

# Recent developments in the nanostructured materials functionalized with ruthenium complexes for targeted drug delivery to tumors

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**Abstract:** In recent years, the field of metal-based drugs has been dominated by other existing precious metal drugs, and many researchers have focused their attention on the synthesis of various ruthenium (Ru) complexes due to their potential medical and pharmaceutical applications. The beneficial properties of Ru, which make it a highly promising therapeutic agent, include its variable oxidation states, low toxicity, high selectivity for diseased cells, ligand exchange properties, and the ability to mimic iron binding to biomolecules. In addition, Ru complexes have favorable adsorption properties, along with excellent photochemical and photophysical properties, which make them promising tools for photodynamic therapy. At present, nanostructured materials functionalized with Ru complexes have become an efficient way to administer Ru-based anticancer drugs for cancer treatment. In this review, the recent developments in the nanostructured materials functionalized with Ru complexes for targeted drug delivery to tumors are discussed. In addition, information on “traditional” (ie, non-nanostructured) Ru-based cancer therapies is included in a precise manner.

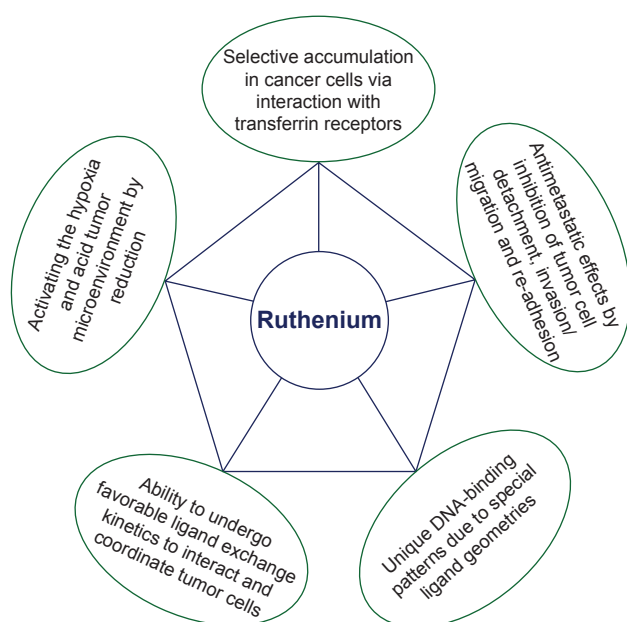
**Keywords:** metallodrugs, nanotechnology, cancer treatment, cell apoptosis, DNA damage, toxicity

## Introduction

Among the currently investigated metal-based chemotherapeutic agents, ruthenium (Ru) and its compounds hold a promising future as these compounds exhibit different oxidation states and lower toxicity compared to other metal-based drugs.<sup>1</sup> In general, Ru compounds with oxidation states II and III have potential applications in the field of medicine, particularly as chemotherapeutic agents for various cancers.<sup>2</sup> As illustrated in Figure 1, Ru possesses unique properties that make it an attractive anticancer chemotherapeutic agent. In addition, Ru forms various structural dimensions when combined with other compounds, and these combined compounds exhibit various modes of action such as interaction with DNA and activation of DNA damage mechanisms, as well as inhibition of the activities of several enzymes, including extracellular metalloproteases.<sup>3</sup> The relationship between function and composition of Ru complexes is summarized in Table 1.

Therefore, Ru complexes are considered more efficient, less toxic, and target-specific noncovalent DNA-binding anticancer drugs.<sup>4</sup> Another property of Ru compounds that makes them ideal candidates for medicinal applications is their ability to mimic iron binding to certain biomolecules such as serum transferrin and albumin, which are utilized by mammals to solubilize and transport iron, thus reducing cellular toxicity.<sup>4,5</sup>

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**Figure 1** Properties of ruthenium that make it an attractive chemotherapeutic agent.

In vivo studies demonstrated that rapidly multiplying cells have increased number of transferrin receptors to sequester more metal-loaded transferrin, thus attracting more Ru.<sup>5,6</sup> There is confirmation to suggest that Ru complexes might directly interfere with specific proteins involved in signal transduction pathways, compared to any other metal complexes including iron complexes, and alter cell adhesion and migration processes.<sup>7</sup> In addition, the redox potential between the different oxidation states of Ru facilitates the body to catalyze oxidation and reduction reactions depending on the physiological environment. Among the other metal complexes, Ru complexes have different geometries, which allow for the design of compounds with a specific cellular target.<sup>8</sup> The rigid and well-defined spatial arrangement of a series of Ru complexes has enabled the preparation of highly

potent and selective enzyme inhibitors, which is a very helpful characteristic feature in cancer therapy. Moreover, the investigations of Ru complexes in clinical trials attest to the possibility of utilizing non-platinum metal-based compounds in the treatment of cancer.<sup>4-6</sup>

Because of these unique properties, Ru is the most promising metal to replace platinum in future medicinal and pharmaceutical applications. However, application of these drugs in cancer treatment has been hampered by the low transport efficiency of their active species to biological targets. This has led to the design and development of new technologies based on nanostructured materials. The nanostructured materials generally act as vectors for metallo-drug delivery or simply as protectors of active species of the complexes to enhance their activities and reduce their degradation.<sup>9</sup> This review focuses on the recent developments in the nanostructured materials functionalized with Ru complexes for tumor-targeted drug delivery.

## Ru complexes and their recent applications in cancer treatment

Cancer is one of the leading causes of death in the world and is becoming an important topic in scientific research. Cancer cells accumulate multiple mutations that confer them a selective growth advantage over other cells, causing them to grow uncontrollably, become invasive, and eventually spread to other parts of the body. In addition, cancer cells typically exhibit aberrations in signaling pathways that regulate various cellular processes, such as cell growth and division, and cell-to-cell communication.<sup>10</sup> Therefore, the genetic and phenotypic heterogeneities of cancer cells make cancer a disease that is difficult to treat. Among the effective anticancer treatments, transition metal complexes play important roles in all living systems and have various

**Table 1** Relationship between composition of Ruthenium (Ru) complexes and their functions

Serial number	Composition of Ru complexes	Function
1	Ru surrounded by Lewis bases with lone pairs	These compounds have some ligands that can be hydrolyzed and therefore help to reach cancerous cells
2	Ru organometallics	These complexes have displayed high water and air stability and an interesting spectrum of anticancer activity
3	Ru platinum mixed-metal compounds	These complexes have the potential of combined efficiency of mechanisms and therefore have higher selectivity against both neoplastic tumors and metastatic cancer
4	Ru cluster complexes	These clusters are known to form supramolecular interactions with arenes and other functions; such interactions are important with respect to their mode of biological activity
5	Ru DNA intercalators	These complexes exhibit a high cytotoxicity due to the two <i>cis</i> chloride ligands, which might be exchanged for biological targets as DNA
6	Ru linked with organic directing molecule	These complexes help to bind Ru directly to the cellular target, which could massively increase the potency of the drug

therapeutic applications.<sup>11</sup> These metals form positively charged ions in aqueous solution that can bind to negatively charged biological molecules. Consequently, the charge can be modified depending on the coordination surroundings involved, leading to the generation of a species that can be anionic, cationic, or neutral. In addition, metal ions with high affinity for electrons can polarize groups that are coordinated to them, fostering the generation of hydrolysis reactions.<sup>12</sup> The oxidation state of a metal is also an imperative consideration in the design of coordination compounds, as it allows the participation in biological redox chemistry and plays a crucial role in determining the optimal dose and bioavailability of the agent administered.<sup>13</sup> Furthermore, transition metals can undergo ligand exchange reaction, and this property allows them to interact with and coordinate to biological molecules.

Among the transition metal complexes, Ru-based complexes are regarded as highly promising drug candidates. Therefore, the field of coordination and organometallic chemistry of Ru has expanded considerably over the past few years.<sup>14,15</sup> As previously discussed, the unique properties of Ru-based complexes, including their high ability to bind nucleic acids and proteins and undergo ligand exchange reaction, the prevalence of the two main oxidation states, Ru(II) and Ru(III), as well as the iron-mimicking property when bound to biological molecules have made them potential drug candidates for various medical applications.<sup>16</sup> In addition, these complexes have reduced toxicity and can be well tolerated *in vivo*.<sup>17</sup> Studies have also shown that most Ru complexes have low systemic toxicity, exhibit slow ligand exchange rates similar to that of platinum compounds, and can accumulate in cancer cells more effectively than platinum. The anticancer mechanisms of Ru complexes have been extensively investigated as illustrated in Table 2. The various mechanisms that mediate the anticancer activities of Ru complexes include inhibition of topoisomerase activity, inhibition of metastasis, production of reactive oxygen species (ROS), interaction with proteins and DNA, as well as induction of apoptosis. In addition, the anticancer effects of Ru complexes depend largely on the ligand involved, characteristics of the complexes, and the presence of uncoordinated sites in the coordination sphere of the metal center.<sup>7,18</sup> As such, much effort has been directed toward exploring the tumor-inhibiting properties of various Ru complexes.<sup>18</sup> As listed in Table 2, although a large number of Ru complexes have shown great promise as potential antitumor agents, only three complexes, NAMI-A, KP1019, and NKP1339 (Table 3), have entered clinical trials.<sup>16,19,20</sup> Clinically, all the three complexes

exhibited promising anticancer activities with minimal side effects; an ideal property of a good anticancer drug (Table 3). In addition, these complexes have octahedral coordination geometry with respect to the Ru(III) metal center; however, they exhibit different biological activities despite their structural and chemical similarities.<sup>19</sup>

Recently, 2,2,6,6-tetramethylpiperidine-1-oxyl radical (TEMPO)-functionalized Ru(II) polypyridyl complexes were screened for their efficiency as theranostic photosensitizers for cancer treatment.<sup>21</sup> The presence of a redox-sensitive TEMPO moiety enhanced the intracellular fluorescence of TEMPO-functionalized Ru(II) complexes in photodynamic treatment, which was observed using confocal microscopy and flow cytometry. Hence, the combination of TEMPO with photosensitizers is a promising strategy for the development of novel photosensitizer-based theranostic platforms, which can induce and monitor photodynamic therapy responses simultaneously. In another study, Gill et al demonstrated that the Ru(II) polypyridyl complex  $[\text{Ru}(\text{dppz})_2(\text{PIP})]^{2+}$  intercalates DNA and acts to stall replication fork progression in human cancer cells, leading to the activation of DNA replication stress signaling responses and inhibition of cell growth by cell-cycle deregulation. Combination of the Ru complex with a pathway-specific DNA damage response inhibitor resulted in synergistic cancer cell killing. In addition, the Ru complex functions as a radiosensitizer in combination with external beam ionizing radiation. These findings indicate that Ru polypyridyl complexes (RuPOPs) are useful tools to study the molecular consequences of DNA intercalation. Hence, the potential benefits and application of these complexes in combination therapy for cancer treatment warrants further investigation.<sup>22</sup>

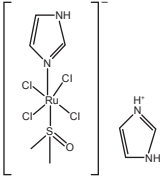
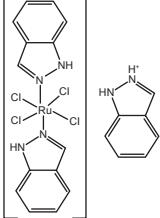
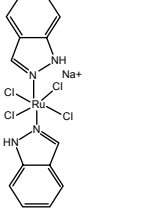
Recently, Koceva-Chyla et al evaluated the *in vitro* anticancer activity of dinuclear trithiolato-bridged arene ruthenium complex diruthenium-1 (DiRu-1) against a panel of human cancer cell lines including HepG2 (hepatocellular carcinoma), MCF-7 (estrogen-responsive breast adenocarcinoma), and MDA-MB-231 (triple-negative breast adenocarcinoma) cells. DiRu-1 was found to be extremely toxic to these cell lines, with half-maximal inhibitory concentration ( $\text{IC}_{50}$ ) values in the low-nanomolar range. The cytotoxic and proapoptotic effects of DiRu-1 were attributed to the increase in intracellular levels of ROS, while the anticancer effect was due to the induction of DNA lesions caused by apoptotic DNA fragmentation and cell-cycle arrest at the  $\text{G}_2/\text{M}$  checkpoint.<sup>23</sup> In summary, the diverse modes of action of Ru anticancer drugs likely enhanced their anticancer activities and minimized the potential for cancer cells to

**Table 2** Recent studies on the anticancer mechanisms of various ruthenium (Ru) complexes

Serial number	Complex	Mechanism(s) involved	References
1	Ru(II) polypyridyl complexes; Ru trithiolato complexes; Ru anthraquinone complexes; [Ru(gly)(bipy)(dppb)]PF <sub>6</sub> complex; Ru ketoconazole and letrazole complexes; Ru sulfoxide complexes; indazole Ru complexes	Cell-cycle arrest/cell apoptosis/DNA damage	16,17,20,41–44
2	Ru polypyridyl complexes; cyclopentadienyl Ru complexes; Ru hydrazine complexes	Cell apoptosis through ROS-mediated mitochondrial dysfunction/cell-cycle arrest/ DNA damage	40,45,46
3	Ru(II) complexes: [Ru(dtzp)(dppz)Cl] <sup>+</sup> and [Ru(dtzp)(dppz)CH <sub>3</sub> CN] <sup>2+</sup> ; Ru phthalocyanine complexes	Photocytotoxic/cell proliferation/cell apoptosis	47–49
4	Ru arene complexes	Interaction with DNA via intercalation of the aromatic ligand between base pairs	50
5	Ru nitrosyl complexes	Nitric oxide release mediated by redox reaction	51
6	Ru carbene complexes	Transmembrane carrier/DNA damage	52
7	Thiazolo arene Ru complex; Ru bistridentate complexes; Ru carbonyl complexes; Ru pyrazole complexes; Ru half sandwich complexes; Ru terpyridine complexes; Ru bridged complexes; Ru pterin complexes; cyclometalated Ru complexes; Ru sandwich complexes; Ru–letrazole complexes; Bis(allyl)–Ru complexes; dihydro phenazine Ru complexes; Ru curcuminoid complexes	Cell proliferation/cell apoptosis/DNA damage	1,20,45,53–67
8	Dinuclear Ru complexes	Cytoplasmic membrane damage	68
9	Ru chalcone complexes	DNA fragmentation/cell-cycle arrest	69
10	Ru carboline complexes	Cell proliferation/mitochondrial pathway dysfunction/inhibition of CDK I and CYCLIN B1/ROS generation/cell-cycle arrest	70,71
11	Ru arene Schiff base complexes	Apoptosis via induction of p53-independent mechanism	72
12	Ru pyridine complexes	Induction of apoptosis via suppression of vascular endothelial growth factor, metalloproteinases 2 and 9 (MMP-2 and -9)	73
13	Ru polypyridine complexes	ROS-induced cell death/DNA damage	74
14	Ru quinaldamide complexes	Inhibition of thioredoxin reductase I (Trx-R)- induced cell death/cell apoptosis	75
15	Ru N-heterocyclic carbene complexes	Induction of cell death via activation of apoptosis signal-regulating kinase I pathway/inhibition of Trx-R-induced cell death	76
16	Ru arene Schiff base and Ru–aniline complexes	Apoptosis via induction of p53-independent mechanism and suppression of vascular endothelial growth factor	72,77,78
17	Chiral Ru complexes	Inhibition of topoisomerase-II/DNA damage	79
18	Diene Ru complexes	Mitochondrial pathway dysfunction/cell apoptosis	80
19	Bidentate Schiff base Ru complexes	DNA cleavage/DNA damage	81
20	Flavanol-derived ligand Ru complexes; Ru(II)–DMSO–chalcone complexes	Inhibition of topoisomerase II and CDK2/DNA damage/cell proliferation	82–84
21	Di- and tricarbonyl Ru complexes	Cell proliferation/cell apoptosis	85

**Abbreviations:** DMSO, Dimethyl sulfoxide; ROS, reactive oxygen species.

**Table 3** Antitumor mechanisms of ruthenium (Ru) complexes which are under Phase II clinical trials

Serial number	Ru complex	Chemical structure	Mechanism involved	References
1	NAMI-A (imidazolium [trans-tetrachloro(DMSO)(imidazole) ruthenate(III)])		Interferes with the interaction between tumor cells and the extracellular matrix by increasing actin-dependent cell adhesion and reducing cell invasiveness and migration	86,87
2	KPI019 (indazolium [trans-tetrachlorobis(1H-indazole) ruthenate(III)])		Disruption of the cellular redox balance, followed by induction of G <sub>2</sub> /M cell-cycle arrest, blockage of DNA synthesis, and induction of apoptosis via the mitochondrial pathway	88
3	NPK-1339 (sodium trans-[tetrachloridobis(1H-indazole) ruthenate(III)])		Disruption of the cellular redox balance, followed by induction of G <sub>2</sub> /M cell-cycle arrest, blockage of DNA synthesis, and induction of apoptosis via the mitochondrial pathway	89

develop resistance against these drugs.<sup>24</sup> Novel approaches to metabolic studies are required to give additional mechanistic insights, which could lead to the rational design of better Ru anticancer drugs.

Despite solving many key issues encountered with conventional anticancer therapies such as chemotherapy, systemic delivery of nanoparticles faces several of its own challenges, one of which is the lack of successful tumor localization. Among the various strategies, nanostructured materials functionalized with metal complexes have attracted the most interest among oncologists and medicinal chemists as a better alternative for administration of metallodrugs in targeted anticancer therapy.<sup>9</sup> In addition, the encapsulation and delivery of metallodrugs in nanostructures have overcome the problems of poor bioavailability, degradation, and side effects.<sup>25</sup>

## Importance of nanostructured materials functionalized with metal complexes in cancer treatment

Nanotechnology currently allows for a unique control of the material world, and any material comprising an average phase or grain size in the order of a nanometer ( $10^{-9}$  m) is defined as a nanostructured material. At this scale, man-made objects are able to gain access to cells as nanostructured materials have enhanced mechanical properties compared to conventional

materials due to their ultrafine microstructure and ability to interface with living cells. Nanostructured materials of varying compositions play important roles in cancer therapeutics due to their passive tumor targeting property.<sup>26,27</sup> In this context, inorganic metal complexes occupy a pioneer niche as they offer a multipurpose platform for drug design and development, and the nanostructures used in the functionalization of metallodrugs act as transport vehicles to deliver the metallodrugs to the biological target. Nanostructured systems, such as macromolecular systems, carbon nanotubes, dendrimers, metallacages, ceramic materials, liposomes, and lipid nanocapsules, as well as metal and polymeric nanoparticles are commonly used for drug delivery. In addition, the optimum loading and sustained release of metallodrugs from nanostructures are essential requirements for every drug delivery system. Therefore, it is important to ensure that metallodrugs are attached to the surface of nanoparticles with adequate strength to withstand the wear and tear during the passage to the target site. However, it is also crucial to ensure that the bond is weak enough to release the metallodrugs at the target site.<sup>9</sup>

In a study conducted by Wu et al, gold nanoparticles (AuNPs) were shown to be efficient carriers for small interfering RNA (siRNA) delivery into cancer cells. In this study, cysteamine-functionalized AuNPs were found to effectively deliver transforming growth factor beta 1 (TGF- $\beta$ 1) siRNA

into hepatoma HepG2 cells, and compared with AuNP-mediated nano carrier (NC) siRNA (AuNP-siNC), AuNP-delivered TGF- $\beta$ 1 siRNA (AuNP-siTGF $\beta$ 1) successfully decreased the level of TGF- $\beta$ 1, increased cell apoptosis, and significantly inhibited the proliferation of recipient tumor cells. Likewise, systemic administration of AuNP-siTGF $\beta$ 1 complexes into human HepG2 xenografted mice reduced TGF- $\beta$ 1 expression and its downstream signaling. Functionally, AuNP-siTGF $\beta$ 1 strongly inhibited tumor growth and improved the survival rate of tumor-bearing mice compared with the control group. These results suggest that AuNP is a highly effective method for delivering RNA interference therapeutics into tumor cells.<sup>28</sup> In another study, titanium dioxide (TiO<sub>2</sub>) was functionally modified with amine, sulfate, and phosphate ions into the biocompatible titania (F-TiO<sub>2</sub>). Due to the porous nature of F-TiO<sub>2</sub>, it can trap drugs into its cavity, allowing it to be used as a nanocarrier. F-TiO<sub>2</sub> showed little to no toxicity when tested at various concentrations in several cancer cell lines, with <10% cell death. These results suggest that F-TiO<sub>2</sub> can be used as a nanostructured carrier to deliver drugs effectively and safely by functionally modifying the surface to increase its affinity toward acidic environment (tumor), thus minimizing toxicity and accumulation in normal cells and tissues.<sup>29</sup>

## Recent developments in nanostructured materials functionalized with Ru complexes for targeted drug delivery

In recent years, Ru complexes have attracted much attention as an alternative to existing platinum drugs, showing remarkable antitumoral and antimetastatic activities with low toxicity.<sup>30,31</sup> However, one of the foremost drawbacks of Ru complexes is their rather limited stability in aqueous solutions. Therefore, designing long-life Ru-based antineoplastic agents is the primary goal to overcome this limitation, and nanostructured materials functionalized with Ru complexes serve as one of the alternatives for targeted drug delivery.<sup>32-35</sup> A recent study by Huang et al showed that the antitumor efficacy of RuPOPs could be enhanced by using cancer-targeted DNA origami as a biocompatible nanocarrier. Under this condition, the formation of unique tetrahedral nanostructure of DNA cages effectively enhanced the partial intercalation of RuPOP, thus increasing the drug-loading efficacy. In addition, conjugation of biotin to the DNA-based nanosystem (Bio-cage@Ru) enhanced its specific cellular uptake, drug retention, and cytotoxicity against HepG2 cells. Unlike free RuPOP and the cage itself, Bio-cage@Ru is

translocated to the cell nucleus after internalization, where it undergoes self-immolative cleavage in response to DNases, triggering drug release, and inducing ROS-mediated cell apoptosis. In the nude mouse model, this nanosystem exhibited satisfactory *in vivo* antitumor efficacy as it specifically accumulated in tumor sites and alleviated RuPOP and tumor xenograft-induced damages to the liver, kidney, lung, and heart function. Therefore, this study demonstrates a strategy for the development of biocompatible and cancer-targeted DNA origami with enhanced anticancer efficacy and reduced toxicity for next-generation cancer therapy.<sup>32</sup>

A novel pH-sensitive nanocapsule was recently shown to effectively deliver tris(1,10-phenanthroline) Ru(II) complex (3P-Ru) into glioma cells. In this study, delivery of 3P-Ru using the pH-sensitive nanocarrier significantly inhibited cell growth in both *in vitro* and *in vivo* models. The nanocapsule-induced cell death was mediated in part through the induction of apoptosis. As such, this novel tumor targeting approach holds great potential for theranostics applications.<sup>33</sup> In another study, a pH-sensitive mesoporous silica nanocarrier, RuNHC@MSNs-chitosan-biotin, was synthesized for the targeted delivery and controlled release of a Ru(II) N-heterocyclic carbene (RuNHC) complex. The authors demonstrated that the complex is selectively internalized by cancer cells through biotin receptor-mediated endocytosis, which enhanced its anticancer activities. Hence, this approach offers a platform for the development of accurately controlled cancer therapy.<sup>34</sup> In another study, a dual-fluorescent nanocarrier was synthesized by coating human serum albumin on Ru complex-loaded lanthanide-doped upconversion nanoparticles to generate Ru-human serum albumin-upconversion nanoparticles. Interestingly, this conjugate showed very low inhibitory effect on cell proliferation in the dark, whereas light irradiation considerably improved its cytotoxicity toward cancer cells. In addition, irradiation activated this Ru complex and the product became highly reactive to DNA. The obtained results suggest the potential application of this conjugate in the controlled release of active anticancer agents in tumor sites.<sup>35</sup> Recently, two novel Ru metalloarenes were synthesized based on anthracene units, and both compounds showed high cytotoxicity against HL-60 cancer cell line, mediated by the induction of apoptosis. In addition, these Ru metalloarenes were successfully encapsulated into two well-known biocompatible and stable mesoporous silicas (MCM-41 and SBA-15) using impregnation and grinding strategies.<sup>36</sup> In a study, Xue et al developed a supramolecular approach that assembles a  $\beta$ -cyclodextrin (CD)-functionalized Ru(II) polypyridyl complex with an adamantane-appended tumor-targeting cyclic

**Table 4** List of nanostructured materials functionalized with ruthenium (Ru) complexes for targeted drug delivery

No	Nanostructured material	Ru complex	Target	References
1	Tetrahedral nanostructure of DNA (height 2.0 nm; size 33.5 nm)	Ru polypyridyl complex	ROS-mediated cell apoptosis (human liver carcinoma cells)	33
2	The core/shell structured nanocapsule (size 103.1±11.3 nm)	Ru complex tris(1,10-phenanthroline) Ru(II) complex (3P-Ru)	Inhibition of cell growth (glioma cells)	34
3	pH-sensitive mesoporous silica nanocarrier (MSN) (size 90 nm)	Ru(II) N-heterocyclic carbene complex (RuNHC) coated with chitosan biotin	Selectivity of RuNHC between cancer and normal cells. The biotin on the surface of the drug-loaded nanoparticles mediated higher accumulation in cancer cells	35
4	Lanthanide-doped up-conversion nanoparticles coated with human serum albumin (size 60–120 nm)	A photo-sensitive Ru complex, [Ru(bpy) <sub>2</sub> (dmbpy)]Cl <sub>2</sub>	Controlled release of active anticancer agents in tumor sites	36
5	Inorganic mesoporous silicas (size 40 nm)	Anthracene-based half-sandwich organometallic Ru(II) compounds	Cytotoxic activity toward leukemia cells (HL-60) via apoptosis	37
6	Self-assembled supramolecular nanoparticles (height 1.5 nm; size 30–50 nm)	β-Cyclodextrin-functionalized Ru(II) polypyridyl complex	Controlled drug release and induce cell death in integrin αvβ3-rich tumor cells	38
7	Single-walled carbon nanotemplates (size ranged from 20 nm)	Ru(II) complexes	Photothermally triggered release	39
8	Functionalized multiwalled carbon nanotubes as carriers (the average diameter is 224.9 nm)	Ru polypyridyl complex (RuPOP)	Induction of cell death by activation of downstream signaling pathways, including DNA damage-mediated p53 phosphorylation, activation of p38, and inactivation of AKT and ERK	40

**Abbreviation:** ROS, reactive oxygen species.

Arg-Gly-Asp c(RGDyK) peptide. In this study, the host–guest system formed stable phosphorescent nanostructures with quantitative drug loading. Consequently, the formed nanoparticles Ru-CD-RGD display high selectivity for integrin αvβ3-rich human glioblastoma (U87MG) cancer cells over integrin αvβ3-deficient cancer cells. Mechanistic studies show that Ru-CD-RGD can induce apoptotic cell death through lysosomal damage, ROS elevation, and caspase activation.<sup>37</sup> In another study, Ru(II) complex-functionalized single-walled carbon nanotubes were synthesized as nanotemplates for bimodal photothermal and two-photon photodynamic therapy. Here, the synthesized single-walled carbon nanotubes have the ability to load a large quantity of Ru(II) complexes via noncovalent π–π interactions. In addition, the loaded Ru(II) complexes are competently released by the photothermal effect of irradiation. The released Ru(II) complexes produce singlet oxygen species (<sup>1</sup>O<sub>2</sub>) upon two-photon laser irradiation and can be used as a two-photon photodynamic therapy agent. Based on the combination of photothermal therapy and two-photon photodynamic therapy, Ru@ single-walled carbon nanotubes have greater anticancer efficacies than either photodynamic therapy using Ru(II) complexes or photothermal therapy using single-walled carbon nanotubes in two-dimensional cancer cell and three-dimensional multicellular tumor spheroid models.<sup>38</sup> In a study by Wang et al, a carbon nanotube-based radiosensitive drug delivery system was developed to provoke

the multidrug resistance in hepatocellular carcinoma. Here, the nanosystem was loaded with RuPOP via π–π interaction and the formation of a hydrogen bond. The functionalized nanosystem enhanced the cellular uptake of RuPOP in liver cancer cells, particularly drug-resistant human hepatoma cell line, through endocytosis.<sup>39</sup> A list of nanostructured materials functionalized with Ru complexes for targeted drug delivery are summarized in Table 4.

In addition to the above-mentioned findings, the miniaturization of metal–organic frameworks (MOFs) has generated great interest among researchers to integrate these materials into various applications such as sensing or drug delivery. Zhang et al demonstrated that Ru complexes combined with MOFs exhibited effective two-photon adsorption for singlet oxygen (<sup>1</sup>O<sub>2</sub>) generation. They successfully synthesized a novel heterogeneous <sup>1</sup>O<sub>2</sub> generation system, which may prove helpful in photodynamic therapy and chemotherapy integrative collaboration for cancer treatment.<sup>40</sup>

## Future prospective and conclusion

Functionalization of metallodrugs into nanostructures is an increasing area of research, and more groundbreaking advances are expected to be made in the future. Nanostructured Ru complexes can be used to enhance the efficacy of cancer treatment by targeted delivery of drugs or genes into cancer cells and reduce the adverse effects and systemic

toxicity by optimization of the pharmacokinetics property of these complexes. Although nanostructured materials functionalized with Ru complexes have shown great potential in the treatment of cancer, there are still many challenges in translating basic research into clinical applications. Therefore, the most promising area in this field is the development of functionalized nanostructured metal complex drug delivery systems for controlled release, which can greatly improve the activity of complexes without causing any severe adverse effects. In spite of their wide application in cancer chemotherapy, the vehicular nanostructures are toxic to both humans and the environment. As a result, there is an urgent need to thoroughly study the pharmacokinetic behaviors of different types of nanoparticles both in vivo and in vitro.

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## Disclosure

The authors report no conflicts of interest in this work.

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