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Golden immunity: gold complexes as emerging triggers of immunogenic cell death

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Cancer immunotherapy has transformed modern oncology, yet its clinical success remains limited by the intrinsically low immunogenicity of many solid tumours. Immunogenic cell death (ICD) has emerged as a powerful strategy to overcome this limitation by converting tumour cell death into a process that stimulates antitumour immunity. Metal complexes are particularly attractive in this context, as their tunable coordination environments and redox properties enable the controlled activation of cellular stress pathways associated with ICD. Among them, gold complexes have recently gained attention as versatile modulators of tumour cell death and immune signalling, owing to their unique chemical reactivity, including redox activity and selective targeting of thiol- and selenol-containing proteins. In this Perspective, we discuss the molecular mechanisms by which metal complexes promote immunogenic cell death and examine the emerging role of gold-based compounds within this framework. By comparing gold complexes with other metal-based ICD inducers, we highlight how coordination chemistry can be exploited to modulate cell-death pathways and immune activation. Finally, we outline key challenges and future opportunities for harnessing metal-based ICD inducers as next-generation chemo-immunotherapeutic agents.

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1. Introduction

In recent years, cancer immunotherapy has reshaped the landscape of oncology, emerging alongside chemotherapy, radiotherapy, and surgery as a major therapeutic pillar.[1] Breakthrough strategies such as immune checkpoint inhibitors, adoptive T-cell transfer,[2] and therapeutic cancer vaccines have

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demonstrated the remarkable capacity of the immune system to selectively recognise and eliminate malignant cells.[3,4] Despite these advances, however, the clinical benefit of immunotherapy remains limited to a subset of patients, largely due to the immunological profile of the tumour itself.[5–7] While some tumours are highly inflamed and responsive to immunotherapy ("hot" tumours), many solid cancers remain immunologically "cold", characterised by low antigenicity, poor immune-cell infiltration, and a strongly immunosuppressive tumour microenvironment (TME).[8,9] As a result, T-cell-centred immunotherapies often show limited efficacy due to insufficient immune priming within the tumour microenvironment.[10,11]

To overcome these limitations, significant efforts have been devoted to "heating up" cold tumours, or inflaming the TME, thereby enhancing tumour visibility to the immune system.[9,12] Strategies aimed at achieving this goal include oncolytic viruses,[13,14] combination regimens with cytokines,[15,16] and chemotherapeutic or photodynamic agents capable of converting immunologically silent cell death into forms that actively stimulate immune responses.[17–19] Among these, the induction of immunogenic cell death (ICD) has emerged as one of the most compelling mechanisms for promoting durable antitumour immunity.[20,21]

The concept of immunogenic cell death (ICD) emerged from pioneering studies by Kroemer and colleagues in 2005, demonstrating that tumour cells killed by specific chemotherapeutic agents, such as anthracyclines, could function as an endogenous vaccine, eliciting protective antitumour immune responses in mice.[3] This discovery established that certain forms of regulated cell death can stimulate adaptive immunity rather than merely eliminating tumour cells.

ICD is now understood as a form of regulated cell death that is capable of activating adaptive immune responses when dying cells provide both antigenicity, the presence of tumour-associated antigens, and adjuvanticity, which is mediated by the emission of danger signals. These signals include the exposure or release of damage-associated molecular patterns (DAMPs) such as calreticulin (CRT) translocation to the plasma membrane, extracellular ATP secretion, and the release of high-mobility group box 1 (HMGB1) and heat-shock proteins (HSP70/90).[22–24] Collectively, these signals promote dendritic-cell recruitment and maturation, facilitate antigen presentation, and ultimately lead to the activation of tumour-specific cytotoxic T lymphocytes capable of eliminating malignant cells (Fig. 1).[25]

ICD represents a functional immune outcome that can originate from different regulated death pathways, including apoptosis, necroptosis,[27] pyroptosis, and ferroptosis.[28] Importantly, this concept establishes a mechanistic link between classical cytotoxic therapies and modern immunotherapy by coupling tumour cell death with immune activation. In the context of metal-based drugs, therapeutic efficacy has traditionally been attributed primarily to direct cytotoxic effects on tumour cells. More recently, however, increasing attention has been directed toward understanding how metal-induced cell death can be rendered immunogenic, thereby integrating cytotoxic mechanisms with immune stimulation.

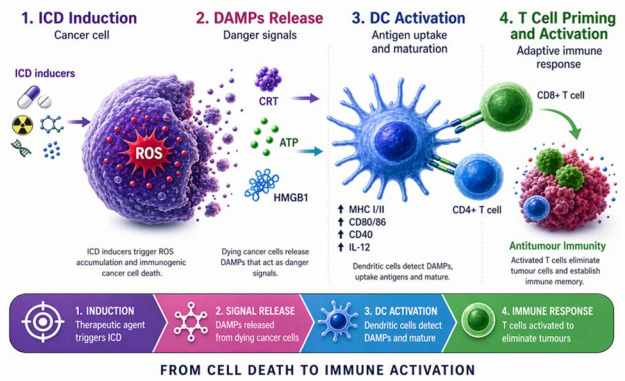


Fig. 1 Overview of the molecular and immunological cascade underlying immunogenic cell death (ICD). Therapy-induced cellular stress triggers the coordinated exposure and release of damage-associated molecular patterns (DAMPs), which promote dendritic cell activation and subsequent cytotoxic T-cell-mediated immune responses.[26]

In this context, metal complexes have emerged as particularly versatile platforms for inducing ICD.[29–31] Their modular coordination environments, accessible redox states, and diverse modes of biomolecular interaction enable precise modulation of cellular stress responses associated with immunogenic signalling. Indeed, platinum(II/IV), ruthenium(II/III), iridium(III), and osmium(II) complexes have demonstrated that redox-active metal centres can promote DAMP exposure and immune activation alongside tumour cell death.[17,32,33] Among metal-based systems, gold complexes represent an especially intriguing comparatively underexplored class of potential ICD inducers.[34–36] The accessible interconversion between Au(I) and Au(III) oxidation states, together with the pronounced affinity of gold for thiol- and selenol-containing proteins,[37–39] enables gold compounds to selectively perturb intracellular redox homeostasis and protein function in cancer cells. While gold compounds have long attracted attention in medicinal chemistry, their capacity to induce immunogenic cell death has only recently begun to be explored, revealing promising opportunities for the development of gold-based chemo-immunogenic agents capable of integrating cytotoxic and immune-activating mechanisms.

2. Hallmarks of immunogenic cell death and detection methods

Having established ICD as a key mechanistic link between cytotoxic stress and antitumour immunity,[40] it is essential to clarify how ICD is defined and how it could be experimentally identified. From a chemical standpoint, ICD should not be studied as a single cell-death pathway. Instead, it reflects a functional immunological outcome that comes from a coordinated sequence of stress responses and danger signalling events. From a chemical and mechanistic perspective, ICD emerges when tumour cell death is accompanied by the emission of immunostimulatory signals capable of activating the adaptive immune system. A critical feature of ICD is that no

single molecular marker is sufficient to define it. Instead, its identification relies on detecting a combination of immunogenic signals that collectively enable the immune system to recognise dying tumour cells and initiate antitumour responses.[41,42] Consequently, ICD is typically validated through a multiparametric evaluation of DAMPs and associated immune-activating processes.

2.1 Defining features and biomarkers of ICD

ICD is primarily characterised by the emission of a set of damage-associated molecular patterns (DAMPs) that are released or exposed in a controlled spatial and temporal manner (Fig. 2).[43] Through these signals, dying cancer cells are converted into an immunologically visible source of antigens that the immune system can efficiently process. Among the various DAMPs described to date, three biomarkers are widely accepted as core hallmarks of ICD: the translocation of calreticulin (CRT) to the outer leaflet of the plasma membrane, the active release of adenosine triphosphate (ATP) into the extracellular space, and the late-stage release of high-mobility group box 1 (HMGB1).[44] CRT exposure occurs early during ICD and functions as an "eat me" signal, promoting the phagocytic uptake of dying tumour cells by antigen-presenting cells. In parallel, extracellular ATP acts as a "find me" signal that recruits and activates immune cells in the tumour microenvironment. At later stages, HMGB1 is released from the nucleus, where it supports antigen processing and downstream immune activation.

Beyond these standard markers, ICD can also involve extra immune-boosting signals. This includes endoplasmic reticulum chaperones like heat-shock proteins (HSP70/90),[45] annexin A1,[46] and inducible mediators such as type I interferons.[44] While these signals are not always necessary for all ICD inducers, their presence can significantly amplify immune activation and shape the quality of the antitumour response. Crucially, effective ICD depends not merely on the presence of individual DAMPs, but on their coordinated and temporally ordered emission, as disruption of any component can markedly attenuate immunogenicity.

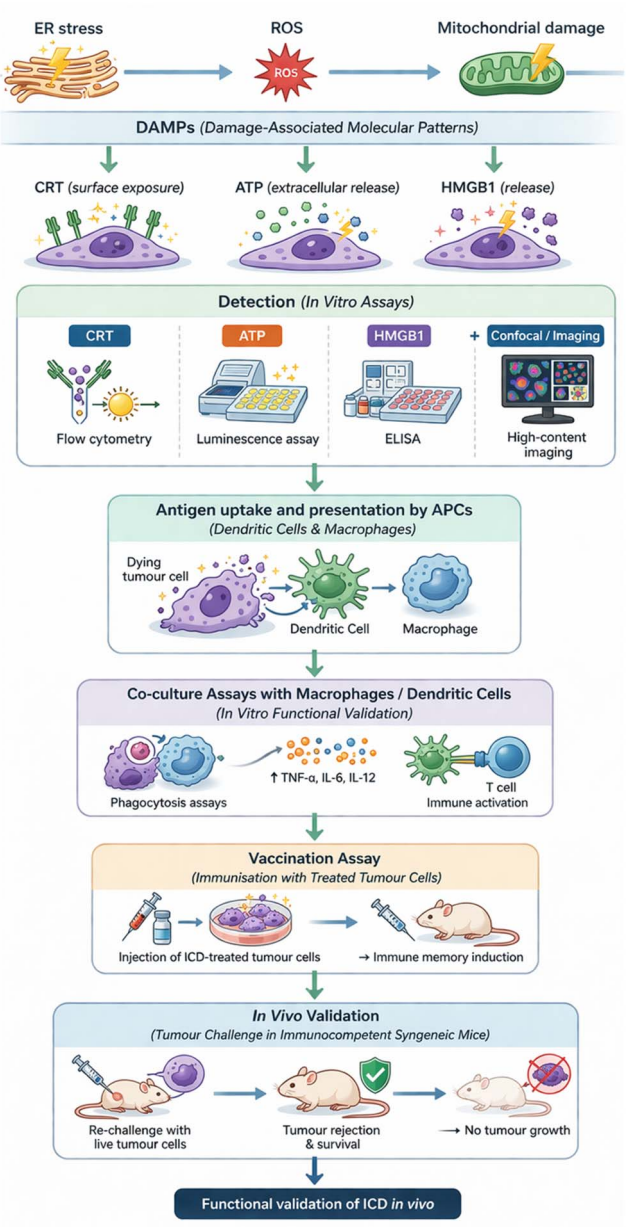


Fig. 2 Integrated workflow for the experimental validation of ICD, showing DAMP emission, corresponding detection methods, and downstream functional validation through antigen-presenting cells and *in vivo* tumour-rechallenge models.

2.2 Experimental approaches for the detection of ICD

In practice, ICD involves a coordinated pattern of surface exposure, active secretion, and late-stage release events, which are best captured through a multi-parametric approach.

Calreticulin exposure is usually measured by flow cytometry on non-permeabilised cells, stained with fluorescent anti-CRT antibodies. Additionally, several studies have also utilised confocal fluorescence microscopy to confirm CRT translocation from the endoplasmic reticulum to the plasma membrane, which is particularly helpful for visualising differences within treated cell populations.[47]

Regarding the release of extracellular ATP, it is usually measured using luciferase-based luminescence tests on culture supernatants, which are commercially available. These tests are highly sensitive and easy to quantify, making them suitable for time-resolved studies since ATP release often occurs before noticeable membrane permeabilisation.[48] Additional methods, such as fluorescent ATP probes or targeted mass spectrometry, can also support ATP measurements when needed.[49] Focusing on the detection of HMGB1. This release typically occurs later in the cell death process and is most often quantified through ELISA or immunoblotting of conditioned media; however, the use of flow cytometry and fluorescence confocal microscopy is gaining relevance.[50]

In addition to these established biomarkers, high-content imaging platforms are becoming increasingly valuable for ICD research. Automated fluorescence microscopy enables the

simultaneous monitoring of multiple parameters, including CRT exposure, mitochondrial integrity, and plasma-membrane permeability, across large cell populations. Furthermore, intracellular stress responses associated with ICD, such as endoplasmic-reticulum stress or oxidative stress, are commonly assessed using fluorescent probes,[51] reporter constructs, or staining for stress-related markers.[52]

It is important to point out that the timing of these events is crucial. Immunogenic signalling usually follows a specific order, with ER stress and ROS production occurring before CRT exposure, ATP release happening in the early stages of cell death, and HMGB1 release appearing later. Capturing this sequence is key for accurate ICD classification, emphasising the need for time-resolved experimental designs instead of single-endpoint measurements, which may lead to misclassification of ICD.[42,44]

Beyond DAMP detection, the workflow also includes downstream functional validation steps, such as antigen uptake by dendritic cells and macrophages, followed by co-culture assays and *in vivo* tumour-rechallenge models to confirm the immunogenic potential of dying cells.

2.3 Mechanistic pathways leading to ICD

Although a wide variety of cellular stressors can induce ICD, mechanistic distinctions are often made between type I and type II ICD inducers, based on how they engage the endoplasmic reticulum (ER).[29]

- Type I ICD inducers act primarily on intracellular targets other than the ER, with ER stress emerging as a secondary consequence of broader proteotoxic or redox imbalance. Many traditional chemotherapeutics fall into this category, where accumulation of misfolded proteins and redox imbalance ultimately activate unfolded protein responses.[53]
- Type II ICD inducers act more directly on the ER, triggering stress responses at an early stage and often producing a more defined pattern of DAMP emission.[54]

Metal complexes are particularly well suited to engage these pathways. Rather than acting through a single molecular target, many metal-based compounds perturb multiple cellular processes simultaneously, including redox homeostasis, proteostasis, and mitochondrial function. This multi-targeted mode of action frequently generates the integrated stress responses required for ICD initiation and provides a mechanistic basis for the growing interest in metal complexes as immunogenic anticancer agents.[29]

3. Gold chemistry and biological reactivity

Among metal-based systems capable of inducing immunogenic stress responses, gold complexes represent a particularly compelling case study owing to their distinctive chemical reactivity and biological targets. A defining feature of gold coordination chemistry is its pronounced affinity for thiol- and selenol-containing proteins, which enables both Au(I) and Au(III) species to interact selectively with redox-active enzymes.

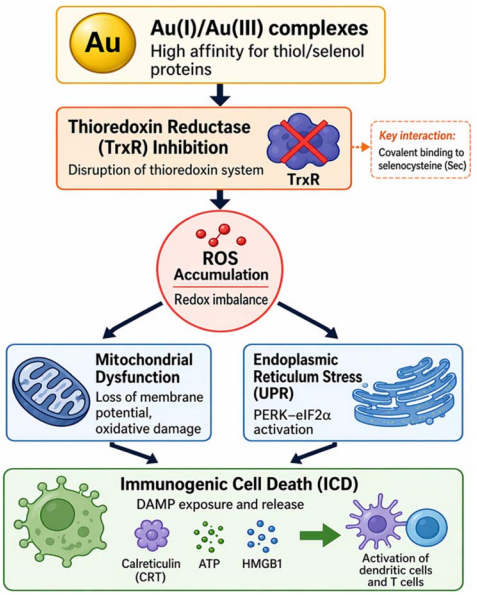


Fig. 3 Proposed mechanistic framework for gold-induced immunogenic cell death. Gold complexes inhibit thioredoxin reductase and related thiol-dependent proteins, leading to redox imbalance, ROS accumulation, mitochondrial dysfunction, and ER stress. These interconnected stress pathways promote the exposure and release of DAMPs, ultimately triggering dendritic-cell activation and antitumour immune responses.

In particular, many gold complexes potently inhibit thioredoxin reductase (TrxR) and related components of the thioredoxin system, thereby disrupting one of the central regulatory nodes of intracellular redox homeostasis (Fig. 3).

Inhibition of TrxR leads to rapid accumulation of ROS, which in turn promotes mitochondrial dysfunction, oxidative stress, and activation of ER stress pathways. These interconnected stress responses are strongly associated with the molecular events that underlie immunogenic cell death, including the exposure and release of DAMPs. From a mechanistic standpoint, the ability of gold complexes to simultaneously perturb multiple redox-regulated pathways provides a plausible explanation for their emerging immunogenic potential.

Consistent with this view, several Au(I) phosphine and N-heterocyclic carbene (NHC) complexes have been shown to induce hallmark features of ICD *in vitro*, and in some cases to generate protective vaccination effects in immunocompetent mouse models. These observations align with earlier mechanistic studies linking gold-mediated TrxR inhibition to oxidative stress signalling,[55] as well as with more recent analyses highlighting the central role of redox modulation in the pharmacology of gold-based anticancer agents.[56] Moreover, translational perspectives on gold therapeutics increasingly emphasise the intersection between redox disruption and immune-related signalling pathways, suggesting that gold complexes may act not only as cytotoxic agents but also as modulators of tumour immunogenicity.[57]

Taken together, these findings highlight how gold coordination chemistry offers a uniquely tunable platform for coupling cytotoxic stress with immune activation. Through rational ligand design, the redox properties, cellular localisation, and protein-targeting profiles of gold complexes can be modulated, providing opportunities to control the cellular stress responses that ultimately drive immunogenic cell death. In this sense, gold complexes should be viewed not merely as conventional cytotoxics but as chemically programmable chemo-immunogenic agents capable of bridging metallodrug development and cancer immunotherapy.

Notably, this mode of action differs from that of classical platinum drugs, which primarily target DNA, highlighting how gold complexes engage a distinct set of cellular pathways that are closely linked to redox signalling and immunogenic stress.

Notably, the immunological consequences of gold-mediated redox modulation are not unidirectional, but depend strongly on biological context. Gold complexes have long been associated with immunosuppressive activity, exemplified by auranofin, which exerts anti-inflammatory effects primarily through inhibition of thiol- and selenol-containing enzymes such as thioredoxin reductase (TrxR). However, the same redox-active properties can be redirected toward immunostimulation in cancer, revealing a context-dependent duality. This behaviour is governed by factors including dose, target selectivity, and cellular context, as tumour cells-characterised by elevated basal oxidative stress, are particularly susceptible to ROS-driven immunogenic signalling. Ultimately, the balance between redox disruption and cellular adaptation determines whether gold-induced stress results in immunosuppression or coordinated DAMP emission. These observations underscore that the immunological effects of gold complexes are not intrinsic but can be tuned through rational design, enabling a shift from anti-inflammatory activity toward selective immune activation in tumour settings.

4. Evidence of immunogenic or ICD-like activity in gold complexes

Although most recent studies have focused on ICD-associated DAMP emission, earlier work already suggested that gold compounds may influence antitumour immunity through broader immunomodulatory mechanisms. In addition to promoting immunogenic tumour-cell death, gold complexes have been reported to modulate innate immune signalling, dendritic-cell maturation, and cytokine production, as well as to affect immune checkpoint pathways and tumour–immune interactions within the tumour microenvironment. These observations indicate that the immunological activity of gold compounds may extend beyond classical ICD pathways, positioning them as multifunctional modulators of tumour immunogenicity.[58]

Over the past five years, several insightful studies have progressively established Au(I) and Au(III) complexes as chemically programmable triggers of immunogenic stress. What is particularly striking is how consistently these systems exploit gold reactivity, thiol affinity, TrxR inhibition, mitochondrial targeting, and redox cycling to engage the ICD cascade.

4.1 Au(I) complexes: redox and mitochondrial stress

One of the earliest demonstrations of this concept was reported in 2020 by Cui, Sessler, Arambula and co-workers, who described a rationally designed redox-active Au(I) bis-N-heterocyclic carbene (bis-NHC), complex **1**, capable of inducing ICD.[59] Importantly, this system was designed to simultaneously target the cancer antioxidant network and promote oxidative stress, combining TrxR inhibition with quinone-mediated redox cycling. This dual mechanism sustains ROS generation and disrupts redox homeostasis, leading to mitochondrial and endoplasmic reticulum stress, both key upstream events associated with ICD. Consistent with this mode of action, complex **1** induced hallmark ICD features *in vitro*, including calreticulin exposure, ATP secretion, and HMGB1 release (Fig. 4). Crucially, vaccination experiments demonstrated that tumour cells pre-treated with **1** could elicit protective antitumour immunity *in vivo*. In a murine CT26 model, cells pre-treated with **1** (10 μM) delayed or prevented tumour growth upon rechallenge, outperforming oxaliplatin despite being used at a substantially lower concentration. This study highlights how rational redox modulation can be translated into immunogenic outcomes, while also underscoring the importance of dose-dependent effects in balancing cytotoxicity and immune activation.

The limitations of complex **1** arising from its poor aqueous solubility have been addressed in subsequent work through the development of second-generation derivatives, demonstrating that redox-active Au(I) bis-NHC scaffolds can be optimised to balance physicochemical properties with sustained ICD activity and long-lived immune responses.[60]

Building on this concept, in 2022 Patil and collaborators developed a library of benzo[*a*]quinolizinium-based Au(I) complexes through an intramolecular amino-auration reaction of pyridino-alkynes.[61] Among all candidates, BQ-AuiPr complex (**2**) induced pronounced ICD-associated DAMP emission, including HMGB1 release, extracellular ATP secretion, calreticulin exposure, and production of inflammatory mediators such as IL-1β and CXCL10. These effects were corroborated through phagocytosis assays in co-culture with immune cells.

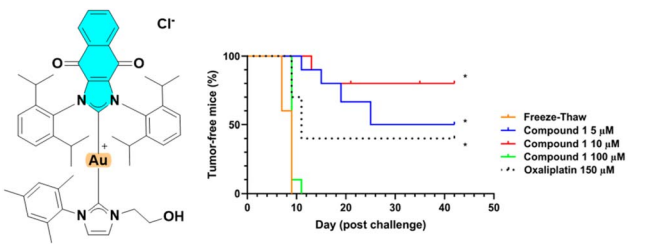


Fig. 4 Chemical structure of **1**, and percentage of tumour-free mice (left flank) after removal of the primary tumour (right flank) before it reached 200 mm^3, $p < 0.005$. Reproduced with permission. Copyright 2020, ACS.[59]

Mechanistic studies indicated that the cytotoxic activity of **2** (IC_{50} values ranging from 0.25 to 0.78 μM across several cancer cell lines) originates from mitochondrial oxidative stress that ultimately triggers mitophagy and immunogenic signalling.

Subsequent studies have introduced increasingly sophisticated molecular architectures, highlighting the development of multifunctional strategies that combine gold centres with complementary biological targets at different levels of tumour biology to enhance tumour selectivity.

In 2023, Liu and co-workers developed tumour-targeting Au(I) NHC complexes bearing glycyrrhetinic acid (GA) as a hepatocellular carcinoma targeting ligand.[62] Complex **3** displayed potent inhibition of TrxR, resulting in intracellular ROS accumulation and G0/G1 cell-cycle arrest. Its mitochondrial localisation led to loss of mitochondrial membrane potential and activation of apoptotic signalling pathways. Notably, ROS-driven endoplasmic reticulum stress induced by **3** promoted DAMPs exposure and downstream immune activation. *In vivo* vaccination experiments further demonstrated that Hepa1-6 cells treated with **3** acquired immunogenic properties and significantly delayed tumour growth upon rechallenge, while exhibiting minimal systemic toxicity (Fig. 5).

Parallel efforts explored hybrid molecular designs capable of simultaneously modulating redox homeostasis and immune signalling pathways. Xu and collaborators reported NSAID–Au(I) hybrid complexes combining ROS-driven ICD induction with regulation of inflammatory signalling.[63] In ovarian cancer models, the lead compound **4** triggered canonical ICD hallmarks such as CRT exposure and HMGB1 release while simultaneously downregulating COX-2 and PD-L1 expression (Fig. 6). This dual activity is particularly notable because it links oxidative stress induction with immune checkpoint modulation. *In vivo* studies further demonstrated enhanced dendritic cell maturation, reduced PD-L1 expression in tumour tissues, and increased infiltration of $CD4^+$ and $CD8^+$ T cells into the tumour microenvironment.

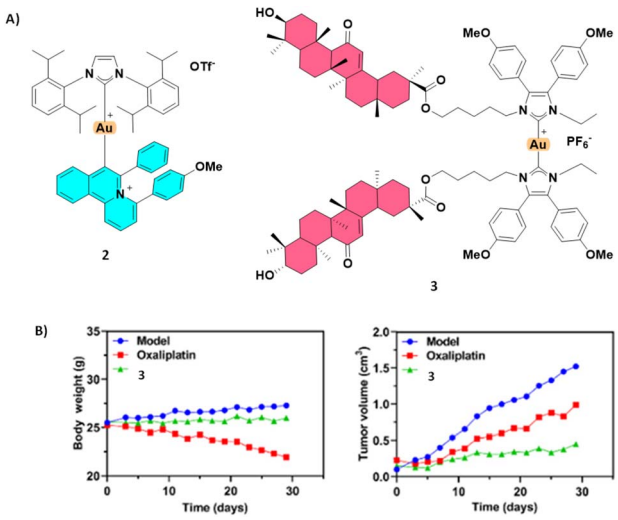


Fig. 5 (A) Chemical structures of complexes **2** and **3**; (B) curves of body weight and tumour volume during treatment with complex **3** ($n = 10$). Reproduced with permission. Copyright 2023, ACS.[61,62]

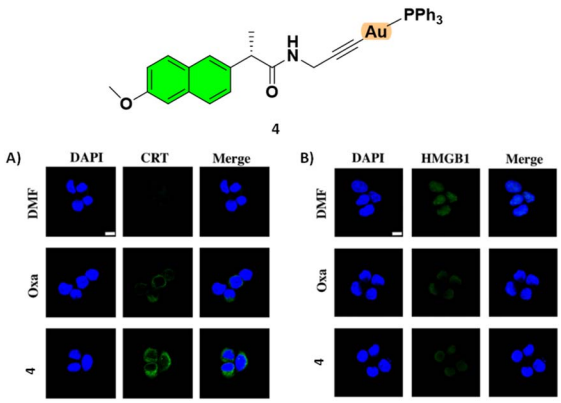


Fig. 6 Chemical structure of complex **4**. Immunofluorescence images of CRT (A) and HMGB1 (B) after treatment with **4** (4 μM) or oxaliplatin (4 μM) in A2780 cells. Scale bar: 10 μm, incubation time: 24 h. Reproduced with permission. Copyright 2023, ACS.[63]

Also in 2023, Liu and co-workers reported another dual-targeting strategy in which the clinical selective estrogen receptor degrader (SERD) candidate G1T48 was covalently linked to an NHC–Au(I) scaffold, generating hybrid complexes capable of simultaneously degrading estrogen receptors and inhibiting TrxR (Fig. 7).[64] The most active compound, complex **5**, combined dose-dependent ER downregulation with covalent inhibition of TrxR *via* interaction with the selenocysteine residue Sec498. This dual mechanism disrupts proliferative signalling while amplifying ROS accumulation, ultimately inducing ER stress and promoting the emission of ICD hallmarks.

At the tumour microenvironment level, gold-based systems have evolved toward designs that target specific biological pathways, combining the induction of immunogenic cell death with the reduction of immune suppression. In particular, the dual targeting of TrxR and the MAPK pathway links oxidative

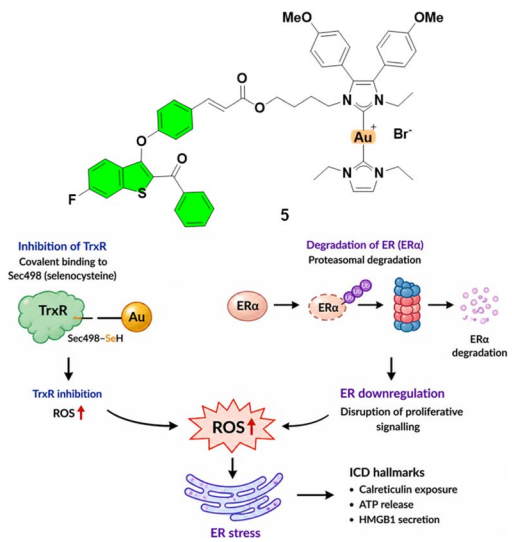


Fig. 7 Chemical structure of complex **5**, and its mechanism of action.

stress with the regulation of immunosuppressive signalling, promoting the release of DAMPs while reducing key mechanisms of immune escape. Notably, Liu's design demonstrates that this strategy can be achieved by combining an NHC–Au(I) scaffold with the natural product glabridin, allowing simultaneous control of redox balance and immune-related signalling pathways.[65]

More recently, this design paradigm has been further expanded to incorporate subcellular targeting and direct immune activation. In 2024, Liu and co-workers reported mitochondria- and liver-targeted Au(I) complexes designed to simultaneously induce ICD and activate the cyclic GMP–AMP synthase-stimulator of interferon genes (cGAS-STING) pathway in hepatocellular carcinoma.[66] Among the developed compounds, complex **6** showed the highest activity (Fig. 8A). Selective mitochondrial accumulation triggered mitochondrial dysfunction and robust ROS production, leading to mitochondrial DNA release into the cytosol. This event activated the cGAS-STING signalling cascade and subsequent type I interferon responses, thereby coupling redox-driven ICD with innate immune activation. Notably, **6** demonstrated pronounced tumour growth inhibition in a patient-derived xenograft (PDX) model of hepatocellular carcinoma, highlighting its translational potential (Fig. 8B).

A recent study by Feng, Tang and co-workers further exemplifies how rational ligand engineering can be exploited to develop multifunctional Au(I)-based ICD inducers. A series of Au(I) complexes **7** was constructed through systematic manipulation of ligand frameworks, enabling tumour-selective targeting and the integration of chemotherapy, phototherapy, and immunotherapy within a single molecular platform (Fig. 9).[35] By combining redox-active Au(I) centres with aggregation-induced emission (AIE) photosensitising ligands, the authors achieved a synergistic therapeutic effect in which thioredoxin reductase inhibition disrupts redox homeostasis, while light-triggered

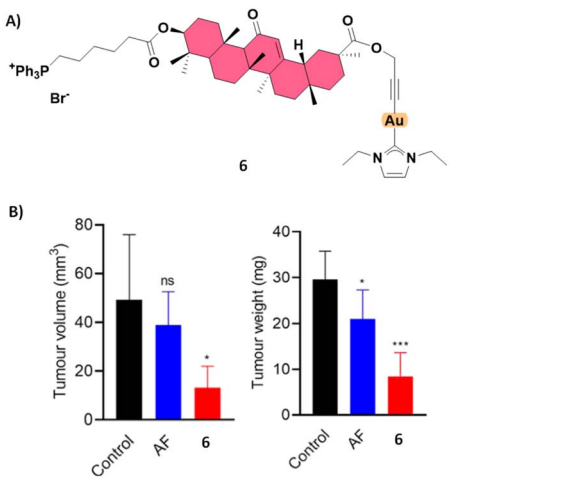


Fig. 8 (A) Depiction of **6**, capable of inhibiting tumour growth in a PDX model of hepatocellular carcinoma; (B) quantitative analysis of tumour volume and weight at the end of the treatment with **6** in a PDX model of hepatocellular carcinoma ($n = 3$; ns, not significant; $^{*}P < 0.05$; $^{***}P < 0.001$). Reproduced with permission. Copyright 2024, ACS.[66]

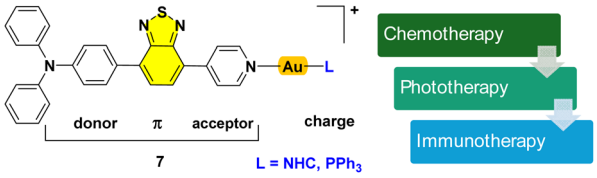


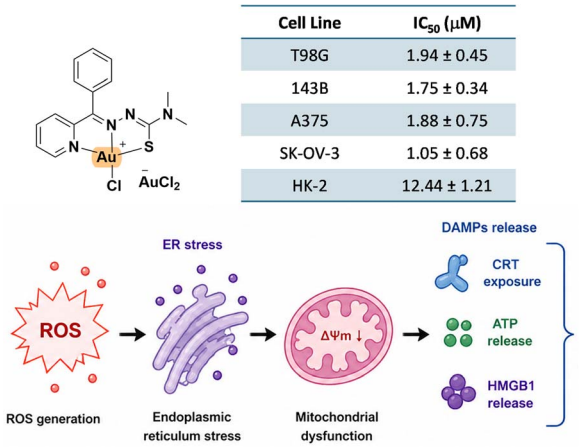
Fig. 9 Rational design of Au complex **7** for combined chemo-, photo-, and immunotherapy, integrating redox modulation, photoinduced ROS generation, and immunogenic cell death induction.

activation enhances ROS generation. This dual mechanism promotes pronounced oxidative stress, particularly at the endoplasmic reticulum and mitochondria, leading to Ca^{2+} release, mitochondrial dysfunction, and robust immunogenic cell death characterised by DAMP emission. Notably, structural tuning of the ligand environment enabled control over photophysical properties, ROS generation efficiency, and subcellular localisation, with the lead complex exhibiting efficient tumour imaging, ER targeting, and strong *in vitro* and *in vivo* therapeutic performance.

4.2 Au(III) complexes: mechanistic diversity

While early work primarily focused on Au(I) complexes, recent studies have expanded this paradigm to Au(III) platforms with enhanced structural and redox versatility. In 2025, Liang, Yang and co-workers reported a rationally designed Au(III) complex **8** capable of suppressing tumour growth and metastasis through ICD induction.[67] In contrast to classical Au(I) systems, this compound was engineered to exploit the higher redox activity and coordination flexibility of Au(III), enabling more effective engagement of intracellular stress pathways. Complex **8** exhibited potent cytotoxic activity against several cancer cell lines, including glioblastoma (T98G), osteosarcoma (143B), and ovarian cancer (SK-OV-3), with IC_{50} values in the low micromolar range. Mechanistic investigations revealed that its activity is driven by the induction of pronounced endoplasmic reticulum stress, accompanied by Ca^{2+} release, mitochondrial membrane potential collapse, and excessive mitochondrial ROS production. These effects are consistent with a design strategy aimed at simultaneously targeting ER and mitochondrial function, thereby amplifying intracellular stress signalling. The resulting self-reinforcing ER–mitochondrial stress loop promotes sustained oxidative imbalance and ultimately triggers robust immunogenic signalling (Fig. 10).

Further expanding the mechanistic diversity of gold-mediated ICD, Wang, Huang, Liang and collaborators recently Au(III) complexes can engage necroptosis as an alternative immunogenic cell-death pathway.[68] In this study, a series of cyclometallated Au(III) compounds incorporating isoquinoline-derived C^N ligands was developed, with complex **9** identified as the lead candidate. This ligand framework was designed to stabilise the Au(III) oxidation state while promoting cellular uptake and redox activity, thereby facilitating efficient targeting of intracellular thiol-dependent pathways. This compound exhibited potent cytotoxicity against CT26 cells ($IC_{50} \approx 1$ μM)



Cell Line	IC_{50} (μM)
T98G	1.94 ± 0.45
143B	1.75 ± 0.34
A375	1.88 ± 0.75
SK-OV-3	1.05 ± 0.68
HK-2	12.44 ± 1.21

Fig. 10 Chemical structure of complex **8** and its IC_{50} (μM) values across different cell lines after 48 h of incubation, together with the proposed mechanism of action.

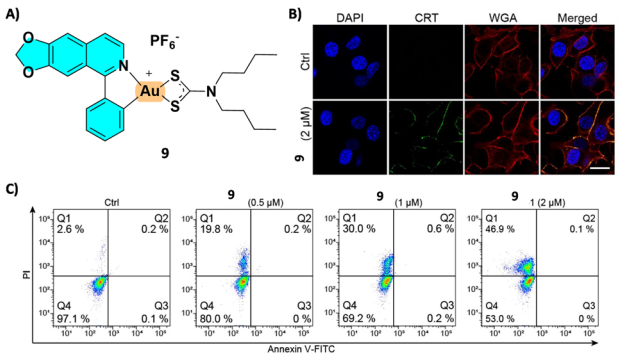


Fig. 11 (A) Chemical structure of complex **9**; (B) confocal microscopy images of CRT exposure in CT-26 cells treated with **9** for 24 h. Scale bar = 20 μm; (C) flow cytometry studies with double staining annexin V-FITC/PI after 24 h of treatment. Reproduced with permission. Copyright 2026, ACS.[68]

and inhibited TrxR, leading to ROS accumulation (Fig. 11). Notably, the resulting oxidative stress did not primarily trigger apoptosis, but instead induced ROS-dependent necroptosis, a regulated cell-death pathway associated with enhanced immunogenicity due to membrane permeabilisation and robust release of intracellular signals. This shift in cell-death modality highlights how subtle changes in chemical design can redirect downstream biological outcomes. In murine tumour models, complex **9** suppressed tumour growth, enhanced $CD8^+$ T-cell activation, reduced regulatory T-cell populations, and showed strong synergy with anti-PD-1 immunotherapy.

Berger, Ang, Babak and co-workers reported a large family of cyclometalated Au(III) complexes bearing dithiocarbamate ligands, providing a systematic platform to probe how structural features influence immunogenic outcomes.[69] In this study, the combination of a cyclometalated scaffold and strongly donating dithiocarbamate ligands was designed to modulate the lipophilicity, stability, and cellular uptake of the complexes, thereby enabling controlled tuning of their biological activity.

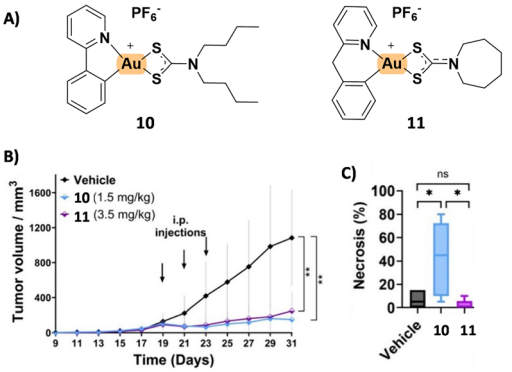


Fig. 12 (A) Structures of the Au(III) complexes **10** and **11**; (B) tumour growth kinetics in the AB12 mesothelioma model following intraperitoneal administration of the complexes at the indicated doses (days 19, 21, and 23 after tumour inoculation). Tumour volumes were monitored over time by calliper measurements; (C) quantitative analysis of necrotic areas in tumour tissues determined from H&E-stained sections collected at the endpoint of the study. Reproduced with permission. Copyright 2025, ACS.[69]

Interestingly, the study highlighted how different death modalities influence the immunogenic outcome. While the highly lipophilic complex **10** produced extensive tumour necrosis *in vivo* and triggered strong CRT exposure in tumour tissues, this damage-driven response did not translate into durable antitumour immunity in vaccination experiments. In contrast, the related complex **11**, which caused minimal tissue necrosis but promoted regulated cell death and efficient phagocytosis of dying cells, generated a long-lasting immune response in vaccinated mice (Fig. 12). These observations suggest that extensive necrotic damage alone is not sufficient to sustain immunogenic signalling. Rather, controlled cell death processes appear more favourable for establishing durable antitumour immunity.

4.3 Heterometallic Au-based systems

A representative example is provided by Sessler and co-workers, who developed a series of Pt(IV)–Au(I) prodrugs that evolved from a first-generation (**12**) proof-of-concept into a more advanced second-generation (**13**) system (Fig. 13).[70] While **12** demonstrated that co-delivery of platinum and gold could

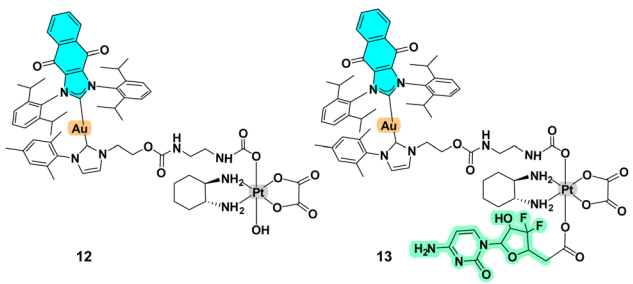


Fig. 13 Chemical structures of heterometallic complexes **12** (Gen 1) and **13** (Gen 2) illustrating the evolution of Au-based multimetal systems for immunogenic cell death induction.

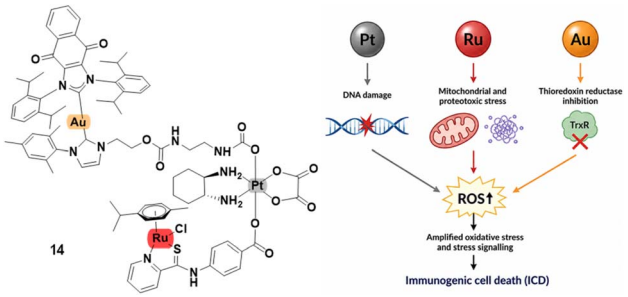


Fig. 14 Chemical structures of heterotrimetallic complex **14** and a schematic representation of its proposed mechanism of action.

enhance early apoptotic events relevant to ICD, it suffered from limited cellular uptake and modest cytotoxicity. In contrast, the rationally redesigned **13** construct incorporates both a redox-active Au(I) bis-NHC fragment and gemcitabine within a Pt(IV) scaffold, enabling simultaneous DNA damage, redox disruption, and antiproliferative activity. This design improves cellular uptake, modulates subcellular distribution, and produces a distinct ICD-associated transcriptional profile, including activation of HMGB1, p53, and dendritic cell signalling pathways. Importantly, the covalent integration of all components ensures synchronised intracellular release and avoids the limitations associated with physical drug mixtures.

In parallel, the development of a trimetallic Au(I)–Pt(IV)–Ru(II) system, **14**, further illustrates how increasing structural complexity can expand mechanistic diversity.[30] In this case, platinum contributes DNA damage, ruthenium promotes mitochondrial and proteotoxic stress, and gold inhibits thioredoxin reductase, collectively amplifying ROS production and stress signalling. Compared to the bimetallic systems, this approach enables the simultaneous engagement of multiple ICD-relevant pathways, resulting in enhanced DAMP emission and improved antitumour immune responses (Fig. 14).

Taken together, these studies highlight the key advantages of Au-containing heterometallic systems: (i) mechanistic complementarity, where redox modulation by gold is coupled with DNA damage and/or mitochondrial stress from additional metals; (ii) spatiotemporal control, achieved through prodrug activation and coordinated release; and (iii) enhanced immunogenic output, arising from the integration of multiple stress pathways. These findings underscore the potential of heterometallic design to overcome the limitations of single-agent ICD inducers and to enable more robust and durable antitumour immunity.

4.4 Design principles for Au-based ICD inducers

Collectively, the studies discussed above outline emerging design principles for gold-based ICD inducers, highlighting how coordination chemistry can be leveraged to tune both cytotoxicity and immune activation. A central feature is the ability of Au(I)/Au(III) complexes to modulate intracellular redox homeostasis, most commonly through inhibition of thiol- and selenol-containing proteins such as thioredoxin reductase. This interaction provides a chemically defined entry point into ROS generation, which acts as an upstream trigger for the integrated stress responses required for ICD. However, effective ICD induction depends not simply on ROS production, but on achieving a controlled and spatially organised stress response, where mitochondrial dysfunction and endoplasmic reticulum stress are coordinated to promote DAMP exposure and immune activation.

Importantly, this behaviour is not merely the result of indiscriminate oxidative damage. Instead, ligand design, oxidation-state selection, and subcellular targeting collectively determine both the intensity and the immunological quality of the response to stress. In this context, mitochondrial localisation amplifies oxidative stress, whereas ER engagement facilitates unfolded protein response signalling and calreticulin exposure, highlighting how organelle-specific targeting can be used to direct ICD-relevant pathways.

The immunogenic outcome is further influenced by the nature of the cell-death pathway engaged. While many gold complexes induce apoptosis-associated ICD, alternative regulated pathways such as necroptosis, pyroptosis, or ferroptosis may also contribute, and even subtle structural variations can shift these outcomes. This sensitivity to chemical structure underscores the challenge of establishing predictive structure–activity relationships for ICD, while also offering opportunities to tune immunogenicity through rational design.

At the molecular level, ligand selection plays a decisive role. N-heterocyclic carbene (NHC) ligands typically confer high stability and strong TrxR inhibition, whereas phosphine-based systems can modulate lipophilicity and cellular uptake. Beyond monofunctional designs, multimodal architectures have emerged as a powerful strategy, integrating redox stress with additional triggers such as phototherapy or targeting moieties to amplify immunogenic signalling.

An emerging extension of these principles involves heterometallic systems, in which gold is combined with complementary metal centres to integrate multiple ICD-relevant mechanisms within a single scaffold. In such constructs, gold often serves as a redox-active module, while additional metals introduce orthogonal effects such as DNA damage or alternative organelle targeting. Notably, recent examples of multimetallic complexes demonstrate enhanced ICD induction by combining redox imbalance with complementary stress pathways, effectively encoding combination therapy at the molecular level.

Taken together, these findings position gold complexes not merely as cytotoxic agents, but as chemically programmable modulators of stress signalling, capable of bridging redox pharmacology and tumour immunology. The ability of both Au(I) and Au(III) systems to orchestrate coupled ER–mitochondrial stress responses highlights the versatility of gold coordination chemistry, and provides a conceptual framework for the rational development of next-generation chemo-immunogenic agents.

4.5 Mechanistic parallels beyond gold: insights from platinum, and other transition metals

4.5.1 Platinum platforms: from DNA damage to ICD. While gold complexes provide a chemically defined entry point into

redox biology, platinum complexes represent a historical milestone in metal-based chemotherapy and the first demonstration that classical cytotoxic mechanisms can, under specific conditions, generate immunogenic signalling. The platinum field illustrates how genotoxic stress can be routed into immune activation when appropriately integrated into cellular stress networks.

Among clinically used platinum drugs, oxaliplatin stands out as the prototypical platinum-based inducer of ICD. In contrast to cisplatin, which predominantly triggers immunologically silent apoptosis,[71] oxaliplatin induces ER stress, calreticulin exposure, ATP secretion, and HMGB1 release.[72] A critical mechanistic distinction lies in the ability of oxaliplatin to induce pre-apoptotic ER stress, a key requirement for efficient calreticulin translocation and dendritic-cell recognition of dying tumour cells.[73,74] At the molecular level, both cisplatin and oxaliplatin exert their cytotoxicity through the formation of Pt–DNA adducts, primarily intrastrand crosslinks that distort the DNA helix and activate the DNA damage response. However, the structural nature of these adducts and the downstream stress differ significantly. The bulky DACH ligand present in oxaliplatin generates DNA lesions that promote a more pronounced proteotoxic and ER stress response, thereby coupling genotoxic damage to immunogenic signalling. Organoplatinum(II) complexes capable of inhibiting protein tyrosine phosphatase 1B (PTP1B) have been reported to trigger ER stress and robust DAMP emission, highlighting that platinum-induced immunogenic signalling can arise from both DNA- and protein-targeting mechanisms.

These findings reinforce the notion that ICD arises from the activation of integrated cellular stress responses rather than a single dominant molecular target.[75]

More recently, attention has shifted toward Pt(IV) prodrugs, which offer an additional level of chemical control over platinum pharmacology.[76] In their octahedral Pt(IV) oxidation state, these complexes are generally kinetically inert and undergo intracellular reduction, often mediated by glutathione, ascorbate, or other biological reductants, to release active Pt(II) species together with axial ligands. This redox-triggered activation enables spatiotemporal control over drug release and provides opportunities to co-deliver bioactive fragments. Recent examples further demonstrate that Pt(IV) complexes can function as multifunctional molecular platforms, in which axial ligands incorporate pharmacologically active moieties capable of modulating complementary pathways. In such systems, platinum-mediated cytotoxicity can be combined with targeted inhibition of immunoregulatory pathways, effectively creating built-in combination therapies within a single coordination scaffold. Importantly, the immunogenic potential of platinum-based agents is not restricted to Pt(IV) systems. A notable example of clinically relevant platinum-induced immunogenic signalling is **PT-112**, a Pt(II) complex currently undergoing phase II clinical evaluation for recurrent thymoma and thymic carcinoma.[77,78] **PT-112** has been shown to induce ICD, while

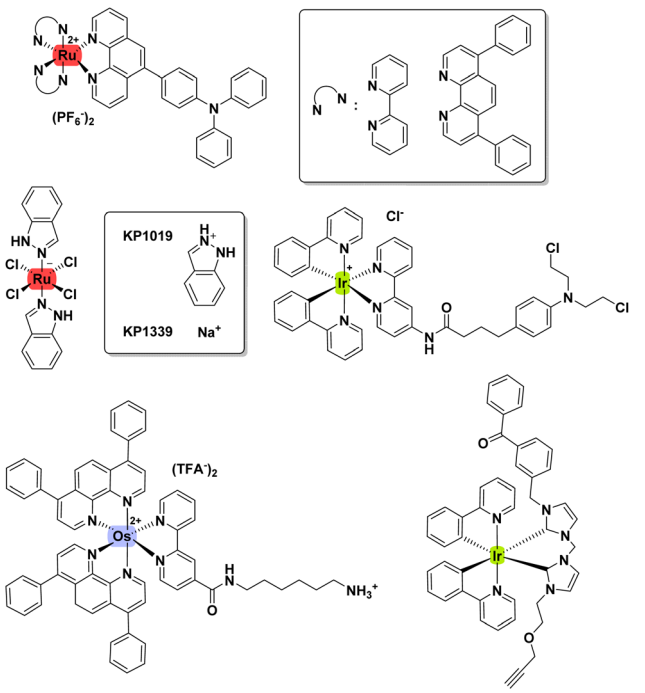


Fig. 16 Chemical structures of some metallodrugs that show efficacy as ICD inducers.

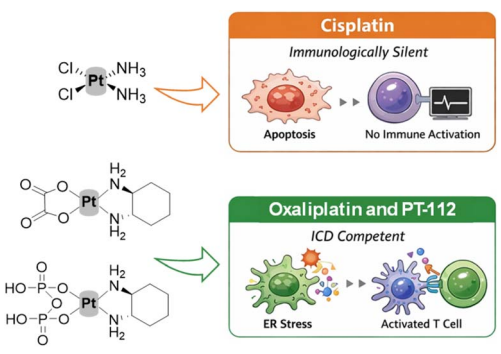


Fig. 15 Representative structures of oxaliplatin, cisplatin, and **PT-112**, and a schematic highlighting differences between cisplatin (immunologically silent) and oxaliplatin (ICD-competent).

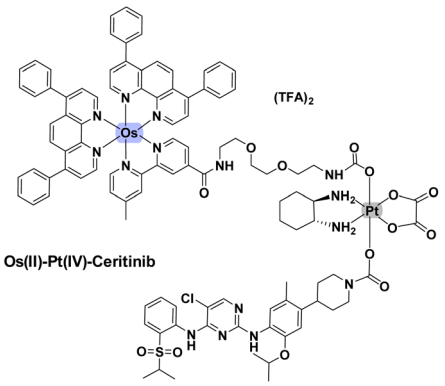


Fig. 17 Chemical structure of the heterometallic complex that has shown the capacity to induce activation of the immune system.[47]

Table 1 Conceptual comparison of the primary chemical triggers and dominant stress pathways leading to immunogenic cell death (ICD) for representative transition-metal platforms discussed in this Perspective

Metal	Primary chemical trigger	Dominant ICD pathway
Au	Thiol/selenol protein targeting (*e.g.*, TrxR inhibition); redox disruption	ROS accumulation → mitochondrial dysfunction → ER stress → DAMP emission
Pt	DNA damage; protein targeting (in some systems); Pt(IV) reductive activation	DNA damage response → ER stress → DAMP exposure
Ru	Redox activation; mitochondrial targeting; protein interactions	Mitochondrial dysfunction → oxidative stress → ICD signalling
Ir	Photoactivated ROS generation; ER targeting	Localised oxidative stress → ER stress → DAMP release
Os	Redox-active organometallic scaffolds	Mitochondrial ROS production → oxidative stress → ICD-associated signalling

simultaneously promoting immune-mediated antitumour responses (Fig. 15).

Taken together, platinum systems demonstrate how genotoxic stress can be converted into immunogenic signalling when appropriately coupled to ER stress and danger pathways. In contrast to the predominantly redox-driven mechanisms associated with many gold complexes, platinum platforms highlight a complementary route to ICD in which DNA damage, protein targeting, and prodrug activation strategies converge to stimulate antitumour immunity.

4.5.2 Ruthenium, iridium and osmium complexes. While gold and platinum complexes have provided much of the conceptual framework for metal-driven immunogenic cell death, the range of metallodrugs capable of inducing immunogenic stress is rapidly expanding (Fig. 16). Increasing evidence suggests that ICD can arise from a broader class of coordination compounds whose physicochemical properties determine how intracellular stress is generated, spatially organized, and temporally regulated. In contrast to the DNA damage-driven mechanisms typically associated with platinum platforms and the redox-protein targeting characteristic of many gold complexes, other transition metals frequently access ICD through organelle-directed oxidative stress and metabolic disruption.

Among these systems, ruthenium complexes represent one of the earliest non-platinum metallodrug families to reach clinical evaluation. Ru(III) scaffolds such as KP1019 and its sodium salt KP1339 were originally developed under the premise of reductive activation in the tumour microenvironment, where the accessible Ru(III)/Ru(II) redox couple enables intracellular conversion into more substitutionally labile Ru(II) species.[79,80] This redox-triggered transformation alters ligand-exchange kinetics and target engagement within the cell. Although early interpretations emphasized DNA and protein interactions, more recent studies indicate that several Ru(II) polypyridyl and arene complexes induce sustained mitochondrial dysfunction and redox imbalance, conditions that favour ICD-associated danger signalling.[81] From a chemical standpoint, ruthenium exhibits an intermediate kinetic regime: ligand substitution is sufficiently slow to avoid reactivity, yet dynamic enough to permit adaptive intracellular engagement.

In contrast, cyclometalated iridium(III) complexes, with their rigid C^N or C^N^N coordination frameworks and pronounced kinetic inertness, confer structural stability, while their cationic and lipophilic character often promotes mitochondrial–lysosomal accumulation.[82,83] Several Ir(III) scaffolds have been shown to induce ICD.[84,85] In photoactivatable systems, excitation-controlled singlet oxygen generation enables spatial and temporal confinement of oxidative stress, effectively transforming the metal centre into a programmable energy transducer. Here, ICD induction is no longer a consequence of intrinsic cytotoxicity but also a regulated redox amplification.[19]

Alternatively, osmium(II) complexes are comparatively less developed. Os(II) scaffolds have been reported to induce sustained mitochondrial ROS production accompanied by ICD-associated signaling.[86]

Gasser, Gibson and co-workers reported a heterometallic Os(II)–Pt(IV)–ceritinib conjugate that exemplifies a rationally designed multimodal therapeutic platform, integrating photodynamic therapy, platinum-based chemotherapy, and kinase inhibition within a single construct, see Fig. 17.[47] In this system, the Pt(IV) centre acts as a prodrug that is reduced intracellularly to release oxaliplatin, a well-established ICD inducer, while the Os(II) polypyridyl fragment functions as a photosensitiser capable of generating ROS upon deep-red irradiation. The inclusion of ceritinib further enhances the design by disrupting mitochondrial function and promoting additional oxidative stress. This combination results in a coordinated amplification of ER stress, ROS production, and downstream DAMP emission.

The mechanistic diversity of these metallodrug platforms is summarised in Table 1, which highlights the primary chemical triggers and dominant stress pathways through which different metal complexes can converge on immunogenic cell death.

5. Conclusions and future perspectives

5.1 Combining gold-based ICD inducers with immunotherapy

Gold-based ICD inducers are particularly well-positioned for combination strategies. Their ability to convert intracellular redox stress into immune priming provides a strong mechanistic rationale for synergy with immune checkpoint inhibitors,

especially in immunologically "cold" tumours characterised by low T-cell infiltration and limited PD-L1 expression.

Experience with other metal-based ICD inducers, such as the platinum complex **PT-112**, supports the concept that stress-inducing metallodrugs can sensitise tumours to checkpoint blockade and reshape the tumour microenvironment in favour of immune activation. By enhancing tumour antigen release, promoting dendritic cell maturation, and facilitating T-cell recruitment, ICD-active complexes may help convert immune-excluded tumours into lesions that become responsive to immunotherapy.[77] For gold complexes specifically, emerging evidence indicates that they can also modulate PD-L1 expression, further strengthening the rationale for combination with anti-PD-1/PD-L1 or anti-CTLA-4 antibodies. In this context, gold complexes should not be viewed as replacements for immunotherapy, but rather as chemical primers capable of enabling and amplifying immune responses.

Beyond checkpoint blockade, several additional therapeutic combinations appear conceptually attractive. STING agonists could reinforce innate immune sensing in parallel with ICD-induced DAMP release. Metabolic modulators targeting the adenosine axis may counteract ATP degradation and local immunosuppression within the tumour microenvironment. Likewise, adoptive T-cell therapies or cancer vaccines could benefit from the enhanced antigen release and immune priming triggered by gold-mediated stress responses.

The opportunity, therefore, lies not merely in adding gold complexes to existing therapeutic regimens, but in positioning them strategically within rationally designed chemo-immunotherapy frameworks, where chemically induced stress provides the initiating immune signal, and immunotherapy amplifies and sustains the resulting antitumour response.

5.2 Experimental and mechanistic challenges

Despite the promising advances discussed above, the field remains at an early stage of mechanistic development. Future progress will depend on moving beyond phenomenological observations toward mechanistically informed design principles.

Several key priorities emerge. First, the precise molecular targets responsible for gold-triggered immunogenic stress must be defined more rigorously. While thiol- and selenol-containing proteins such as thioredoxin reductase are frequently implicated, a systematic understanding of the broader target landscape remains incomplete. Second, the molecular circuitry linking gold-induced redox imbalance to ER–mitochondria crosstalk, including Ca^{2+} flux, mitochondrial outer membrane permeabilisation, and ROS amplification, requires deeper investigation.

Equally important will be distinguishing coordinated immunogenic stress from nonspecific oxidative damage. Not all ROS-generating compounds induce ICD, and ensuring that immune activation follows the correct temporal sequence of DAMP exposure and release will be essential. Standardised experimental frameworks, including vaccination assays, immune-memory assessment, and comprehensive immune profiling *in vivo*, should therefore become routine in the evaluation of new metallodrugs.

Finally, expanding the scope of immunogenic cell death beyond classical apoptotic pathways represents an exciting frontier. Non-apoptotic immunogenic modalities such as ferroptosis or other metal-regulated cell-death programs may intersect with the redox chemistry of gold complexes, offering additional opportunities for designing immunogenic stress responses.

5.3 Final remarks

Over the past two decades, immunogenic cell death has evolved from a biological curiosity into a chemically addressable therapeutic objective. As emphasised throughout this Perspective, ICD should not be viewed as a discrete cell-death pathway but rather as a functional immune outcome arising from coordinated intracellular stress signalling. Its successful induction depends not simply on cytotoxicity, but on the integration of organelle stress, redox imbalance, and temporally regulated DAMP emission capable of engaging the adaptive immune system.

Within this framework, metal complexes occupy a unique position at the interface of chemistry and immunology. Across Ru(II), Ir(III), Os(II), Pt(II/IV), and Au(I/III) platforms, a recurring mechanistic theme emerges: persistent oxidative or proteotoxic stress overwhelms cellular adaptive responses, culminating in the emission of immunogenic danger signals.

Gold complexes, in particular, illustrate how chemical reactivity can be deliberately embedded into immunological design. Their privileged interaction with thiol- and selenol-containing proteins provides a defined biochemical entry point into redox regulation. Importantly, ligand architecture, oxidation state, and organelle targeting are not merely structural variables but key parameters that determine the magnitude and immunological quality of the stress response. Properly designed Au(I) and Au(III) systems, therefore, function not as indiscriminate ROS generators but as redox modulators capable of steering cellular stress toward immunogenic outcomes.

Despite these advances, the field remains in a transitional phase. Many reported systems convincingly demonstrate DAMP emission and tumour growth inhibition, yet relatively few establish durable adaptive immune memory through rigorous vaccination models. Molecular target identification remains incomplete, and structure–activity relationships linking coordination chemistry to immunological potency are still emerging. Without systematic mechanistic validation, there is a risk that ICD is inferred rather than conclusively demonstrated.

The next phase of development should therefore prioritise mechanistically grounded engineering of immunogenic stress. Integrating chemoproteomics, genetic validation, time-resolved stress mapping, and standardised *in vivo* immune assays will be critical for establishing robust design principles. Equally important will be the rational integration of metal-based ICD inducers with immune checkpoint blockade and other

immunomodulatory strategies capable of overcoming the barriers imposed by immunologically "cold" tumours.

In summary, gold complexes occupy a distinctive position within the landscape of metal-based immunogenic cell death (ICD) inducers. Unlike classical metallodrugs that primarily act through DNA damage, gold compounds operate predominantly *via* redox modulation and selective targeting of thiol- and selenol-containing proteins, enabling direct engagement of intracellular signalling pathways that regulate stress responses. This mode of action provides a chemically defined route to induce coordinated mitochondrial and endoplasmic reticulum stress, key processes underlying ICD.

A central advantage of gold coordination chemistry lies in its exceptional tunability, where oxidation state, ligand framework, and subcellular targeting can be systematically adjusted to control both the magnitude and the quality of the induced stress response. As highlighted throughout this work, even subtle structural variations can shift the balance between different cell-death pathways and markedly influence immunogenic outcomes. This level of control is particularly valuable for designing agents that promote regulated, immunogenic cell death rather than nonspecific cytotoxicity.

Furthermore, the compatibility of gold complexes with multimodal and heterometallic strategies offers additional opportunities to integrate complementary mechanisms, such as redox disruption, organelle targeting, and immune activation, within a single molecular platform. Collectively, these features position gold complexes not only as effective cytotoxic agents, but as chemically programmable modulators of tumour immunogenicity, providing a promising foundation for the development of next-generation chemo-immunotherapeutic agents.

Author contributions

The authors contributed to the conception, writing, and revision of the manuscript and approved the final version.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Abbreviations

ICD	Immunogenic cell death
TME	Tumour microenvironment
DAMPs	Damage-associated molecular patterns
CRT	Calreticulin
ATP	Adenosine triphosphate
HMGB1	High-mobility group box 1
HSP70/90	Heat-shock proteins 70/90
ER	Endoplasmic reticulum
ROS	Reactive oxygen species
APCs	Antigen-presenting cells
TrxR	Thioredoxin reductase
NHC	N-heterocyclic carbene
GA	Glycyrrhetinic acid
SERD	Selective estrogen receptor degrader
MAPK	Mitogen-activated protein kinase
cGAS	Cyclic GMP–AMP synthase
STING	Stimulator of interferon genes
PDX	Patient-derived xenograft
SAR	Structure–activity relationship
COX-2	Cyclooxygenase-2
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
IL-1β	Interleukin-1 beta
CXCL10	C–X–C motif chemokine ligand 10
H&E	Hematoxylin and eosin
IC_{50}	Half-maximal inhibitory concentration
CAR-T	Chimeric antigen receptor T-cell
DNA	Deoxyribonucleic acid
PTP1B	Protein tyrosine phosphatase 1B
DMF	Dimethylformamide
MPM	Malignant pleural mesothelioma
i.p.	Intraperitoneal
Sec	Selenocysteine

Data availability

No primary research data were generated as part of this study. All information supporting the discussion in this Perspective is available within the article and the cited literature. Additional details may be obtained from the authors upon reasonable request.

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