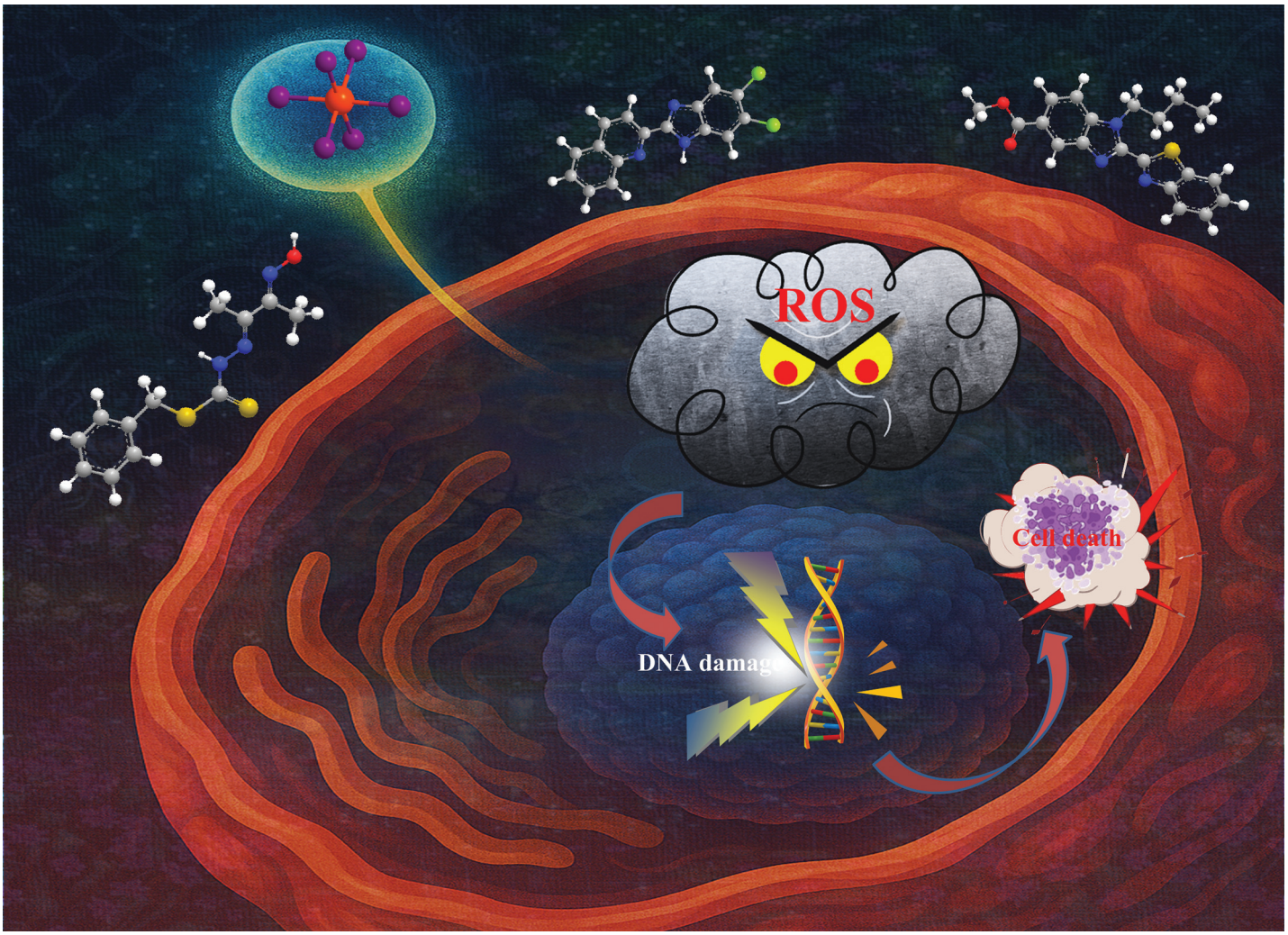

Showcasing research from Professor Priyankar Paira's laboratory, School of Chemistry, Vellore Institute of Technology, Vellore, India.

Exploring the Synthesis of Ru(II)/Ir(III)/Re(I)/Rh(III) based complexes as anticancer metallopharmaceuticals: Significance, Challenges and future perspective

This frontier article highlights recent advancements in the synthesis of mono-, bi-, and mixed-metallic Ru(II)/Ir(III)/Re(I)/Rh(III) complexes for anticancer applications. The article focuses on Ru(II)/Ir(III)/Re(I)/Rh(III) complexes bearing distinct ligands designed to enhance anticancer metallopharmaceutical efficacy through diverse therapeutic strategies.

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Exploring the synthesis of Ru(II)/Ir(III)/Re(I)/Rh(III)-based complexes as anticancer metallopharmaceuticals: significance, challenges and future perspective

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Metal complexes exhibit significant potential in the field of anticancer metallotherapeutics due to their high selectivity toward cancer cells and their effectiveness in targeted drug delivery. This frontier article summarizes recent advances in the synthesis of mono-, bi-, and mixed-metallic Ru(II)/Ir(III)/Re(I)/Rh(III) complexes for anticancer applications. Additionally, various therapeutic approaches and their mechanisms of action in Ru(II)/Ir(III)/Re(I)/Rh(III)-based complexes are discussed. In this study, we provide insights into the contributions of various research groups toward the development of transition metal complexes with promising therapeutic potential. This study also addresses the challenges encountered throughout the designing and application process as well as the future perspectives of these metallopharmaceuticals.

Introduction

Cancer is the most critical chronic disease and the second leading cause of death worldwide, following heart disease.[1] Some primary causes of cancer include metastasis, uncontrolled proliferation, confrontation to apoptosis, infection, organ damage, blood cell issues, *etc*.[2] Chemotherapy, radiation therapy, and surgery are the main treatment strategies to get rid of this menace. In 1965, Barnett Rosenberg[3] opened the door to a new era of metal complexes with the serendipitous discovery of cisplatin, which would be used in cancer therapy, heralding the beginning of modern inorganic medicinal chemistry. This stupendous discovery has some major side effects

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and drawbacks like lack of selectivity, drug resistance, and serious toxicity,[4,5] which make the treatment procedure of cancer a challenging work. Therefore, the development of non-platinum metallodrugs,[6] particularly Ru(II)/Ir(III)/Re(I)/Rh(III)-based complexes,[7–10] has attracted significant interest over the past few decades for their potential as anticancer metallopharmaceuticals.

Ru is a transition metal belonging to group VIII of the periodic table and commonly exhibits two oxidation states, +2 and +3, which may exist in other less common oxidation states (+4, +6, and +8) depending on the chemical environment. Under the pH of cancer cells, Ru(III) is reduced to its more active form Ru(II).[11] The first Ru(III) complex NAMI-A paved the way to enter the phase-1 clinical trial, which failed to pass the phase-2 trial due to some therapeutic constraints. The discovery of another Ru(III) complex, KP1019, by the Keppler group for clinical trial started the development in this field, followed by a further modified complex, KP1339,[11] which is currently recognized as BOLD-100. The photoactive Ru(II) complex TLD1433 is considered another milestone that passed clinical trial phase-1 for the treatment of bladder cancer.[12–14]

Ir(III) complexes, characterized by low spin, kinetic inertness and high stability, exhibit properties comparable to those of Ru(II) complexes. They are known for their remarkable quantum yields, substantial Stokes shifts, long emission lifetimes, catalytic activity, and flexible coordination geometry. Additionally, Ir(III) complexes are highly photostable and exhibit relatively low toxicity, with their stability contributing to minimal off-target effects in tumor microenvironments. Their excellent cellular permeability, pronounced redox characteristics, and effective ligand exchange capabilities further enhance their potential as promising candidates for anticancer therapy.[15,16]

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Rhenium possesses several oxidation states, *viz.* +1, +2, +3, +4, +5, +6, +7, −1 and −3. Re(I) complexes are highly photostable, and their photodynamic properties are noteworthy. Redox-active tricarbonyl complexes of Re(I) exhibit a high quantum yield, large Stokes shift and significant luminescent lifetime.[17,18] Noble and rare metal, rhenium, has important applications in the fields of catalysis and medicinal chemistry. Most rhodium complexes are in the preclinical stage and have not yet been extensively tested in clinical trials.

Ru(II)/Ir(III)/Re(I)/Rh(III)-based complexes were designed to maximize their anticancer efficacy by incorporating the following key features: (a) inherent biological activity, (b) efficient towards cancer cell environment (hypoxic, high GSH, low pH), (c) extended π-conjugation to enhance fluorescent properties for bioimaging, (d) hydrophobic moieties that improve cellular accumulation by enhancing membrane permeability and intracellular uptake, and (e) strong interaction with DNA (Fig. 1). Cancer cells tend to overexpress glutathione (GSH) and elevate the reduced state of adenine dinucleotide phosphate (NADPH) production to counteract oxidative stress because NADPH plays a key role in regenerating GSH from its oxidized form (GSSG) *via* glutathione reductase. Targeting this redox buffering system – either by depleting GSH or inhibiting NADPH regeneration – has emerged as an effective anticancer strategy. Additionally, the reduced state of nicotinamide adenine dinucleotide (NADH) contributes to redox homeostasis by regulating the NAD^+/NADH. High levels of reactive oxygen species (ROS) generated by the complex can oxidize NADH, disrupting the redox balance and ultimately inducing cancer cell death.

In this perspective, we highlight recent advances in the synthesis of monometallic, dimetallic and mixed metallic Ru(II)/Ir(III)/Re(I)/Rh(III) based complexes, discuss their significance, address related challenges, and explore future directions in the field.

Significance and challenges of monometallic complexes in cancer therapy

Ru(II) metalopharmaceuticals

Ruthenium complexes exhibit high solubility in water, whereas the ligand exchange rate in aqueous solution is relatively slow. These complexes also exhibit high activity towards cisplatin resistant cells and low toxicity compared with commonly used anticancer drugs. One crucial property of Ru(II) complexes is that they can bind with the biological molecules present in blood plasma, *e.g.* albumin, transferrin, *etc*. like iron. Therefore, the transportation process of the Ru(II) complexes to cancer cells is facilitated with negligible side effects. The high water tolerance property of these complexes makes them the best possible alternatives to anticancer agents.[19,20] The incorporation of arene moieties having extended π conjugation is an excellent idea for maintaining the hydrophilicity and

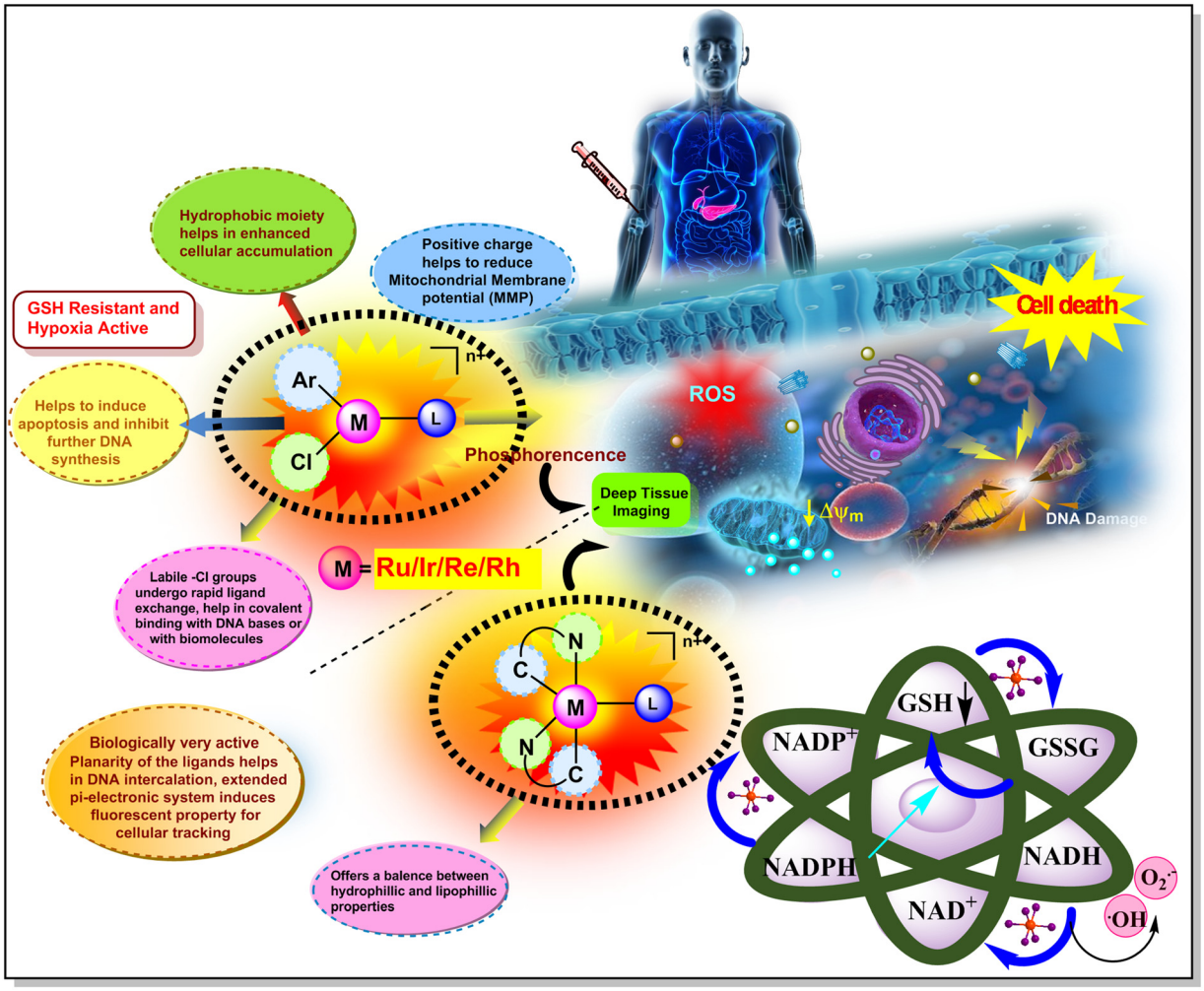

Fig. 1 Design of Ru(II)/Ir(III)/Re(I)/Rh(III)-based complexes as anticancer metallopharmaceuticals.

lipophilicity of the Ru(II) complexes.[21,22] These complexes are commonly referred to as half-sandwich complexes, which are important innovations and play a key role in modern drug discovery. In these complexes, the η^6 arene moiety serves as the seat, with the remaining three positions occupied by ligands, resulting in a piano-stool geometry. One labile leaving group, typically a chloride (–Cl), is included, and together with two ligands, it forms the legs of the stool.

For the synthesis of Ru(II)-based complexes as anticancer metallopharmaceuticals, researchers have focused on incorporating ligands with nitrogen (N) and phosphorus (P) donor atoms. In this regard, bipyridine, phenanthroline, *etc.* ligands are a common choice. Synthesis is initiated with a suitable Ru precursor and the corresponding ligand to achieve the desired product with stability and biological activity towards cancer cell lines. The biological activity and cancer cell targeting specificity of the synthesized complexes can be tuned by altering the ligand structure.

Furoyl thiourea ligand was introduced by Dorairaj *et al.* (**1**) into Ru(II) metal to act as an anticancer agent for the breast cancer cell lines MDA-MB-231, T47-D, and MCF-7. Their studies have shown that the introduction of Ru metal increases its activity. The incorporation of the PPh_3 group also increases the potentiality of the complexes. *In vivo* studies have also been performed with significant results.[23] Khater *et al.*[24] synthesized two Ru(II) flavone complexes (**2**), studied their potency against two breast cancer cell lines, MCF-7 and MDA-MB-231, and found significantly improved activity. Non-intercalative interactions were observed between the c-myc i-motif and VEGF DNA sequences. Varieties of ligands have been incorporated into Ru metal for complex formation by Antonets *et al.* (**3**),[25] Sahu *et al.* (**4**),[26] Qi *et al.* (**5**),[27] Marco *et al.* (**6**),[28] and Abad-Montero *et al.* (**30**).[29]

Low solubility, marginal stability, and low cellular uptake are the main challenges of Ru-based complexes as anticancer agents. Low aqueous solubility, short half-life in *in vivo* method, and short circulation time pose significant challenges in clinical applications. Therefore, intravenous injection remains the only viable administration route, leading to low bioavailability and reduced accumulation in target tumor cells.

Numerous researchers have adapted various approaches to address these challenges. One of the most effective approaches is the introduction of nanosystems into drug delivery due to their stability, solubility, and sustainable release of drugs into the target organ.[30–32]

Ir(III) metalopharmaceuticals

Recently, there has been growing interest among researchers in the strategic design and synthesis of iridium(III) complexes due to their exceptional photoluminescent properties and promising anticancer activity. Naphthacene-based ligand (**7**) was introduced by Gonzalo-Navarro *et al.* for application in photodynamic therapy (PDT). Light-driven antiproliferative activity was studied extensively under dark conditions. π-Expansive ligands were used for designing the ligand.[33] Phenanthroline based naphthalene diimide ligand (**8**), was used by Yang *et al.*[34] in the synthesis of Ir complexes, and their effects on hypoxic tumors were investigated. *In vitro* studies were conducted in detail for phototoxicity under hypoxic and normoxic conditions. *In vivo* studies performed after laser activation of tumor cells show excellent results.

Das *et al.* reported an imidazole-based quinoline-containing PTA complex (**9**) and studied its activity in the presence of GSH against the MDA-MB-231 cell line and found an excellent result, with an IC_{50} value of 2.8 μM.[35] Extensive studies have demonstrated that the reported compound functions as a highly selective and hypoxia-effective metallodrug for the treatment of triple-negative breast cancer. He *et al.* designed and synthesized a 4,7-dichloro-1,10-phenanthroline-based iridium complex (**10**). Among the three potent complexes, the one with the highest lipophilicity demonstrated the strongest anticancer activity against HeLa cells, with an IC_{50} value of 0.83 μM. This compound also exhibited significant tumor growth inhibition in *in vivo* experiments in a mouse xenograft tumor model.[36] A diverse library of compounds has been developed by researchers in the quest for innovative anticancer metallodrugs. Notably, Pivovarova *et al.* (**11**),[37] Kowalik *et al.* (**12**),[38] Ramos *et al.* (**13**),[39] Chu *et al.* (**14**),[40] Łomzik *et al.* (**15**),[41] Negi *et al.* (**34**),[42] Ortega-Forte *et al.* (**35**),[43] and Linero-Artiaga *et al.* (**36**)[44] have introduced various ligands for the complexation of Ir complexes.

Re(I) metalopharmaceuticals

Naphthyl-based Re complexes were designed by Darshani *et al.*[45] and studied their *in vitro* cytotoxic activity using non-small cell lung cancer cells, NCI-H292, and normal lung cell line MRC-5. Compound **16** exhibited the highest cytotoxicity (IC_{50} = 9.91 μM) and may be a potent drug for lung cancer. Aminoquinoline-based ligands (**17**) were introduced by Zinman *et al.* and used against the hormone-dependent breast cancer cell line MCF-7 and hormone-independent breast cancer cell line MDA-MB-231. The synthesized compound was three-fold more active than the common drug, cisplatin. The binding affinity of the synthesized complexes with calf thymus DNA and bovine serum albumin was excellent and was supported by *in silico* studies.[46]

Kushwaha *et al.* synthesized three Re(I) complexes (**18**) and compared the effectiveness of photoactivated cancer therapy and sonodynamic therapy (SDT). The rhenium complex attached with the $-NO_2$ group exhibited no cytotoxicity upon ultrasound exposure, whereas the complex with the $-NH_2$ group demonstrated cytotoxic effects against HeLa cells.[47] The IC_{50} values were calculated to be 2 μM and 5 μM under light and sound exposure, respectively. Kushwaha *et al.* and Marco *et al.* introduced a new class of ligands for the synthesis of Re complexes with potential anticancer activity (**19**, **20**). Interesting results have been studied by the researchers upon the incorporation of different ligands in designing Re complexes by Kushwaha *et al.* (**19**)[48] and Marco *et al.* (**20**).[49]

Rh(III) metalopharmaceuticals

Two isoquinoline-based Rh(III) complexes were designed and synthesized by Khan *et al.* The anticancer potency of these complexes was extensively studied and demonstrated promising results towards T24 cell lines. These complexes induce apoptosis through mitochondrial dysfunction and arrest the cell cycle in the S-phase. *In vivo* studies were performed in the T-24 xenograft mouse model, and the synthesized Rh complex **21**, exhibited inhibition towards tumor growth. The *in vivo* safety profile of one Rh complex is better than that of the commonly used drug cisplatin.[50]

A series of picolinamide-based Rh complexes were synthesized by Gu *et al.*, among which two emerged as the most effective candidates against the tested cancer cell lines. These complexes possess high antiproliferative properties *via* different modes of action, *viz.* apoptosis, autophagy, and cell cycle arrest. These Rh complexes (**22**) inhibited the growth of breast and bladder cancer cell metastasis in the xenograft model.[51] In the continuous search for new ligands for the preparation of Rh complexes, Josa *et al.* (**23**),[52] Wei *et al.* (**24**),[53] and Sink *et al.* (**25**)[54] introduced ligand varieties for synthesizing new Rh complexes with potential anticancer activity.

Significance and challenges of multinuclear complexes as anticancer agents

The application of multinuclear metal complexes has garnered attention from researchers because of their high potentiality and greater degree of selectivity compared to that of their mononuclear congeners. Notably, the platinum-based trinuclear complex also known as triplatin, BBR3464, is a revolutionary breakthrough that still propagates biostability and reduced activity in a phase II trial.[55]

A series of cationic dinuclear Ru *para*-cymene complexes were reported by Dyson *et al.* They used thiolato bridges with different substituents. These dinuclear ruthenium complexes were found to be more active towards breast cancer cell line, A270. Studies were also conducted against cisplatin-resistant A2780cisR in the nanomolar range. Compound **26** was claimed

to be the most potent one, having the highest toxicity and lowest IC_{50} values, making it the most cytotoxic one.[56] Six dinuclear Ir complexes were synthesized by Sheldrick *et al.* by varying the bridging ligands and were studied against the cell lines MCF-7 and HT-29. Two compounds (**27**) exhibited the lowest IC_{50} values (<5 μM). Moreover, they exhibited strong DNA intercalation properties.[57]

Novel metallocyclophanes (**28**) were reported by Manimaran *et al.*, and extensive biological studies revealed that the latter compound displayed superior activity across various cancer

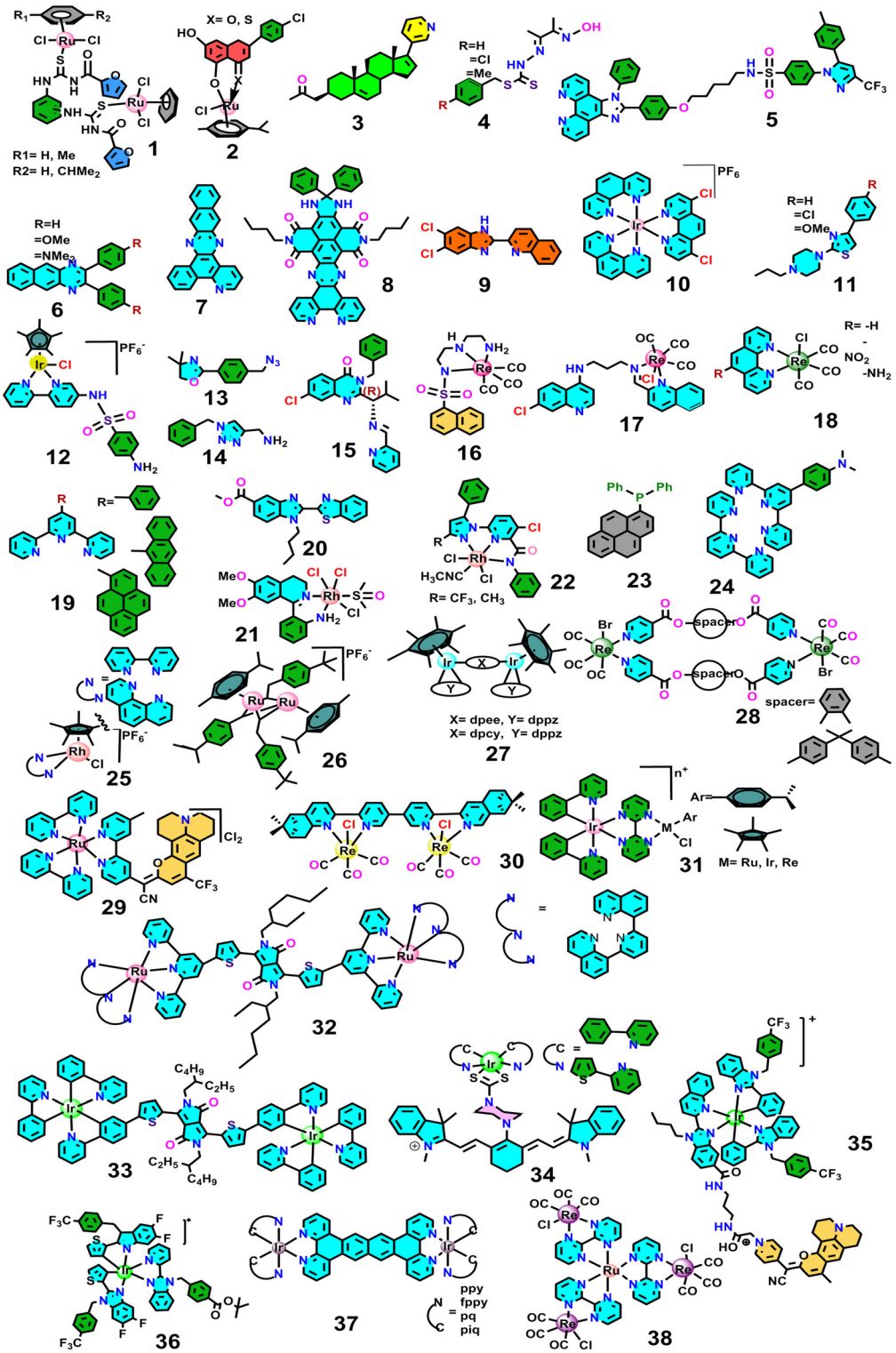

Fig. 2 Few selected representative metal complexes and ligands used for complexation.

cell lines. The activity of the former one was found to be better against HepG2 cell lines (IC_{50} value 14.2 μM). On the other hand, the latter one was found to show its activity against HeLa cells (IC_{50} value 12.8 μM). IC_{50} values reveal the better activity of these complexes compared with that of cisplatin.[58] Diastereomeric dinuclear Re(I) complexes (**29**) containing chiral ligand pynene-bipyridine moiety were developed by Solea *et al.* The research group has demonstrated a clear relationship between stereochemistry and the biological activity of these complexes. Among all stereoisomers, the diastereomer of compound **30** exhibited exceptional cytotoxicity results against the colon and breast cancer cell lines tested (HCT116 and MCF-7).[59]

Roy *et al.* synthesized cyclometalated and half-sandwich multinuclear complexes (**31**) for chemodynamic therapy (CDT), a novel tumor treatment strategy coined by Bu *et al.*, generates ROS through Fenton or Fenton-like reactions in the tumor microenvironment and, unlike PDT, operates without the need for light activation. These complexes follow a novel sialic acid-targeted chemotherapeutic strategy in triple-negative breast cancer cells. Among the complexes, the dinuclear iridium complex showed its potency as a ferroptosis inducer.[60] Tang *et al.* synthesized novel dinuclear Ir(III) complex nanoparticles (**33**) for sonodynamic therapy.[61] Upon ultrasound irradiation, this complex nanoparticle generated singlet oxygen and hydroxyl radicals, followed by immunogenic cell death. Wei *et al.* reported four NIR-based diruthenium complexes (**32**) and studied their anticancer activity, which is triggered by light (700 nm LED light).[62] A series of dinuclear Ir(III) complexes were synthesized by Zeng *et al.* for PDT and photothermal therapy (PTT) against cisplatin-resistant cancer cells (**37**). In PTT, light energy is converted into heat, leading to the

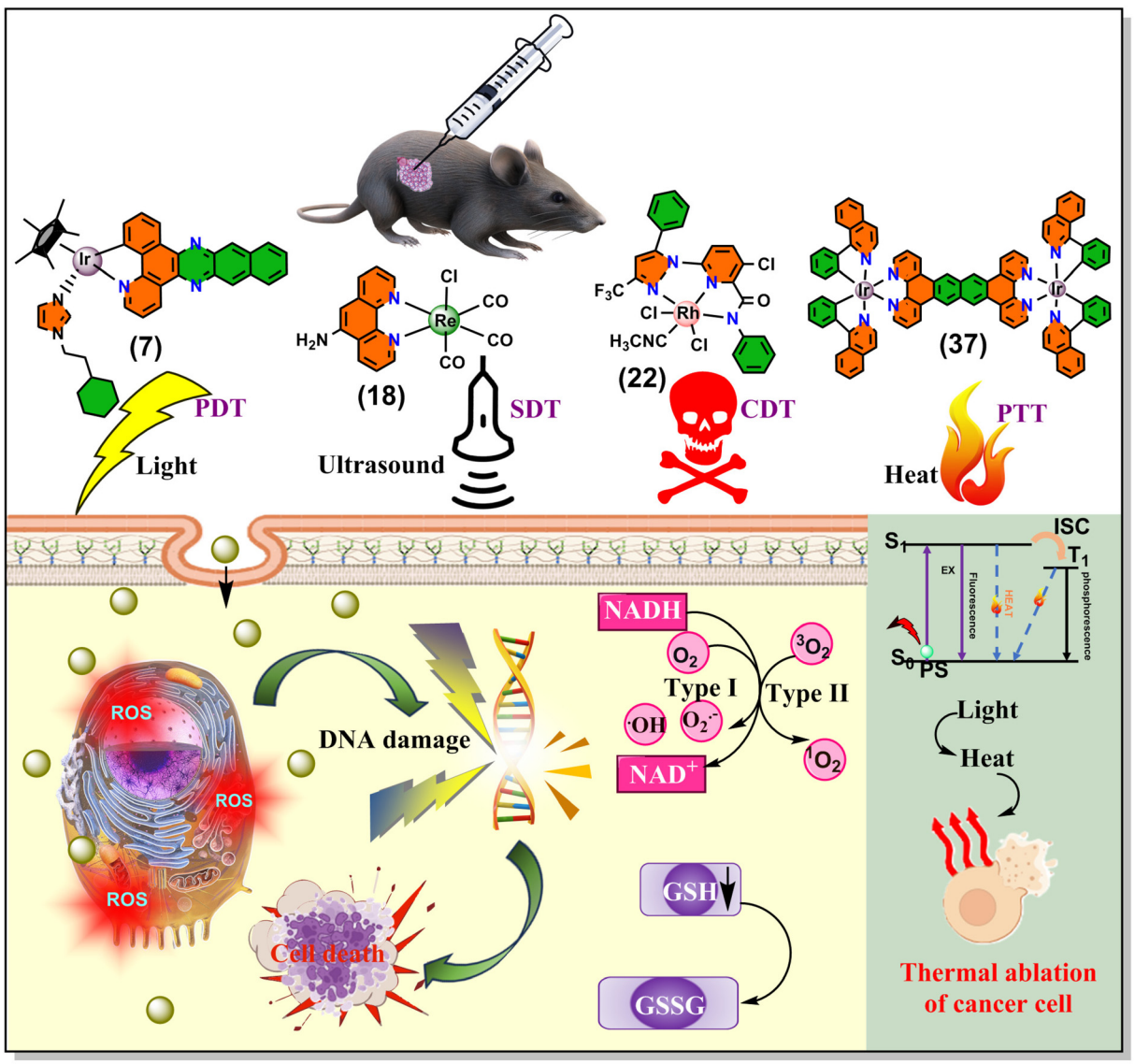

Fig. 3 Schematic of the mechanism of action of different therapeutic techniques used in metal-based anticancer complexes.

thermal ablation of cancer cells. Upon exposure to infrared (IR) radiation, these complexes induce reactive oxygen species (ROS)-mediated cell disruption alongside thermal ablation, enhancing their therapeutic efficacy.[63]

A plethora of heteromultinuclear complexes has been designed with different metals containing more than one metal center. These complexes collectively acquire the advantages of the metals present in one complex. Many research groups have reported the presence of heteromultinuclear complexes with strong anticancer activity.[64,65] Notably, the first Ru–Re bimetallic tetranuclear complex **38**, based on 2,2′-bipyrimidine, was successfully synthesized in Karges' laboratory.[66] Necrosis-induced cell death has been observed by the novel mixed metallic complex when tested against multiple cancer cell lines, *viz*. colon, breast, pancreas, and human fibroblast cancer cell lines (Fig. 2).

Conclusion and future perspective

Ru/Rh/Re/Ir-based anticancer complexes employ various therapeutic mechanisms, including photodynamic therapy (PDT), sonodynamic therapy (SDT), chemodynamic therapy (CDT), and photothermal therapy (PTT), to enhance their anticancer efficacy (Fig. 3). Despite extensive ongoing research on metallopharmaceuticals as anticancer agents, a huge number of unsolved hurdles are decorated in the pathway, *e.g.* intracellular targets, and pharmacokinetic behavior. Additionally, the toxicity of the metallodrugs cannot be ruled out. Before the application of metallodrugs, emphasis should be given to the biodistribution process. Extensive *in vivo* studies should be performed using different models, such as tumor xenograft models and animal species. The mechanism of drug resistance can be addressed through a multitargeted approach in the design of Ru/Rh/Re/Ir-based drugs for cancer therapy. Additional research is urgently required to address long-term safety issues and related potential adverse effects. In drug designing technique, one of the major challenges is the lack of pharmacokinetic data and *in vivo* toxicity, which directly affect the clinical trial phase of metallodrugs and are a primary reason for their failure in later stages of clinical application. The pharmacological features of metallodrugs should be studied in detail to clarify the mechanisms underlying their anticancer effects of the metallopharmaceuticals. Smart drug designing (synthetic) techniques in combination with tumor biology will hopefully generate novel anticancer drug molecules through interdisciplinary research among chemists, biologists, and pharmacologists to alleviate the pain of patients with cancer in a major way.

Synthetic routes should be modified to increase yield and scalability, whereas the introduction of organelle-targeted ligands could help explore the possibilities for better action. Further fine-tuning of these metal complexes is required to reach the clinical trial phase. Focus should be given to rigorous *in vivo* studies, with a strong emphasis on understanding pharmacokinetics, biodistribution, immunogenicity, long-term toxicity reduction, and clinical studies. Tumor-specific drug delivery can be achieved through the designing of metallopharmaceuticals increasing strong binding affinity with carriers like human serum albumin, high charge density, low toxicity, high cell permeability, and high dissociating ability within the target cell. In this regard, photodynamic therapy is proven to be the better option, where after reaching the target, the complexes show their photoactivity upon irradiation with light energy. Additionally, receptor-mediated targeting and nanoparticle-based drug delivery systems enhance the selective accumulation of the complex in cancer cells, thereby minimizing the toxicity to healthy cells. We hope that this frontier will stimulate researchers to explore and focus on developing new metallopharmaceuticals that can act as new anticancer agents.

Author contributions

S. U., R. C. and P. P. designed and wrote the manuscript.

Data availability

All the data are included in the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

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