–3–32. PMID: 18662401; PMCID: PMC2494992.
111. Van Trappen PO, Cullup T, Troke R, Swann D, Shepherd JH, Jacobs IJ, Gayther SA, Mein CA. Somatic mitochondrial DNA mutations in primary and metastatic ovarian cancer. Gynecol Oncol. 2007 Jan;104(1):129–33. doi: 10.1016/j.ygyno.2006.07.010. Epub 2006 Aug 30. PMID: 16942794.
112. Katoh Y, Itoh K, Yoshida E, Miyagishi M, Fukamizu A, Yamamoto M. Two domains of Nrf2 cooperatively bind CBP, a CREB binding protein, and synergistically activate transcription. Genes Cells. 2001 Oct;6(10):857–68. doi: 10.1046/j.1365–2443.2001.00469.x. PMID: 11683914.
113. Zhu M, Li W, Lu C. Role of alpha-synuclein protein levels in mitochondrial morphology and cell survival in cell lines. PLoS One. 2012;7(4):e36377. doi: 10.1371/journal.pone.0036377. Epub 2012 Apr 27. PMID: 22558453; PMCID: PMC3338674.
114. Menazza S, Blaauw B, Tiepolo T, Toniolo L, Braghetta P, Spolaore B, Reggiani C, Di Lisa F, Bonaldo P, Canton M. Oxidative stress by monoamine oxidases is causally involved in myofiber damage in muscular dystrophy. Hum Mol Genet. 2010 Nov 1;19(21):4207-15. doi: 10.1093/hmg/ddq339. Epub 2010 Aug 17. PMID: 20716577.
115. Devine MJ, Plun-Favreau H, Wood NW. Parkinson's disease and cancer: two wars, one front. Nat Rev Cancer. 2011 Oct 24;11(11):812–23. doi: 10.1038/nrc3150. PMID: 22020207.
116. Dalla Pozza E, Fiorini C, Dando I, Menegazzi M, Sgarbossa A, Costanzo C, Palmieri M, Donadelli M. Role of mitochondrial uncoupling protein 2 in cancer cell resistance to gemcitabine. Biochim Biophys Acta. 2012 Oct;1823(10):1856–63. doi: 10.1016/j.bbamcr.2012.06.007. Epub 2012 Jun 15. PMID: 22705884.
117. Pawlak M, Schick E, Bopp MA, Schneider MJ, Oroszlan P, Ehrat M. Zeptosens' protein microarrays: a novel high performance microarray platform for low abundance protein analysis. Proteomics. 2002 Apr;2(4):383–93. doi: 10.1002/1615–9861(200204)2:4<383::AID-PROT383>3.0.CO;2-E. PMID: 12164697.
118. Ashwell S, Zabludoff S. DNA damage detection and repair pathways--recent advances with inhibitors of checkpoint kinases in cancer therapy. Clin Cancer Res. 2008 Jul 1;14(13):4032–7. doi: 10.1158/1078–0432.CCR–07–5138. PMID: 18593978.
119. Pucci C, Martinelli C, Ciofani G. Innovative approaches for cancer treatment: current perspectives and new challenges. Ecancermedicalscience. 2019;13:961. doi: 10.3332/ecancer.2019.961. PMID: 31537986; PMCID: PMC6753017.
120. Unger JM, Cook E, Tai E, Bleyer A. The Role of Clinical Trial Participation in Cancer Research: Barriers, Evidence, and Strategies. Am Soc Clin Oncol Educ Book. 2016;35:185-98. doi: 10.1200/EDBK_156686. PMID: 27249699; PMCID: PMC5495113.
121. Mühlgassner G, Bartel C, Schmid WF, Jakupec MA, Arion VB, Keppler BK. Biological activity of ruthenium and osmium arene complexes with modified paullones in human cancer cells. J Inorg Biochem. 2012 Nov;116(5):180–7. doi: 10.1016/j.jinorgbio.2012.06.003. Epub 2012 Jun 13. PMID: 23037896; PMCID: PMC3492762.
122. Gaiddon, C.; Gross, I.; Meng, X.; Sidhoum, M.; Mellitzer, G.; Romain, B.; Delhorme, J.-B.; Venkatasamy, A.; Jung, A.C.; Pfeffer, M. Bypassing the Resistance Mechanisms of the Tumor Ecosystem by Targeting the Endoplasmic Reticulum Stress Pathway Using Ruthenium- and Osmium-Based Organometallic Compounds: An Exciting Long-Term Collaboration with Dr. Michel Pfeffer. Molecules 2021, 26, 5386. https://doi.org/10.3390/molecules26175386
123. Coverdale JPC, Guy CS, Bridgewater HE, Needham RJ, Fullam E, Sadler PJ. Osmium-arene complexes with high potency towards Mycobacterium tuberculosis. Metallomics. 2021 Apr 8;13(4):mfab007. doi: 10.1093/mtomcs/mfab007. PMID: 33693931; PMCID: PMC8026400.
124. Nabiyeva T, Roufosse B, Odachowski M, Baumgartner J, Marschner C, Verma AK, Blom B. Osmium Arene Germyl, Stannyl, Germanate, and Stannate Complexes as Anticancer Agents. ACS Omega. 2021 Jul 12;6(29):19252–19268. doi: 10.1021/acsomega.1c02665. PMID: 34337263; PMCID: PMC8320079.

125. Crochet, P.; Cadierno, V. Arene-Osmium(II) Complexes in Homogeneous Catalysis. Inorganics 2021, 9, 55. https://doi.org/10.3390/inorganics9070055
126. van Rijt SH, Peacock AF, Johnstone RD, Parsons S, Sadler PJ. Organometallic osmium(II) arene anticancer complexes containing picolinate derivatives. Inorg Chem. 2009 Feb 16;48(4):1753–62. doi: 10.1021/ic8020222. PMID: 19146436.
127. Giorgi, E.; Binacchi, F.; Marotta, C.; Cirri, D.; Gabbiani, C.; Pratesi, A. Highlights of New Strategies to Increase the Efficacy of Transition Metal Complexes for Cancer Treatments. Molecules 2023, 28, 273. https://doi.org/10.3390/molecules28010273
128. Dragutan, I.; Dragutan, V.; Demonceau, A. Editorial of Special Issue Ruthenium Complex: The Expanding Chemistry of the Ruthenium Complexes. Molecules 2015, 20, 17244–17274. https://doi.org/10.3390/molecules200917244
129. Ma, D.-L.; Wu, C.; Wu, K.-J.; Leung, C.-H. Iridium(III) Complexes Targeting Apoptotic Cell Death in Cancer Cells. Molecules 2019, 24, 2739. https://doi.org/10.3390/molecules24152739
130. Ioele G, Chieffallo M, Occhiuzzi MA, De Luca M, Garofalo A, Ragno G, Grande F. Anticancer Drugs: Recent Strategies to Improve Stability Profile, Pharmacokinetic and Pharmacodynamic Properties. Molecules. 2022 Aug 25;27(17):5436. doi: 10.3390/molecules27175436. PMID: 36080203; PMCID: PMC9457551.
131. Zhu, T., Sha, Y., Yan, J. et al. Metallo-polyelectrolytes as a class of ionic macromolecules for functional materials. Nat Commun 9, 4329 (2018). https://doi.org/10.1038/s41467–018–06475–9
132. Huang C, Huang W, Ji P, Song F, Liu T, Li M, Guo H, Huang Y, Yu C, Wang C, Ni W. A Pyrazolate Osmium(VI) Nitride Exhibits Anticancer Activity through Modulating Protein Homeostasis in HepG2 Cells. Int J Mol Sci. 2022 Oct 24;23(21):12779. doi: 10.3390/ijms232112779. PMID: 36361570; PMCID: PMC9656236.
133. Saptarshi SR, Duschl A, Lopata AL. Interaction of nanoparticles with proteins: relation to bio-reactivity of the nanoparticle. J Nanobiotechnology. 2013 Jul 19;11:26. doi: 10.1186/1477–3155–11–26. PMID: 23870291; PMCID: PMC3720198.
134. Hildebrandt J, Häfner N, Kritsch D, Görls H, Dürst M, Runnebaum IB, Weigand W. Highly Cytotoxic Osmium(II) Compounds and Their Ruthenium(II) Analogues Targeting Ovarian Carcinoma Cell Lines and Evading Cisplatin Resistance Mechanisms. Int J Mol Sci. 2022 Apr 29;23(9):4976. doi: 10.3390/ijms23094976. PMID: 35563367; PMCID: PMC9102668.
135. Monro S, Colón KL, Yin H, Roque J 3rd, Konda P, Gujar S, Thummel RP, Lilge L, Cameron CG, McFarland SA. Transition Metal Complexes and Photodynamic Therapy from a Tumor-Centered Approach: Challenges, Opportunities, and Highlights from the Development of TLD1433. Chem Rev. 2019 Jan 23;119(2):797–828. doi: 10.1021/acs.chemrev.8b00211. Epub 2018 Oct 8. PMID: 30295467; PMCID: PMC6453754.
136. Sonkar C, Sarkar S, Mukhopadhyay S. Ruthenium(ii)-arene complexes as anti-metastatic agents, and related techniques. RSC Med Chem. 2021 Sep 15;13(1):22–38. doi: 10.1039/d1md00220a. PMID: 35224494; PMCID: PMC8792825.
137. Muralisankar, M.; Chen, J.-R.; Haribabu, J.; Ke, S.-C. Effective and Selective Ru(II)-Arene Complexes Containing 4,4′-Substituted 2,2′ Bipyridine Ligands Targeting Human Urinary Bladder Cancer Cells. Int. J. Mol. Sci. 2023, 24, 11896. https://doi.org/10.3390/ijms241511896
138. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics, 2021. CA Cancer J Clin. 2021 Jan;71(1):7–33. doi: 10.3322/caac.21654. Epub 2021 Jan 12. Erratum in: CA Cancer J Clin. 2021 Jul;71(4):359. PMID: 33433946.
139. Feldman DR, Bosl GJ, Sheinfeld J, Motzer RJ. Medical treatment of advanced testicular cancer. JAMA. 2008 Feb 13;299(6):672–84. doi: 10.1001/jama.299.6.672. PMID: 18270356.
140. Dasari S, Tchounwou PB. Cisplatin in cancer therapy: molecular mechanisms of action. Eur J Pharmacol. 2014 Oct 5;740:364–78. doi: 10.1016/j.ejphar.2014.07.025. Epub 2014 Jul 21. PMID: 25058905; PMCID: PMC4146684.
141. Sharma P, Jhawat V, Mathur P, Dutt R. Innovation in cancer therapeutics and regulatory perspectives. Med Oncol. 2022 Feb 23;39(5):76. doi: 10.1007/s12032–022–01677–0. PMID: 35195787; PMCID: PMC8863908.
142. Waldman, A.D., Fritz, J.M. & Lenardo, M.J. A guide to cancer immunotherapy: from T cell basic

science to clinical practice. Nat Rev Immunol 20, 651–668 (2020). https://doi.org/10.1038/s41577–020–0306–5
143. Cervinka J, Gobbo A, Biancalana L, Markova L, Novohradsky V, Guelfi M, Zacchini S, Kasparkova J, Brabec V, Marchetti F. Ruthenium(II)-Tris-pyrazolylmethane Complexes Inhibit Cancer Cell Growth by Disrupting Mitochondrial Calcium Homeostasis. J Med Chem. 2022 Aug 11;65(15):10567–10587. doi: 10.1021/acs.jmedchem.2c00722. Epub 2022 Aug 1. PMID: 35913426; PMCID: PMC9376960.
144. Qin QP, Wang ZF, Huang XL, Tan MX, Shi BB, Liang H. High in Vitro and in Vivo Tumor-Selective Novel Ruthenium(II) Complexes with 3–(2'-Benzimidazolyl)-7-fluoro-coumarin. ACS Med Chem Lett. 2019 May 22;10(6):936-940. doi: 10.1021/acsmedchemlett.9b00098. PMID: 31223451; PMCID: PMC6580534.
145. Legina, M.S., Nogueira, J.J., Kandioller, W. et al. Biological evaluation of novel thiomaltol-based organometallic complexes as topoisomerase IIα inhibitors. J Biol Inorg Chem 25, 451–465 (2020). https://doi.org/10.1007/s00775–020–01775–2
146. Maillet, A., Yadav, S., Loo, Y. et al. A novel Osmium-based compound targets the mitochondria and triggers ROS-dependent apoptosis in colon carcinoma. Cell Death Dis 4, e653 (2013). https://doi.org/10.1038/cddis.2013.185
147. Domenichini, A., Casari, I., Simpson, P.V. et al. Rhenium N-heterocyclic carbene complexes block growth of aggressive cancers by inhibiting FGFR- and SRC-mediated signalling. J Exp Clin Cancer Res 39, 276 (2020). https://doi.org/10.1186/s13046–020–01777–7
148. Bridgewater, H.E., Bolitho, E.M., Romero-Canelón, I. et al. Targeting cancer lactate metabolism with synergistic combinations of synthetic catalysts and monocarboxylate transporter inhibitors. J Biol Inorg Chem 28, 345–353 (2023). https://doi.org/10.1007/s00775–023–01994–3
149. Ma, D.-L.; Wu, C.; Cheng, S.-S.; Lee, F.-W.; Han, Q.-B.; Leung, C.-H. Development of Natural Product-Conjugated Metal Complexes as Cancer Therapies. Int. J. Mol. Sci. 2019, 20, 341. https://doi.org/10.3390/ijms20020341
150. Huang, Y.; Li, X.; Zhang, Z.; Xiong, L.; Wang, Y.; Wen, Y. Photodynamic Therapy Combined with Ferroptosis Is a Synergistic Antitumor Therapy Strategy. Cancers 2023, 15, 5043. https://doi.org/10.3390/cancers15205043
151. National Research Council (US) Committee on Prudent Practices in the Laboratory. Prudent Practices in the Laboratory: Handling and Management of Chemical Hazards: Updated Version. Washington (DC): National Academies Press (US); 2011. 4, Evaluating Hazards and Assessing Risks in the Laboratory. Available from: https://www.ncbi.nlm.nih.gov/books/NBK55880/
152. Yao Y, Zhou Y, Liu L, Xu Y, Chen Q, Wang Y, Wu S, Deng Y, Zhang J, Shao A. Nanoparticle-Based Drug Delivery in Cancer Therapy and Its Role in Overcoming Drug Resistance. Front Mol Biosci. 2020 Aug 20;7:193. doi: 10.3389/fmolb.2020.00193. PMID: 32974385; PMCID: PMC7468194.
153. Din FU, Aman W, Ullah I, Qureshi OS, Mustapha O, Shafique S, Zeb A. Effective use of nanocarriers as drug delivery systems for the treatment of selected tumors. Int J Nanomedicine. 2017 Oct 5;12:7291–7309. doi: 10.2147/IJN.S146315. PMID: 29042776; PMCID: PMC5634382.
154. Díaz, M.R.; Vivas-Mejia, P.E. Nanoparticles as Drug Delivery Systems in Cancer Medicine: Emphasis on RNAi-Containing Nanoliposomes. Pharmaceuticals 2013, 6, 1361–1380. https://doi.org/10.3390/ph6111361
155. Cheng, Z., Li, M., Dey, R. et al. Nanomaterials for cancer therapy: current progress and perspectives. J Hematol Oncol 14, 85 (2021). https://doi.org/10.1186/s13045–021–01096–0
156. Cook N, Hansen AR, Siu LL, Abdul Razak AR. Early phase clinical trials to identify optimal dosing and safety. Mol Oncol. 2015 May;9(5):997–1007. doi: 10.1016/j.molonc.2014.07.025. Epub 2014 Aug 14. PMID: 25160636; PMCID: PMC4329110.
157. Bhatt A. Evolution of clinical research: a history before and beyond james lind. Perspect Clin Res. 2010 Jan;1(1):6–10. PMID: 21829774; PMCID: PMC3149409.
158. ROSENBERG, B., VAN CAMP, L. & KRIGAS, T. Inhibition of Cell Division in Escherichia coli

by Electrolysis Products from a Platinum Electrode. Nature 205, 698–699 (1965). https://doi.org/10.1038/205698a0
159. Housman G, Byler S, Heerboth S, Lapinska K, Longacre M, Snyder N, Sarkar S. Drug resistance in cancer: an overview. Cancers (Basel). 2014 Sep 5;6(3):1769–92. doi: 10.3390/cancers6031769. PMID: 25198391; PMCID: PMC4190567.
160. Ruth Nussinov, Chung-Jung Tsai, Hyunbum Jang,Anticancer drug resistance: An update and perspective,Drug Resistance Updates,Volume 59,2021,100796,ISSN 1368–7646, https://doi.org/10.1016/j.drup.2021.100796
161. Moahamed Sikkander A, Manisankar P , Vedhi C Utilization of sodium montmorillonite clay for enhanced electrochemical sensing of amlodipine,Indian Journal of Chemistry-Section A(IJCA) 55 (5), 571-575DOI: 10.56042/ijca.v55i5.11669
162. 162. Sivakumar ,R GopalakrishnanP, Abdul RazakMS,Comparative analysis of anti-reflection coatings on solar PV cells through TiO_2 and SiO_2 nanoparticles,Pigment & Resin Technology 51 (2), 171–177.https://doi.org/10.1108/PRT-08–2020–0084
163. Mohamed Sikkander A, Nasri NS., Review on Inorganic Nano crystals unique benchmark of Nanotechnology,Moroccan Journal of Chemistry 1 (2), 1–2 (2013) 47–54.https://doi.org/10.48317/IMIST.PRSM/morjchem-v1i2.1892
164. Mohamed Sikkander A., Bassyouni F, Yasmeen K, Mishra S.R, Lakshmi V.V. Synthesis of Zinc Oxide and Lead Nitrate Nanoparticles and their Applications: Comparative Studies of Bacterial and Fungal (E. coli, A. Niger). J. Appl. Organomet. Chem., 2023, 3(4), 255–267. https://doi.org/10.48309/JAOC.2023.415886.1115

