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Niacin-Ligated Platinum(IV)-Ruthenium(II) Chimeric Complexes Synergistically Suppress Tumor Metastasis and Growth with Potentially Reduced Toxicity *in Vivo*

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Niacin-ligated platinum(IV)-ruthenium(II) chimeric complexes (PtRu 1-4) have been synthesized and evaluated for their antitumor performance. Using the optimal complex, PtRu-1, we show that this water-soluble chimeric prodrug not only potently inhibits the metastasis and proliferation of tumor cells but also has an unexpectedly higher safety margin in animals compared with the traditionally-used, clinically approved drug cisplatin.

Chemotherapy is still used for the treatment of patients with cancer and has improved the life expectancy of countless patients.[1] Unfortunately, a large proportion of patients do not respond to this treatment yet still experience substantial side effects as well as tumor recurrence and metastasis. Chemotherapy generally is not capable of suppressing metastasis.[2] More disappointingly, emerging evidence suggests that chemotherapeutics achieve local tumor control but occasionally promote the dissemination of cancer cells to distant organs.[3] Clinically, metastatic cancer accounts for the majority (~90%) of human death.[4] Platinum(II) (Pt(II)) complexes, including cisplatin, oxaliplatin, and carboplatin, have been extensively used as a mainstay anticancer chemotherapy.[5] These agents induce DNA damage and arrest cell division, eventually leading to apoptotic cell death. However, the efficacy of these platinum drugs in patients has been greatly compromised by dose-limiting toxicity, inherent or acquired resistance, and tumor recurrence and metastasis.[6] Systemic administration of platinum agents results in prolonged local tumor control but is unable to inhibit treatment escape pathways.[7] To address these unmet medical needs, we attempted to combine anti-metastatic and cytotoxic therapies into a single platinum platform that would be likely to provide long-term survival benefit to patients.

Octahedral Pt(IV) complexes generally perform as prodrugs to improve the therapeutic index relative to that of their parent Pt(II) drugs.[7] Through oxidizing planar Pt(II) drugs and subsequent chemical derivatization of axial hydroxide ligands, toxic Pt(II) compounds can be rationally engineered into clinically relevant agents with enhanced efficacy and safety profiles. The presence of a hydroxyl group on the axial ligand makes this oxidized Pt(IV) species accessible for modification.[8] To date, numerous bioactive agents, such as clinically approved drugs, enzyme inhibitors, and activators or suppressors for signaling pathways, have been installed at the axial positions of a Pt(IV) prodrug, yielding a synergistic effect with cytotoxic platinum drugs.[9] Pt(IV) prodrugs are inert outside tumor cells but can be activated following intracellular reduction, thus regenerating the Pt(II) complexes and the two axially ligated bioactive agents.[9]

Recently, ruthenium (Ru)-based compounds have attracted a surge of interest and been regarded as promising anticancer candidates due to the diversity of their structures and functions.[10] Several groups, including ours,[11] have reported that Ru complexes possess unique activities, such as anti-metastasis and anti-angiogenesis activities, that platinum agents do not possess.[11] More intriguingly, Ru complexes generally exhibit a lower systemic toxicity than other metallodrugs.[12] As a well-documented example, [imiH]*trans*-[Ru(*N*-imi)(*S*-dmso)Cl_4] (NAMI-A) was demonstrated to have efficient anti-metastatic activity, although this agent had negligible cytotoxicity in preclinical studies.[13] Specifically, Ru(II)-arene complexes have shown remarkable efficacy against metastases.[14]

Inspired by these findings, we employed the Pt(IV) prodrug approach to facilitate the incorporation of Ru(II) species with anti-metastatic capacity to address the limitations of platinum agent-based therapies. In addition to combined cytotoxic and anti-metastatic mechanisms, this class of hetero-nuclear hybrid complexes showed substantially reduced toxicity in animals, thus deserving further exploration in terms of dose intensification and clinical translation.

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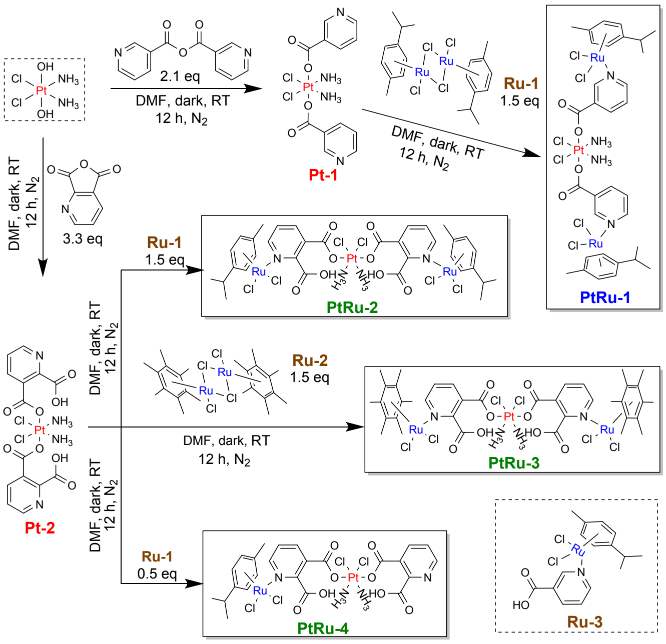

Scheme 1. Synthetic route and chemical structures of Pt(IV)-Ru(II) complexes.

To proceed toward this goal, we chose nicotinic acid (niacin, also known as vitamin B_3 or vitamin PP) and its derivatives as ligands to ligate two metal centers. This class of compounds has a nitrogen in the pyridine ring that can be coordinated through an electron-donating pair and does not cause side effects in humans.[15] Moreover, **Ru-1** (i.e., *p*-cymene Ru(II) dichloride dimer) or **Ru-2** (i.e., Hexamethylbenzene Ru(II) dichloride dimer) was selected as the antimetastatic precursor to coordinate with niacin. Accordingly, we constructed four niacin-ligated Pt(IV)-Ru(II) chimeric complexes, as shown in **Scheme 1**. First, the oxidation of cisplatin with 30% hydrogen peroxide yielded the Pt(IV) pedestal (*c,c,t*-$[Pt(NH_3)_2Cl_2(OH)_2]$) intermediate with two axial hydroxyl groups at a high yield (99%).[7b, 16] Second, modification of the hydroxyl moiety with nicotinic anhydride generated **Pt-1** (*c,c,t*-$[Pt(NH_3)_2Cl_2(nicotinate)_2]$) at a yield of 45%. Finally, the adduct **PtRu-1** was generated under mild conditions through complexing **Pt-1** with **Ru-1** and was purified by silica gel chromatography. Using a similar protocol, the hybrid Pt(IV)-Ru(II) complexes **PtRu-2**, **3**, and **4** were also synthesized. All reactions involving metallic elements and the storage of compounds were carefully conducted in the dark. The detailed synthetic procedures and characterization using NMR spectroscopy, infrared absorption spectra, and mass spectra are provided in the supporting information (**Figure S1-S13**, ESI†). In addition, we attempted to crystalize these Pt(IV)-Ru(II) complexes but unfortunately failed to obtain single crystals. Thus, only the structure of intermediate **Pt-1** was confirmed by the single-crystal X-ray structure analysis (**Figure S14**, **Table S1**, and **S2**, ESI†). The complexes **PtRu-1-4** were stable over several months when stored at room temperature and showed no degradation, as determined by HPLC analysis. Furthermore, choosing **PtRu-1** as a model compound, we found that this compound remained stable in the DMSO solvent for at least 24 days as evidenced by ^{1}H NMR measurements (**Figure S15**). We further incubated **PtRu-1** with excess equiv of sodium ascorbate to mimic the intracellular reduction. As a result, the formation of **Ru-3** was observed in ^{1}H NMR spectroscopy, supporting the reduction-triggered release of active drugs (**Figure S16**).

We next evaluated the cytotoxicity of these compounds against human cancer cell lines, including the ovarian carcinoma A2780, lung carcinoma A549, gastric cancer SGC7901, and colon cancer LoVo cell lines. After exposing cells to the compounds for 72 h, the cell viability was determined by a standard MTT assay, and the half-maximal inhibitory concentrations (IC_{50}) were extrapolated from the dose-response curves (**Table 1** and **Figure S17-20**, ESI†). Ru-based compounds (i.e., **Ru-1**, **Ru-2**, and **Ru-3**) alone did not produce inhibition of cancer cells after treatment at 128 μM, suggesting low cytotoxicity. Moreover, Pl(IV) species such as Pt-1 and Pt-2 showed moderate activity in cells, probably due to reduced cellular uptake and the reduction required to convert inert Pt(IV) into active Pt(II). Interestingly, among the four complexes, PtRu-1 was the most effective based on extrapolation from the *in vitro* dose-response curves. Compared with that of the other complexes, the increased cytotoxicity of PtRu-1 could be attributable to the lipophilicity imparted by niacin derivatives. We therefore used PtRu-1 for further investigation.

To elucidate the mechanism of action causing cell death, the acridine orange (AO)/ethidium bromide (EB) assay was used to examine cell apoptosis. AO penetrates the membrane of both live and dead cells and emits green fluorescence, while EB only enters necrotic cells with damaged membranes, emitting red fluorescence. Thus, in this assay, necrotic and late apoptotic cells fluoresced orange, and early apoptotic and healthy cells appeared green. We found that late apoptosis, characterized by orange nuclear fragmentation, appeared in A2780 cells treated with cisplatin and the **PtRu-1** complex (**Figure 1a**). Further quantification validated the superiority of **PtRu-1** in terms of apoptosis-inducing capacity; however, the difference was not statistically significant (**Figure 1b**). An Alexa Fluor 488 annexin V/propidium iodide (PI) staining assay in A2780 cells confirmed that cell death induced by **PtRu-1** was indeed due to apoptosis (**Figure S21a** and **S21b**, ESI†). Furthermore, cell cycle analysis indicated that **PtRu-1** treatment arrested the cells in G2 phase, whereas cisplatin blocked the cells at S phase (**Figure S21c** and **S21d**), probably due to the cytotoxic effect induced by Ru complexes.

Metastasis remains the major cause of death and is associated with poor prognosis of cancer patients.[17] Unfortunately, there is no effective therapy despite significant advances in new anticancer strategies. Migration and invasion are crucial steps in metastatic colonization, known as the invasion-metastasis cascade. Previous studies indicated that Ru-based metallodrugs have the ability to inhibit tumor cell metastasis.[18] Using **PtRu-1** as a target complex, we investigated its potential to inhibit the migration and invasion of cancer cells. A Transwell assay (invasion assay) verified that the **PtRu-1** and **Ru-3** complexes reduced the number of human umbilical vein endothelial cells (HUVECs) that penetrated through Matrigel (**Figure 1c** and **1d**). In a wound-healing assay (migration assay), the cell

Cell line	Cisplatin	Pt-1	Pt-2	Ru-1	Ru-2	Ru-3	PtRu-1	PtRu-2	PtRu-3	PtRu-4
SGC7901	8.19±1.99	14.01±0.65	76.27±22.73	90.00±13.36	>128	>128	1.81±0.14	1.95±0.53	30.75±7.43	6.79±0.68
LoVo	6.32±0.24	35.73±1.64	23.66±2.75	>128	>128	>128	1.35±0.15	28.69±1.47	68.29±7.77	6.00±0.68
A2780	2.86±0.10	6.57±0.62	8.98±1.31	>128	>128	>128	6.52±0.64	14.92±1.20	28.49±2.207	5.40±0.54
A549	4.90±0.30	14.72±1.28	20.95±1.37	>128	>128	>128	6.57±0.58	14.89±0.76	43.27±11.25	14.86±1.51

Table 1. *In vitro* cytotoxicity of Pt(IV)-Ru(II) complexes. Cell viability was determined by an MTT assay after a 72-h treatment (expressed as IC_{50} ± SD in μmol/L).

migration of A2780 cancer cells (**Figure 1e**) and HUVECs (**Figure S22**, ESI†) was clearly reduced after drug treatment. Moreover, **PtRu-1** exhibited a higher suppression rate than **Ru-3** in A2780 cells (**Figure 1f**).

Tumor growth and metastasis require angiogenesis and formation of microvessels to provide oxygen and nutrients.[19] Thus, we examined the inhibitory effect of **PtRu-1** on *in vitro* angiogenesis using the Matrigel tube formation assay. The tube-forming ability of HUVECs was significantly impeded by treatment with the **PtRu-1** and **Ru-3** complexes, whereas cisplatin did not have an inhibitory effect (**Figure S23** and **S24**, ESI†). Collectively, these *in vitro* results provide compelling evidence that ruthenium-based agents retained anti-metastasis and anti-angiogenesis capacities irrespective of the complex coordination.

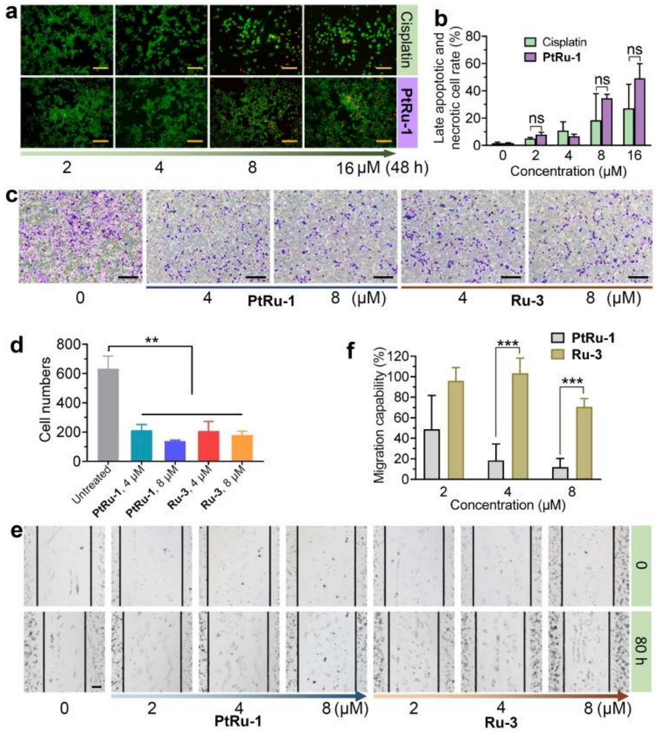

Figure 1. a) *In vitro* cytotoxicity examined by AO/EB double staining assay after the treatment with different concentrations of cisplatin and **PtRu-1**. **b**) Quantification of the percentage of apoptotic cells. **c**) Ru complexes **Ru-3** and **PtRu-1** inhibit the invasion of HUVECs. The cells that passed through the Matrigel appear violet when observed under the microscope. **d**) Quantification of penetrated cells. **e**) Migration of A2780 cells after the treatment with **PtRu-1** and **Ru-3** for 80 h as determined by a wound-healing assay. Culture medium with 1% FBS. **f**) Migration capability expressed as the percentage of the distance that cells moved compared with that of untreated cells. ns, not significant, **p<0.01, ***p<0.001. Scale bars: 200 μm.

Due to the inertness of Pt(IV) complexes, we expected that these chimeric complexes would be able to alleviate the systemic toxicity induced by conventional platinum drugs. By choosing **PtRu-1** as a target complex, we assessed drug tolerability in animals in a dose escalation manner. Healthy ICR mice were given five doses of **PtRu-1** *via* intraperitoneal injection. As controls, saline and cisplatin were also injected. The change in body weight and mouse death were monitored following injections over a period of 15 days. Unfortunately, only a dose of 2.5 mg/kg of cisplatin could be tolerated, which also caused a significant drop (~12.4%) in body weight in ICR mice (**Figure 2a**). Higher doses, such as 5 or 10 mg/kg, of cisplatin caused mouse death. Very encouragingly, the mice were able to tolerate **PtRu-1** at a dose of 77 mg/kg, which is equivalent to 20 mg/kg of cisplatin, representing at least an 8-fold increase in the maximum tolerated dose (MTD) compared to that of clinically used cisplatin. Histological analysis was performed to examine the potential organ damage produced by different treatments. As shown in **Figure 2b**, in kidneys, cisplatin treatment (2.5 mg/kg) caused extensive atrophy of the renal capsule, accompanied by the disappearance of Bowman's space and the loss of cell polarity. Moreover, cytoplasmic relaxation and vacuolization (accumulation of white vesicles) indicated hydropic degeneration in liver parenchyma as well as the high toxicity of cisplatin. Noticeably, organs excised from the mice receiving **PtRu-1** at an 8-fold cisplatin-equivalent dose (20 mg/kg) still presented normal histopathological features that were similar to those in saline-treated mice (**Figure 2b** and **Figure S25**, ESI†).

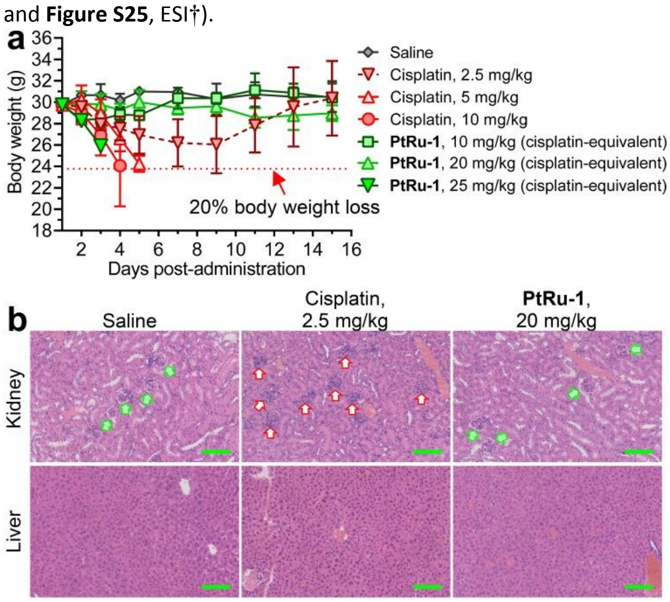

Figure 2. Evaluation of drug toxicity in healthy ICR mice. **a**) Body weight changes in different treatment groups. **b**) Histological examination of organs excised from the ICR mice. Green and red arrows indicate normal and damaged glomeruli, respectively. Scale bars: 100 μm.

Ovarian cancer is the second most common cause of malignancy-caused death among women because of its high capacity for metastasis and invasion in cancer patients.[20] We thus evaluated the therapeutic efficacy of **PtRu-1** using a transcoelomic metastatic A2780 ovarian cancer model in Balb/c nude mouse **(Figure S26**, ESI†). In this model, A2780 cells are intraperitoneally injected into mice, which enables to form primary tumors throughout the abdomen. Subsequently, these aggressive cancer cells potentially metastasize to the organs including the ovary, liver, and spleens.[21] Considering the difference in drug tolerance between Balb/c and ICR mice, we administered cisplatin at a dose equivalent to the 30% MTD observed in ICR mice. At the end of the study, mice were sacrificed, and tumors in abdominal cavities (primarily in mesenteries) were excised for analysis. The ovaries, livers, and spleens were also collected for quantification. Compared with cisplatin treatment, **PtRu-1** at a low dose of 0.75 mg/kg was more effective in terms of reducing the number of abdominal tumors and the total tumor number, but the difference was not statistically significant. Because **PtRu-1** had a higher safety margin than cisplatin, we thus increased the dosages to 1.5 and 3 mg/kg in this model to assess the efficacy. Impressively,

administration of **PtRu-1** at both tolerable doses significantly reduced primary tumor growth (**Figure 3a**, **3b** and **3c**) as well as metastasis to other organs (**Figure 3a**, **3d** and **3e**). Moreover, at all treatment doses of **PtRu-1**, the low drug toxicity and the tolerability in nude mice was supported by stable body weights (**Figure 3f**). Specifically, the reduction in metastatic burden could benefit the long-term survival of patients when considering future use in the clinic. Together, these data demonstrate that the hybrid Pt(IV)-Ru(II) complex not only inhibited the growth of bulky primary tumors but also reduced the potential of metastasis to distant organs, thereby validating this design rationale for generating multifunctional anticancer agents with excellent *in vivo* tolerability.

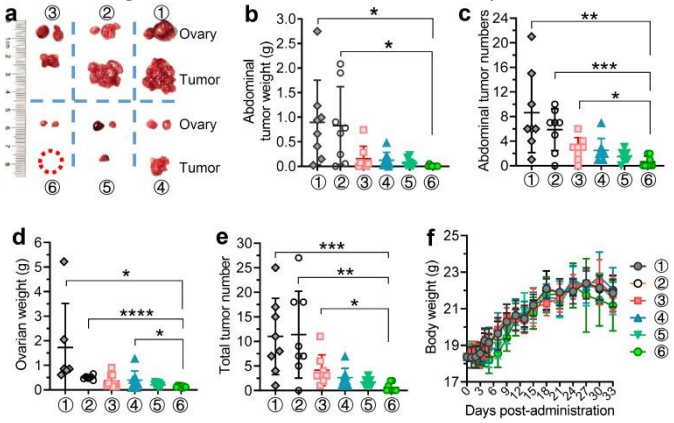

Figure 3. Therapeutic efficacy of **PtRu-1** in a Balb/c nude mouse model bearing human ovarian A2780 cancer cells. **a**) Representative ovaries and tumors excised from the mice in each group at the endpoint of the study. Treatment regimens: Saline (①); **Ru-3**, 6 mg/kg (②); cisplatin, 0.75 mg/kg (③); **PtRu-1**, 0.75 (④), 1.5 (⑤) and 3 (⑥) mg/kg (cisplatin equivalent). Abdominal tumor weights (**b**), abdominal tumor numbers (**c**), ovarian weights (**d**), and total numbers of tumors excised from the abdominal cavity, liver, and spleen (**e**) in each mouse group. **f**) Body weight changes in the mice after receiving the treatments. **p*<0.01, ***p*<0.01, ****p*<0.001.

Combinations of multiple therapies with distinct mode-of-action in single platforms hold great promise for synergistically addressing the issues of tumor recurrence and metastasis. In this study, we successfully constructed Pt(IV)-Ru(II) hybrid chimeric complexes that combine a Pt(IV) prodrug approach and a hetero-nuclear active center to address multiple challenges posed by Pt(II)-based chemotherapy. Among the four synthesized complexes, we identified **PtRu-1** as a potent agent that spanned cytotoxic and anti-invasive mechanisms according to numerous *in vitro* and *in vivo* results. Further investigation revealed the substantially alleviated systemic toxicity of **PtRu-1** in animals, showing at least an 8-fold increase in the MTD relative to cisplatin. The unexpectedly high MTD could be associated with the low toxicity of the Pt(IV) species and the Ru(II) ligands.[22] We foresee that this molecular design approach holds the potential to yield additional clinically translatable multimetallic agents that can combat metastatic cancer.

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Conflicts of interest

There are no conflicts to declare.

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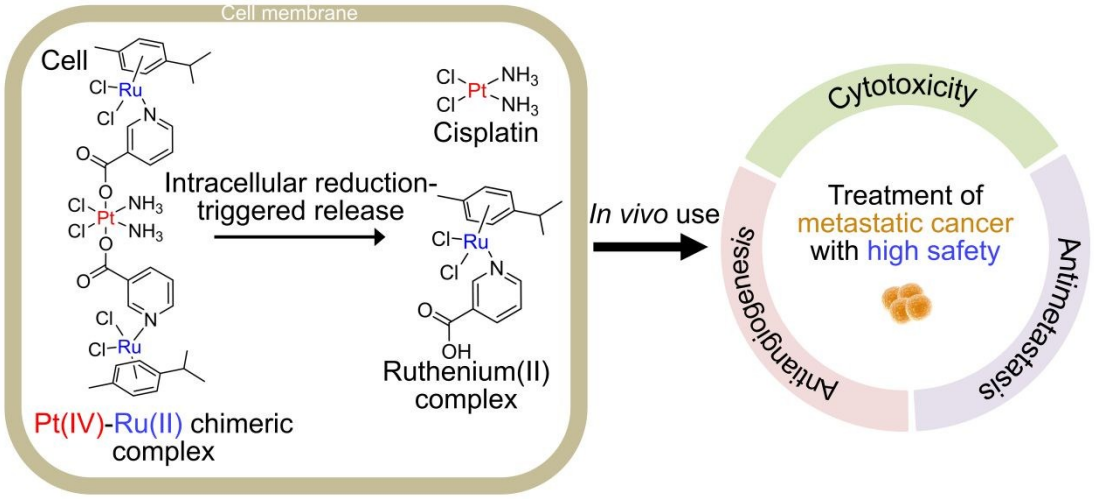

The chimeric Pt(IV)-Ru(II) complex was designed to simultaneously release cytotoxic cisplatin and antimetastatic Ru(II)-arene compound, thereby producing potent anticancer activity with high drug tolerability in animals.