Metal Coordination Complexes as Therapeutic Agents for Ischemia-Reperfusion Injury

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ABSTRACT

Ischemia-reperfusion injury (IRI), which describes the cell damage and death that occurs after blood and oxygen are restored to ischemic or hypoxic tissue, is a significant factor within the mortality rates of heart disease and stroke patients. At the cellular level, the return of oxygen triggers an increase in reactive oxygen species (ROS) and mitochondrial calcium ($_m Ca^{2+}$) overload, which both contribute to cell death. Despite the widespread occurrence of IRI in different pathological conditions, there are currently no clinically approved therapeutic agents for its management. In this Perspective, we will briefly discuss the current therapeutic options for IRI and then describe in great detail the potential role and arising applications of metal-containing coordination and organometallic complexes for treating this condition. This Perspective categorizes these metal compounds based on their mechanisms of action, which include their use as delivery agents for gasotransmitters, inhibitors of $_m Ca^{2+}$ uptake, and catalysts for the decomposition of ROS. Lastly, the challenges and opportunities for inorganic chemistry approaches to manage IRI are discussed.

1. Introduction

Researchers have leveraged the unique features of metal ions to develop metal-based small molecules for various applications within biology, marking an important research area within bioinorganic chemistry. In particular, the use of metal complexes with either therapeutic or diagnostic properties has led to the field of metals in medicine. Perhaps the most influential metal-based drug is the simple Werner coordination complex *cis*-$[Pt(NH_3)_2Cl_2]$ known as cisplatin. This compound is a highly effective anticancer drug that is used clinically for several different cancer types, including ovarian and testicular.[1] The success of cisplatin subsequently led to the investigation and worldwide clinical approval of two other platinum-based drugs oxaliplatin[2] and carboplatin.[3] Mechanistically, these platinum-based drugs induce their anticancer properties through the formation of covalent DNA adducts, which inhibit transcription in cancer cells.[4] The success of these compounds has motivated significant efforts to develop new metal complexes as cytotoxic anticancer drugs with an emphasis on tuning their abilities to bind to DNA.[5–7] In fact, one could argue that the field of metals in medicine is dominated by such cytotoxic metal complexes with secondary aspects of research within the development of diagnostic agents like gadolinium-based magnetic resonance imaging (MRI) contrast agents.[8] An alternative role for metal complexes, however, is one that provides protective effects to cells, an approach that can lead to therapeutic agents for conditions like stroke and heart disease. The use of metal complexes as cytoprotective agents has only been scarcely explored with most efforts directed toward the development of superoxide dismutase (SOD) mimics for removing deleterious reactive oxygen species (ROS).[9–12] In this Perspective, we discuss the pathophysiological condition known as ischemia-reperfusion injury (IRI) for which metal complexes can play an important therapeutic role.

IRI describes the irreparable cell death and tissue damage that is caused by the rapid reoxygenation and restoration of blood flow to hypoxic and ischemic organs (**Figure 1**). This process occurs after the medical intervention of stroke and heart failure, as well as in transplanted organs.[13] Although restoration of oxygen and blood is essential for immediate treatment, it also triggers the damaging effects of IRI that can negatively affect the success rates of these procedures and long-term patient survival. Thus far, there are no clinically approved drugs for the prevention or minimization of IRI. Consequently, IRI has been referred to as a "neglected therapeutic target,"[14] a concerning designation given its implication in heart failure and stroke, two of the leading causes of death in the United States.[15]

To develop therapeutic agents for this condition, an understanding of the cellular pathways that trigger its pathology are needed (**Figure 1**). When cells are deprived of oxygen, they switch their metabolic pathways from O_2-dependent oxidative phosphorylation in the mitochondria to anaerobic glycolysis in the cytosol.[13] This change has two key implications on the intracellular environment. First, the mitochondrial membrane potential (MMP) is depolarized due to the lack of the transmembrane H^+ gradient that would normally be generated by oxidative phosphorylation. Second, the production of lactic acid by anaerobic glycolysis leads to an excess of H^+ ions in the cytosol, which are swapped for Ca^{2+} ions via the sequential operation of the Na^+/H^+ and Na^+/Ca^{2+} exchanger proteins.[16] When reperfusion occurs, blood flow is restored, and oxygen is returned to cells. With oxygen levels suddenly elevated, the formation of ROS occurs, and the cell switches back to oxidative phosphorylation as its primary metabolic pathway, reestablishing the MMP.[17] Consequently, the return of the MMP provides a strong driving force for the cytosolic Ca^{2+} ions to enter the mitochondria via a transporter known as the mitochondrial calcium uniporter (MCU),

triggering the phenomenon of mitochondrial Ca^{2+} ($_mCa^{2+}$) overload and subsequent opening of the mitochondrial permeability transition pore (mPTP) that leads to cell death.[18]

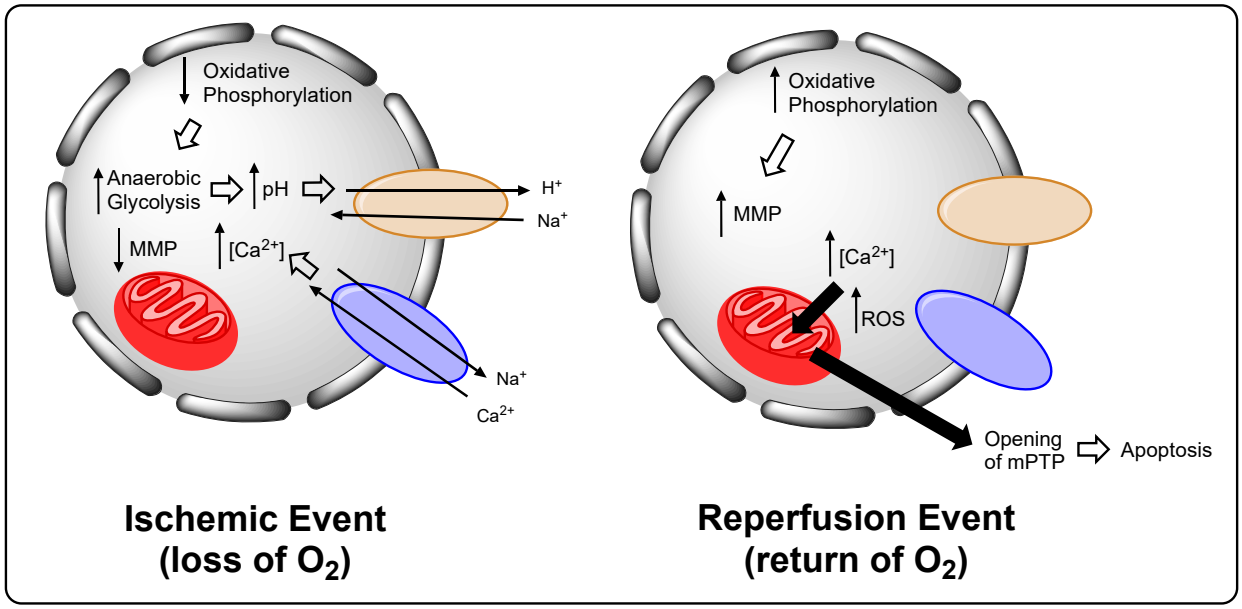


Figure 1. The intracellular biochemical events that contribute to IRI.

These cellular events that precede and trigger IRI provide opportunities and therapeutic targets to address this condition. The most commonly investigated drug candidate for IRI is the organic natural product cyclosporin A, which inhibits the opening of the mPTP.[19] Despite preclinical success with this compound, it has not advanced to clinical approval, due to its variable efficacies in trials[20] as well as side effects like neurotoxicity and chronic neprotoxicity.[21] Thus, alternative drugs are needed, ideally ones that target different parts of the IRI pathway. In this Perspective, we will examine recent efforts to use the novel properties of metal-containing small molecules to develop therapeutic agents for IRI. To date, three main approaches have been investigated to leverage the unique properties of metal complexes. First, researchers have used coordination and organometallic complexes to deliver the gasotransmitters carbon monoxide

(CO), nitric oxide (NO), and hydrogen sulfide (H_2S), which are known to elicit cytoprotective effects at low concentrations. Second, metal complexes have been used as inhibitors of the MCU to prevent $_m Ca^{2+}$ overload. Finally, the ability of metal complexes to cycle through different oxidation states has made them effective antioxidants that can catalytically decompose the harmful ROS produced during IRI. Each of these three strategies is discussed within this Perspective, highlighting the important role that the field of metals in medicine plays in the management of IRI.

2. Gasotransmitter Delivery

The three toxic gases CO, H_2S, and NO have been recognized to be endogenously produced gasotransmitters that play an important role in regulating a variety of biological processes and give rise to anti-inflammatory, anti-apoptotic, and antioxidant effects.[22] The appropriate application of these gasotransmitters can also protect against IRI.[23] In this section, an overview of the efficacy of these gasotransmitters as cytoprotective agents against IRI is given, followed by a highlight on specific recent examples of how metal complexes have been leveraged for their delivery to manage this pathological condition.

2.1. Carbon Monoxide (CO)

CO is well known for its toxicity. Concentrations above 10,000 ppm are lethal due to the ability of this gas to bind tightly to hemes, a property that stops mitochondrial respiration via inhibition of cytochrome *c* oxidase.[24] At lower concentrations, however, CO is produced endogenously and plays a vital role in cellular function and regulation.[25,26] The primary origin of endogenous CO is from the enzyme heme oxygenase-1 (HO-1), which is responsible for the catabolism of heme and is activated by a number of different cellular processes. The CO that is produced by HO-1-mediated heme decomposition provides a regulatory feedback loop in response

to different biological stimuli.[27,28] The physiological importance of CO was demonstrated in HO-1-deficient mice, where the addition of this gasotransmitter exogenously was able to overcome the pathological effects associated with this defect.[29,30]

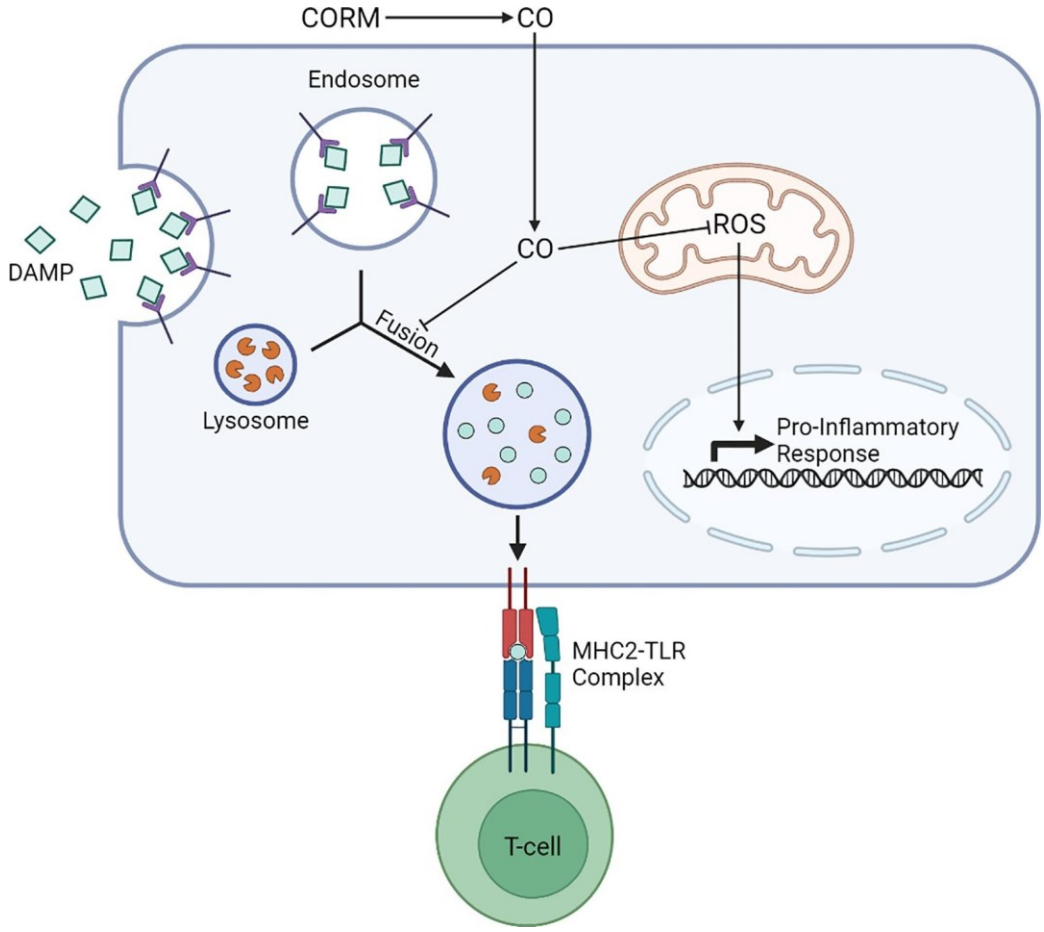
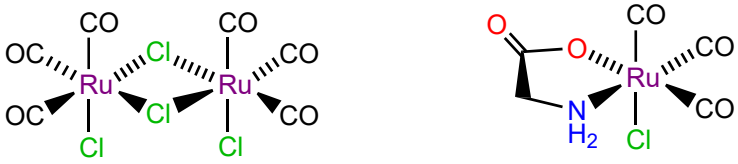


Figure 2. Mechanism of protection of CO against IRI. DAMPs (damage-associated molecular patterns) are molecules released in damaged or dying cells. Upon their release, these molecules trigger endosomal and lysosomal fusion and activate toll-like receptors (MHC2-TLR), which trigger a damaging inflammatory response. CO prevents lysosomal and endosomal fusion and can therefore attenuate this inflammatory response. In addition, CO decreases ATP production in the mitochondria, lowering the presence of ROS and slowing apoptosis. Reproduced with permission from ref. 28. Copyright 2022 Elsevier Inc.

With the importance of endogenously produced CO recognized, researchers have also studied the biological and medicinal effects of exogenously administered CO. At low

concentrations, this gasotransmitter has demonstrated therapeutic effects for a variety of pathophysiological conditions, such as cardiovascular disease, sepsis, and cancer, as well as beneficial properties for organ transplantation.[31–33] Notably, extensive in vitro and in vivo studies have shown that CO can protect against IRI.[34–42] These protective effects include the mitigation of apoptosis by decreasing the production of ATP and consequent lowering of mitochondrial ROS generation, the suppression of dendritic cell maturation, and the inhibition of toll-like receptor (TLR) activation by preventing endosomal and lysosomal fusion (**Figure 2**).[28] However, challenges associated with the direct administration of gaseous CO at therapeutically beneficial levels indicate that alternative approaches are needed for its controlled delivery to hypoxic or ischemic tissue. As a means of accomplishing this goal, the development of CO-releasing molecules (CORMs), which comprise both organic and metal-containing complexes that act as prodrugs for this gasotransmitter, is an active field of biomedical research.[43] Because CO is a highly effective ligand for metal ions,[44] a property that is reflected by the long history of metal-carbonyl compounds dating back to the late 19th century,[45] coordination and organometallic complexes comprise a promising platform for the delivery of small, therapeutically relevant concentrations of this gasostransmitter for IRI.



1 **2**

Chart 1. Structures of CORM-2 (**1**) and CORM-3 (**2**) that have shown protective effects against IRI.[46,47] These compounds release CO via ligand substitution displacement with solvent molecules.

Among the wide variety of metal-carbonyl complexes that have been investigated as CORMs,[46] CORM-2[46] (**1**, **Chart 1**) and CORM-3[47] (**2**, **Chart 1**) are arguably the most thoroughly

studied with respect to their activities for the management of IRI. Compound **1**, a dinuclear, chlorido-bridged ruthenium (Ru) compound, showed a protective effect in several models of IRI by releasing CO into the extracellular milieu.[48–55] Despite the promising therapeutic effects of this complex, its low aqueous solubility and fast CO-release limited its use in further studies. A more soluble CORM, **2**, is also able to reduce the effects of IRI.[47,52,56–61] The primary limitation of **2** for this application, however, arises from its challenging synthesis and solvent-dependent speciation.[62] Furthermore, recent studies suggest that some of the biological effects of this compound arise from the Ru byproducts rather than CO.[63–66] Based on these limitations, researchers have sought to develop CORMs with different transition metals[27,67] and metal-free CORMs.[68,69] The use of alternative metal CORMs, as specifically applied for IRI, is described below.

2.1.1. Manganese CORMs

Manganese (Mn) complexes with CO-releasing properties have been thoroughly investigated for biological applications over the past decade.[27] For many of these complexes, however, poor water solubility and fast CO release have limited their biomedical applications. The Mn(I) tetracarbonyl complex, CORM-401 (**3**, **Chart 2**), contains a bidentate dithiocarbamate ligand with a terminal carboxylic acid group that enhances water solubility while releasing three equivalents of CO.[70] This compound exhibits protective effects against IRI both in vitro within H9c2 cardiomyocytes[71] and ex vivo within pig kidneys.[72] In these studies, treatment of the cells or tissue with **3** prior to subjection to IRI led to improvement in cell viability and tissue integrity. Within the pig kidney model, these protective effects were accompanied by a significant increase in blood CO levels, suggesting that this gasotransmitter is the active protecting agent.

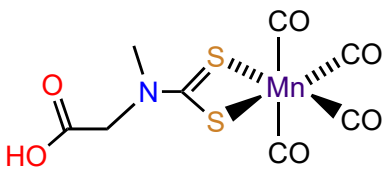


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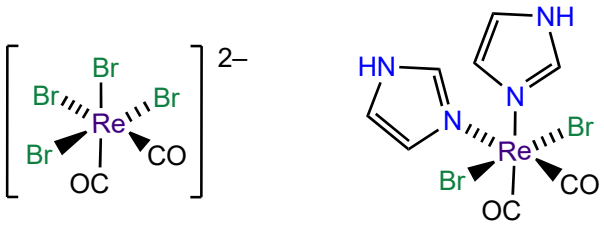
Chart 2. Structure of the Mn-based CORM-401 (**3**) that shows protective effects against IRI.[70] This compound releases CO by ligand substitution with water molecules in solution.

2.1.2. Rhenium CORMs

Although rhenium (Re) carbonyl complexes have been thoroughly investigated for their photochemical and catalytic properties, recent studies have revealed their potential for biomedical applications.[73,74] In particular, this class of compounds has found use as CORMs,[75–78] with several of them being specifically investigated as therapeutic agents for IRI. The Re(II) carbonyl complexes of the general formula *cis*-$[Re(CO)_2Br_2L_2]^{n-}$ (**Chart 3**) are promising examples of Re-based CORMs for IRI.[79] The CO-release kinetics of these complexes under physiological conditions are comparable to those of the well-studied CORM-3 (**2**). For these complexes, L was altered to be different monodentate nitrogen-donor ligands to assess structure-activity relationships. Based on CO-release profiles, *cis*-$[Re(CO)_2Br_4]^{2-}$ (**4**, **Chart 3**) and *cis*,*trans*-$[Re(CO)_2Br_2(Im)_2]$ (**5**, **Chart 3**), where Im = imidazole, were identified to be the most promising complexes from this class. Accordingly, when neonatal rat ventricular cardiomyocytes in the presence or absence of these compounds were exposed to a short period of hypoxia followed by a brief reoxygenation period to model IRI, only **4** and **5** were able to increase cell survival relative to the untreated control. Importantly, cellular uptake studies revealed that these two compounds were not taken up by cells, suggesting that the delivery of extracellular CO is sufficient to elicit their cytoprotective effects. Based on these studies, it is clear that these Re(II) dicarbonyl complexes represent an important class of therapeutic agents for IRI.



4 **5**

Chart 3. Structures of Re(II) CORMs that shows protective effects against IRI.[79] The mechanism of CO-release of these complexes is still currently unknown, but is postulated to be through ligand substitution in physiological environments.

Building upon the success of *cis*-$[Re(CO)_2Br_4]^{2-}$, researchers sought to improve its biological properties by conjugating it to cyanocobalamin (vitamin B_{12}) and an *N*-nitrosoamine-functionalized version of vitamin B_{12}, adding to the growing number of multimetallic Re carbonyl complexes that have been investigated for biological applications.[80,81] In comparison to **4**, which lacks the cyanocobalamin vector, compound **6** (**Chart 4**) exhibited improved stability in aqueous solution and demonstrated a more substantial cytoprotective effect within neonatal rat cardiomyocytes in a model of IRI.[82] To further increase the functionality of this compound class, *N*-nitrosamines were appended to the vitamin B_{12} carriers to afford compounds **7**–**9** (**Chart 4**).

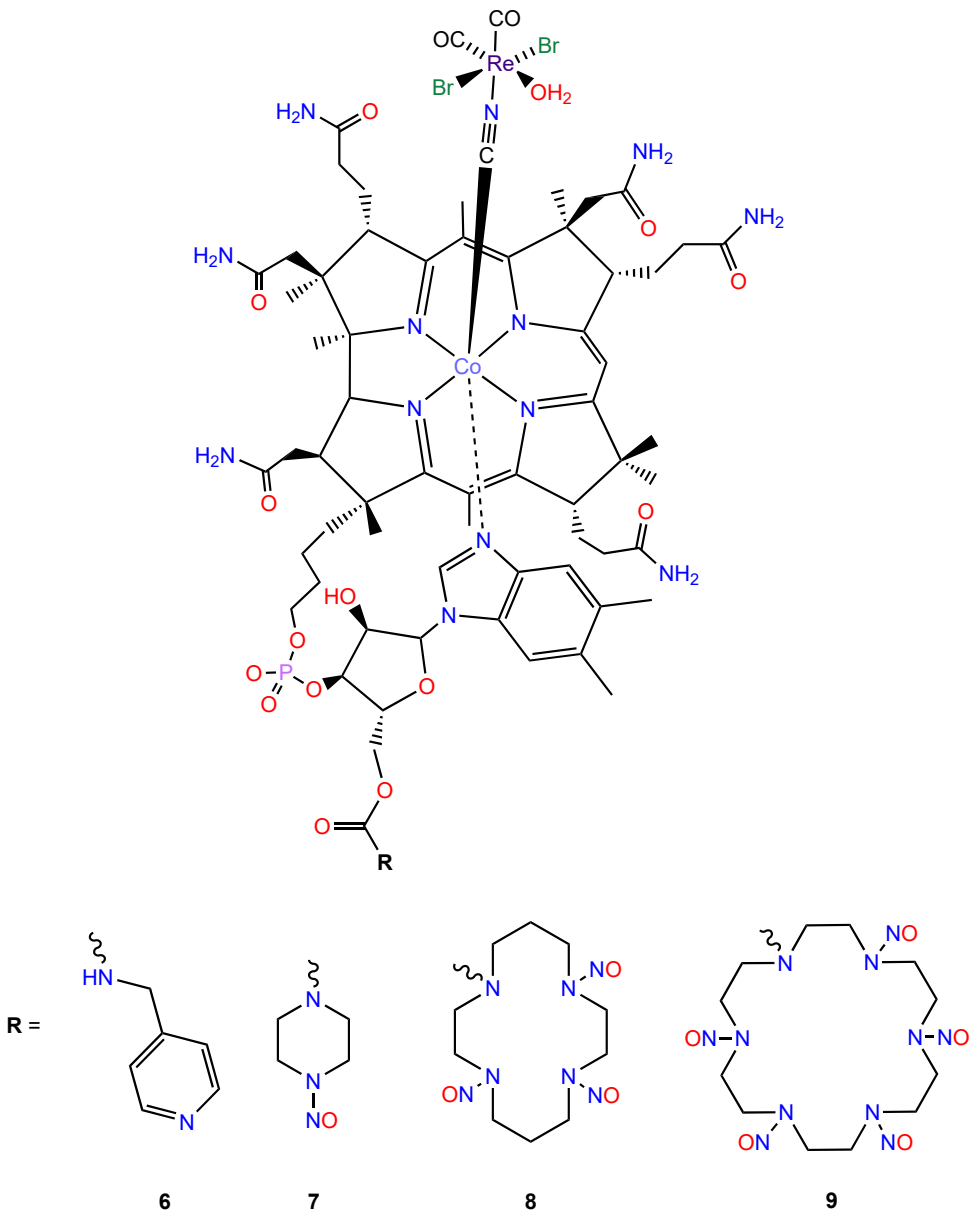


Chart 4. Heteronuclear Co and Re complexes designed to simultaneously release CO and NO to reduce cell death in models of IRI.[82,83] The Re(II) component releases CO in a similar manner as compounds **4** and **5**, whereas NO arises from the macrocyclic *N*-nitrosamines that can undergo protolytic denitrosation in water.

The presence of both the *N*-nitrosamine and Re carbonyl enables these complexes to be used for the release of both NO and CO, providing a dual-action basis for their therapeutic activities against IRI.[83] To assess the therapeutic efficacy of these compounds, 3T3 mouse

fibroblast cells were incubated in the presence and absence of each complex and then exposed to a short period of hypoxia followed by a brief reoxygenation period. Cells that were treated with **7**–**9** demonstrated a 50% reduction in cell death compared to untreated cells. Despite these promising results, the cytoprotective effects of **7**–**9** were not greater than those of **4**, the *N*-nitrosamine functionalized vitamin B_{12} alone, or **6**, which contains vitamin B_{12} but lacks the *N*-nitrosamine (**Figure 3**). Although these results indicate that the dual NO and CO delivery strategy did not lead to significant enhancement of activity, it did highlight the value of vitamin B_{12} as a conjugate that can improve biological compatibility of CORMs.

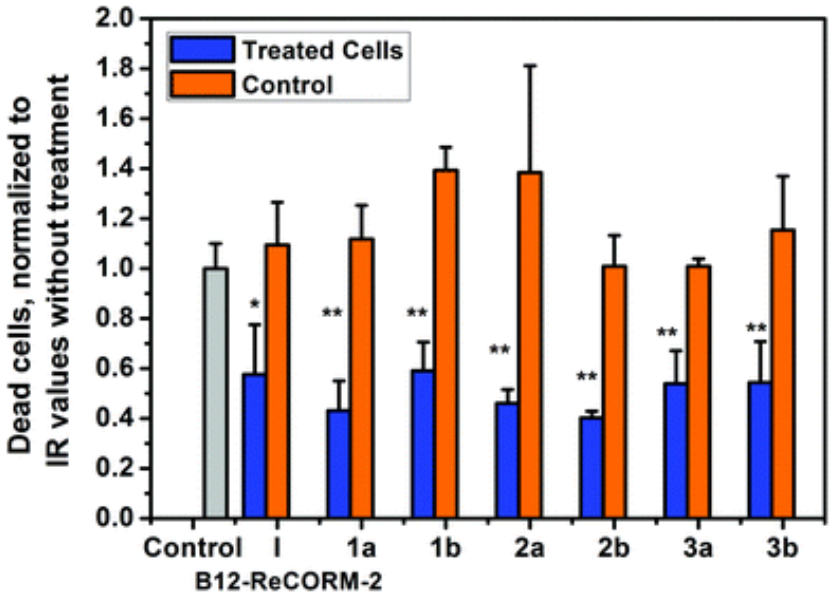


Figure 3. Protective effect of compounds **6**–**9** in an in vitro model of IRI. Blue traces represent cells treated with 30 μM of each compound, whereas orange traces represent untreated cells. In this figure, compound **6** is B12-ReCORM-2, compound **7** is 1b, compound **8** is 2b, and compound **9** is 3b. The designations for 1a, 2a, and 3a are the vitamin B_{12} conjugates without the appended *cis*-$[Re(CO)_2Br_4]^{2-}$. Reproduced with permission from ref. 83. Copyright 2016 Royal Society of Chemistry.

2.2. Hydrogen Sulfide (H_2S)

Most commonly known as a toxic gas with a rotten egg smell, H_2S has recently emerged as the third gasotransmitter, joining NO and CO in this important biological regulatory role.[84] Over the past two decades, endogenous H_2S and related polysulfides (H_2S_n), produced via different enzymatic processes,[85] have been implicated in a wide variety of biological processes,[86] including cancer progression,[87] cellular metabolism,[88] neurological regulation,[89,90] cell death pathways,[91] and the regulation of cardiovascular function.[92] Three H_2S-generating enzymes, cystathionine-β-synthase (CBS), cystathionine-γ-lyase (CSE), and 3-mercaptopyruvate sulfurtransferase (3MST), are the primary producers of endogenous H_2S and play a vital role in the aforementioned processes.[93] This importance has generated interest in the exploration of exogenous H_2S as a therapeutic agent for pathological conditions such as stroke and IRI.[94–96]

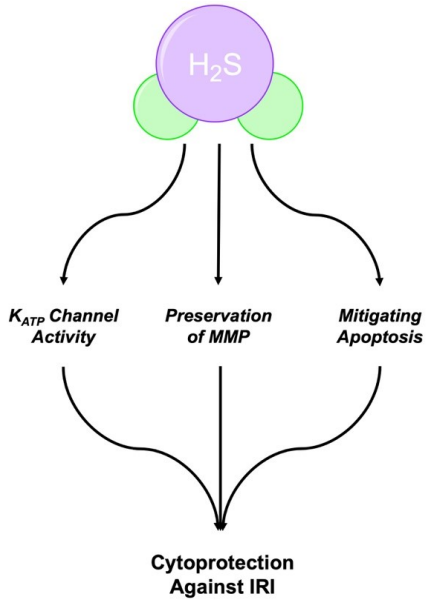


Figure 4. Mechanisms of H_2S cytoprotection during events of IRI. Adapted with permission from ref. 97. Copyright 2010 Elsevier, Inc.

With respect to the role of H_2S in myocardial IRI, the endogenous production of H_2S is vital to heart health.[98] Consequently, the infarct size of isolated rat hearts is larger when endogenous H_2S production is inhibited, and the introduction of exogenous H_2S reverses this effect.[99] In addition, the overexpression of CSE in isolated rat hearts reduces the effects of IRI, demonstrating that both endogenous and exogenous H_2S can protect tissues from IRI.[100] H_2S has additionally shown an attenuation of injury in ischemic stroke, demonstrating its efficacy in neurological systems.[101–106]

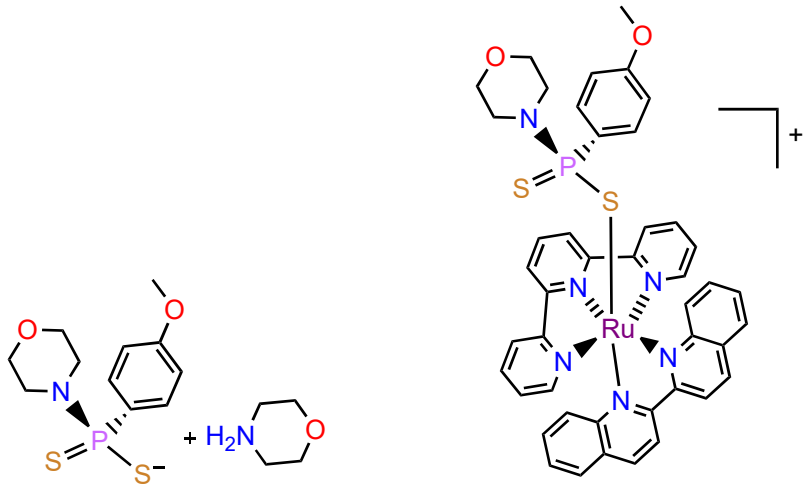
The cytoprotective properties of H_2S in IRI are mediated by several targets (**Figure 4**).[97] The most well-documented mechanism is based on its activity on mitochondrial K_{ATP} channels. This activation stimulates K^+ uptake in the mitochondria, which attenuates the MMP after reperfusion and diminishes the driving force for cytotoxic ${}_m Ca^{2+}$ overload.[107] Furthermore, H_2S inhibits cytochrome *c* oxidase,[108] which slows the production of ROS as reperfusion occurs and mitochondrial oxidative phosphorylation is restored.[109] A third cytoprotective mechanism of H_2S arises from its ability activate several important enzymes, like phosphatidylinositol-3-kinase (PI-3-kinase), which are involved in upregulated cell survival pathways and apoptosis prevention.[110]

Despite these beneficial effects, its toxicity at high concentrations and challenges associated with administering it as a gas have sparked significant research efforts to develop small molecules that can deliver H_2S to biological systems at suitable concentrations for therapeutic use.[95] The design and implementation of stimuli-activated H_2S donors has been particularly fruitful, yielding compounds that are triggered by external light,[111–119], ROS,[120,121] biological thiols,[122–124] enzymatic activity,[125,126] and pH.[127] Notably, in contrast to CORMs, which are mostly coordination and organometallic complexes, H_2S donors are predominately organic compounds. The redox activity and acidity of H_2S leads to challenges in affording metal-based donors of this

gas that have only recently been addressed. Recent examples of metal-based H_2S donors and their applications in IRI are described below.

2.2.1. Light-Activated H_2S Delivery

The organic compound morpholin-4-ium 4-methoxyphenyl-(morpholino)phosphinodithioate (GYY4137, **Chart 5**) is a well-studied H_2S donor[128,129] that releases this gasotransmitter via hydrolysis over a timescale of several hours,[130] enabling its use for the treatment of IRI.[131] The hydrolysis of and H_2S release from this compound occurs instantaneously upon dissolution in water, limiting the conditions in which it can be applied therapeutically. In an effort to control this H_2S-release process, it was coordinated to a photoactive Ru^{2+} polypyridyl complex (**10**, **Chart 5**).[132] When bound to the Ru^{2+} center, the hydrolysis of GYY4137 is suppressed. Upon irradiation of **10** with red (631 nm) light, this H_2S-donating ligand dissociates from the Ru^{2+} coordination sphere, allowing it to undergo hydrolysis and release H_2S in solution. In an in vitro model of IRI, H9c2 rat cardiomyoblast cells that were treated with **10** and irradiated with 631 nm light had substantially higher viability compared to untreated cells and treated cells not exposed to light (**Figure 5**), indicating that this light-activation process operates in the cellular milieu as well. This complex, a red light-activated H_2S donor, highlights the value of using metal complexes to leverage their photochemistry for this application.



GYY4137 10

Chart 5. Structures of the H_2S donor GYY4137 of the and the red light-activated Ru^{2+} H_2S donor (**10**). GYY4137 releases H_2S via hydrolysis of the P–S bonds. Compound **10** undergoes a photosubstitution reaction to release GYY4137, which subsequently hydrolysis to produce H_2S.[132]

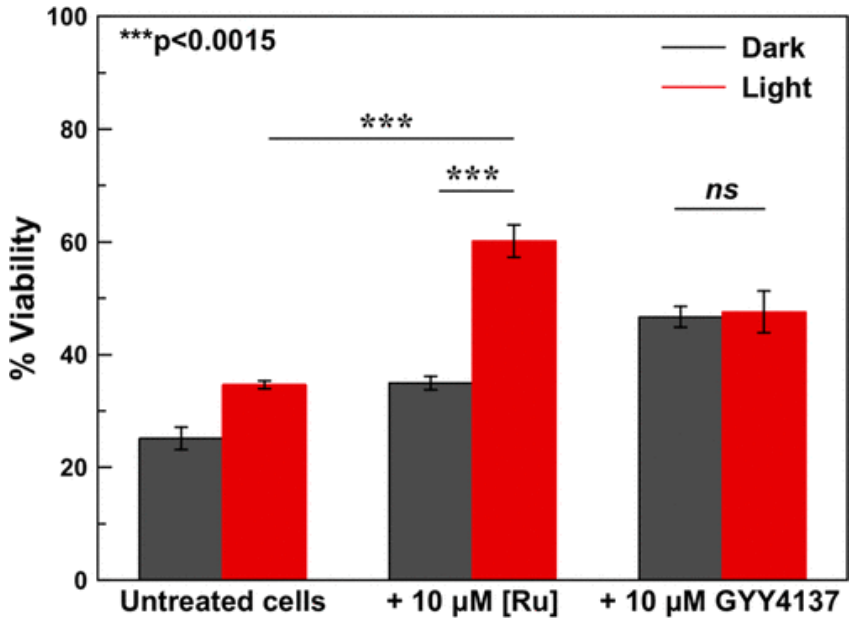
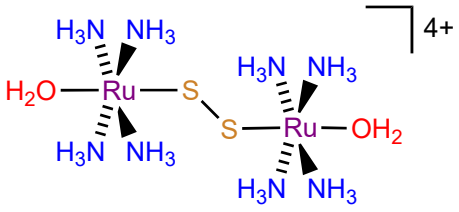


Figure 5. Protective effect of compound **10** ([Ru]) and GYY4137 in cells subjected to an in vitro model of IRI. Reproduced with permission from ref. 132. Copyright 2018 American Chemical Society.

2.2.2. Reduction-Activated H_2S Delivery

The hypoxic nature of ischemic cells and tissues gives rise to a reducing environment that could potentially be leveraged for the activation of anti-IRI agents. In this context, the redox activity of metal complexes can be used to design compounds that are reduced under these conditions. This concept was investigated recently for the selective delivery of H_2S from a Ru coordination compound. Upon chemical reduction of the dinuclear persulfide-bridged (μ-S_2^{2-}) Ru compound[133] (**11**, **Chart 6**), the S–S bond is cleaved, leading to the release of H_2S as a byproduct.[134] Importantly, it was demonstrated that this process occurs in the presence of biologically relevant reducing agents in aqueous solution, suggesting that this compound could be used for the therapeutic delivery of this gasotransmitter. To test this hypothesis, H9c2 rat cardiomyoblast cells were treated with **11** and then subjected to lethal hypoxia-reoxygenation. Under these conditions, the viability of the cells increased in the presence of higher concentrations of the complex. Thus, the initial hypoxic conditions found during IRI may be sufficient to activate this and related metal complexes by chemical reduction.



11

Chart 6. Structure of a redox-activated persulfide-bridged Ru complex (**11**).[134] Upon chemical reduction, the S–S bond is cleaved, leading to a terminal Ru–SH complex that releases H_2S upon protonation in water.

2.3. Nitric Oxide (NO)

The biochemistry of NO has been studied extensively.[135] In particular, its protective effects against IRI have been widely reported, with both the endogenously produced[136–143] and exogenously delivered[139,144–146] NO giving rising to these therapeutic properties. Although high concentrations of NO are cytotoxic, small doses have anti-inflammatory, antioxidant, and anti-apoptotic effects.[147] The primary mechanism of protection of NO involves the inhibition of tumor necrosis factor α (TNF-α), which is responsible for the activation of transcription factor NF-κB. This transcription factor triggers various events that lead to downstream apoptotic and inflammatory events. By suppressing TNF, these pathways are prevented, decreasing the damaging effects of IRI. In addition, NO acts as a radical scavenger and binds to cytochrome *c* oxidase, giving rise to its antioxidant properties. Finally, NO binds to and activates soluble guanylate cyclase (s-GC) in cells. This enzyme produces cyclic guanosine monophosphate (c-GMP), a messenger molecule that mitigates apoptosis through the modulation of caspase production (**Figure 6**).[148] In order to use NO as a therapeutic agent, it needs to be delivered in small, regulated quantities. To address this challenge, researchers have developed nitric oxide-releasing molecules (NORMs), which are capable of slow and sustained release of NO. Given the long-standing history and well known photochemistry of metal nitrosyl complexes,[149,150] this compound class forms a promising basis for photoactivated NORMs for biological use.[151,152]

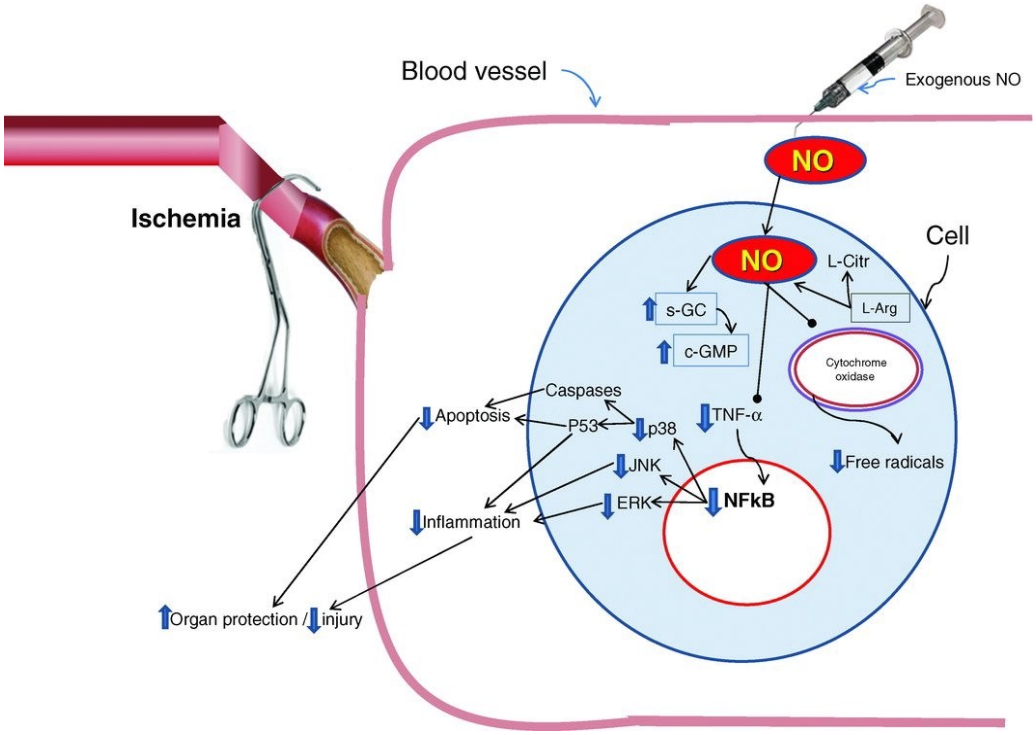
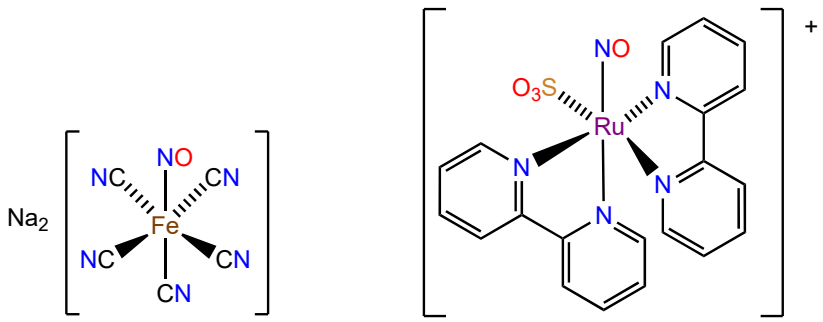


Figure 6. Mechanisms of protection against IRI by exogenous NO. NO lowers the production of free radicals by binding to cytochrome *c* oxidase. It also inhibits TNF-α, which deactivates NF-κB, shutting down several mitogen-activated protein kinases such as p38, extracellular signal-regulated kinases (ERK), and c-Jun N-terminal kinases (JNK). These kinases are linked to intensifying inflammation and apoptosis through the release of caspases and the tumor protein p53. Finally, NO activates s-GC, leading to an enhanced production of c-GMP. Reproduced with permission from ref. 148. Copyright 2009 Taylor & Francis Group.

The longest used therapeutic NORM is arguably sodium nitroprusside, $Na_2[Fe(CN)_5(NO)]$ (**12**, **Chart 7**). This iron (Fe) compound has been extensively applied in different models of IRI, demonstrating good efficacy in minimizing the damaging effects of this condition.[153–157] The release of NO from this complex is triggered by chemical reduction by biological reducing agents like cysteine and glutathione.[158] Compound **12** has been used in human patients for this condition as well.[159] Cancer patients with chest pains associated with myocardial ischemia and were treated with a cotton pad soaked in 1.5 M **12** on the abdomen. Elevated levels of NO were detected in plasma taken from patients, and patients exposed to **12** showed a significantly lower death rate

caused by acute myocardial infarction. These results suggest that NO can help reduce damage associated with IRI and that metal-based compounds are suitable delivery agents for this gas.

Despite the frequent use of the Fe-based **12**, researchers have more extensively studied Ru-based NORMs to leverage the greater inertness of this 4d transition metal. Although a large number of these Ru NORMs have been studied, in general, they have not yet been extensively applied to address IRI.[160] A notable example of one such NORM used for this purpose is the Ru nitrosyl complex *cis*-$[Ru(bpy)_2(SO_3)(NO)]^+$ (**13**, **Chart 7**).[161] The protective effects of this compound against an in vivo model of cerebral IRI were investigated in rats. Cessation of arterial blood flow to the brain via occlusion of the carotid artery for 30 min, followed by a 60 min reperfusion period, led to the formation of significant infarct regions within the brain. In rats pretreated with this complex via intraperitoneal (i.p.) injection, however, the size of the infarct regions of 2,3,4-triphenyltetrazolium chloride (TTC)-stained coronal brain sections were significantly smaller, demonstrating the therapeutic viability of this compound (**Figure 7**). Furthermore, elevated levels of nitrite, an in vivo metabolite of NO, and decreased NF-κB expression in the hippocampus were detected in the treated rats, implicating NO to be the mediator of the observed biological effects.



12 **13**

Chart 7. Structures of sodium nitroprusside (**12**) and *cis*-$[Ru(bpy)_2(SO_3)(NO)]^+$ (**13**), an NO-releasing molecule with demonstrated neuroprotective effect against IRI.[161] These compounds release NO upon reaction with biological thiols.

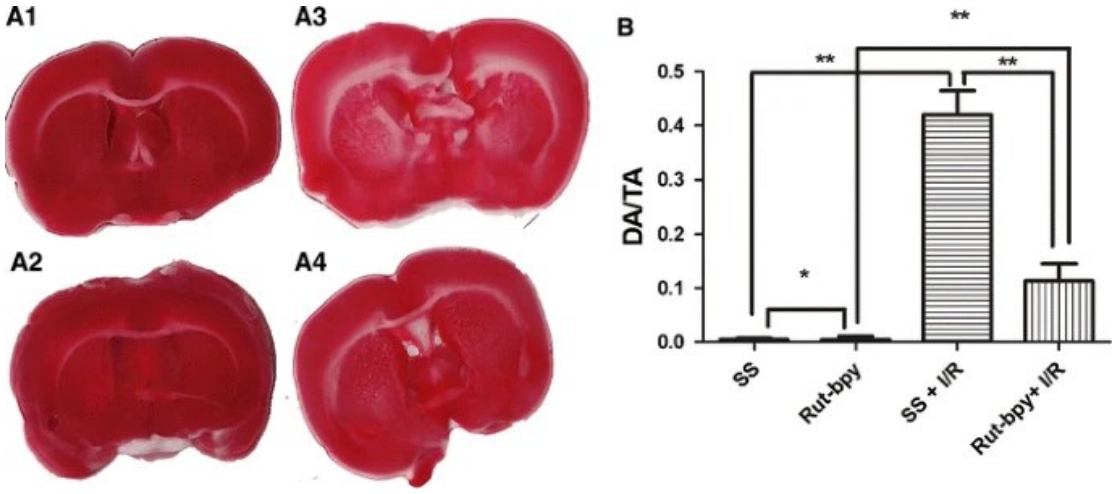


Figure 7. (A) TTC-stained coronal brain sections treated with either saline solution (SS) or compound **13** (Rut-bpy). Sections A1 (SS-treated) and A2 (**13**-treated) did not undergo IRI, while sections A3 (SS-treated) and A4 (**13**-treated) were exposed to an IRI model. (B) The calculated damaged area (DA) to total area (TA) ratio of each TTC-stained brain section. Reproduced with permission from ref. 161. Copyright 2011 Springer Science Business Media, LLC.

3. Preventing Mitochondrial Calcium Overload

As mentioned in the Introduction, $_m Ca^{2+}$ overload is one of the key intracellular processes that causes the harmful effects of IRI. Thus, inhibition of $_m Ca^{2+}$ uptake to prevent $_m Ca^{2+}$ overload has been proposed and investigated as a therapeutic strategy to prevent IRI. These efforts have focused on targeting the MCU, a transmembrane protein complex that mediates Ca^{2+} uptake into the mitochondria.[162–166] The tetrameric MCU complex[167–170] comprises the MCU subunit and the regulatory EMRE,[171] MICU1,[172] and MICU2[173] subunits. The EF-hand domains of the MICU1 and MICU2 subunits can recognize and respond to high cytosolic Ca^{2+} concentrations, dissociating from the pore-forming MCU subunit to allow for $_m Ca^{2+}$ uptake.[173–176] The MICU regulatory proteins interact with a highly conserved solvent-exposed DXXE motif at the pore of the MCU subunit (**Figure 8**).[167,168] This motif interacts directly with and mediates the uptake of Ca^{2+}

ions.[177,178] Although a number of organic compounds that possess MCU-inhibitory activities have recently been identified,[179–184] the earliest and most commonly used MCU inhibitors are metal coordination complexes. These complexes, as well as new discoveries in this area, are discussed below.

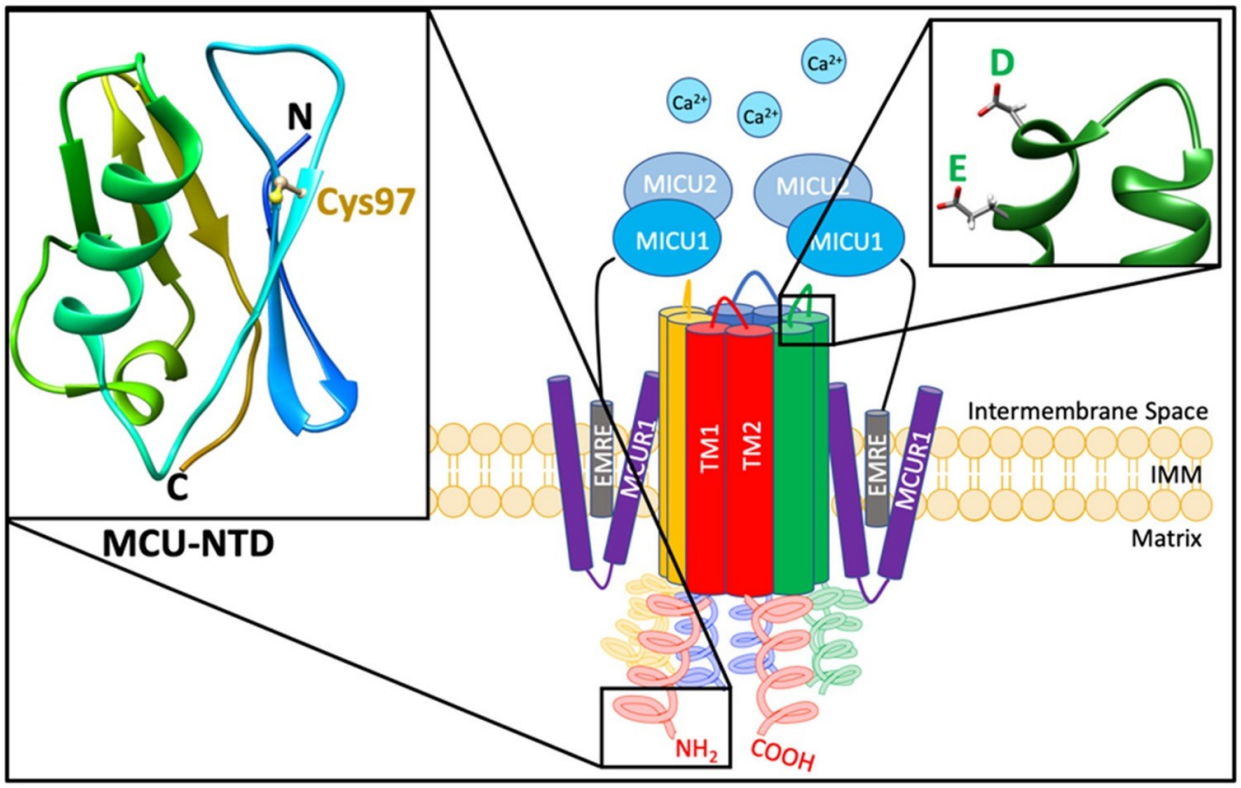


Figure 8. Topology of the MCU. Shown are the relevant regulatory proteins EMRE, MCUR1, MICU1, and MICU2 and the orientation of the transmembrane domains (TM1 and TM2) of the MCU within the inner mitochondrial membrane (IMM). The insets depict (left) the N-terminal domain of the MCU (MCU-NTD) and (right) the location of the DXXE motif in the MCU pore. Adapted with permission from ref. 185. Copyright 2019 American Chemical Society.

3.1. Multinuclear Ruthenium Complexes

The oxo-bridged trinuclear Ru complex ruthenium red[186,187] (**14**, **Chart 8**) was one of the first compounds discovered to inhibit $_{m}Ca^{2+}$ uptake.[188] Although it was originally used as a cytological stain,[189] its MCU-inhibitory activity led to its widespread implementation in different

biological studies,[188,190–192] and it was demonstrated to attenuate the downstream effects of IRI in an ex vivo model.[193] The use of **14** for these applications, however, has been limited by its poor purity, which has led to batch to batch variations in activity depending on the supplier.[194–196] An important observation from these studies was that the $_m$Ca^{2+} uptake-inhibitory properties of **14** actually decreased as the purity of the compound increased, implying that another species was primarily responsible for this property.[197] Accordingly, the dinuclear oxo-bridged complex, Ru360 (**15**, **Chart 8**), was identified as an impurity within **14** that possesses potent nM $_m$Ca^{2+} uptake inhibitory properties.[198–200] Since this discovery, **15** has become the most frequently used MCU inhibitor, employed primarily as a tool to study $_m$Ca^{2+} dynamics and regulation. Although its therapeutic potential for the prevention of IRI was demonstrated,[201,202] its more widespread applicability is limited by its poor cell permeability and stability.[203] The axial formate ligands of **15** undergo a rapid aquation reaction in buffered solutions, affording the diaqua-capped analogue Ru360′ (**16**, **Chart 8**), which can be synthesized independently.[204] The rapid aquation of **15** implies that **16** is the active inhibitor.

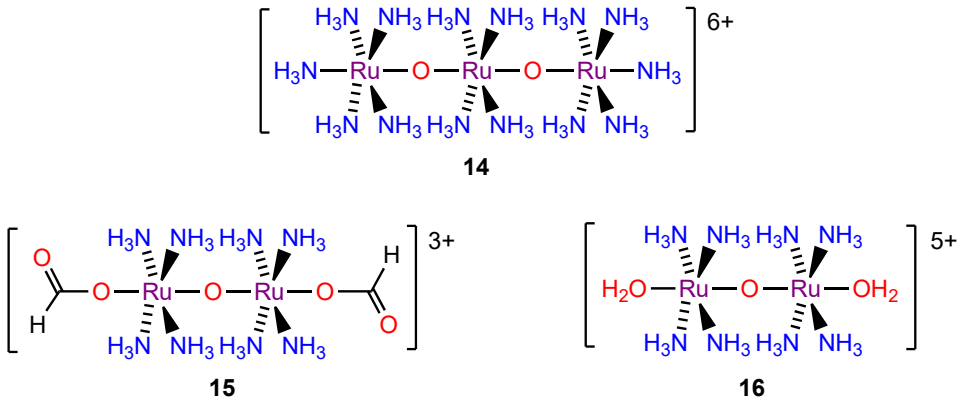
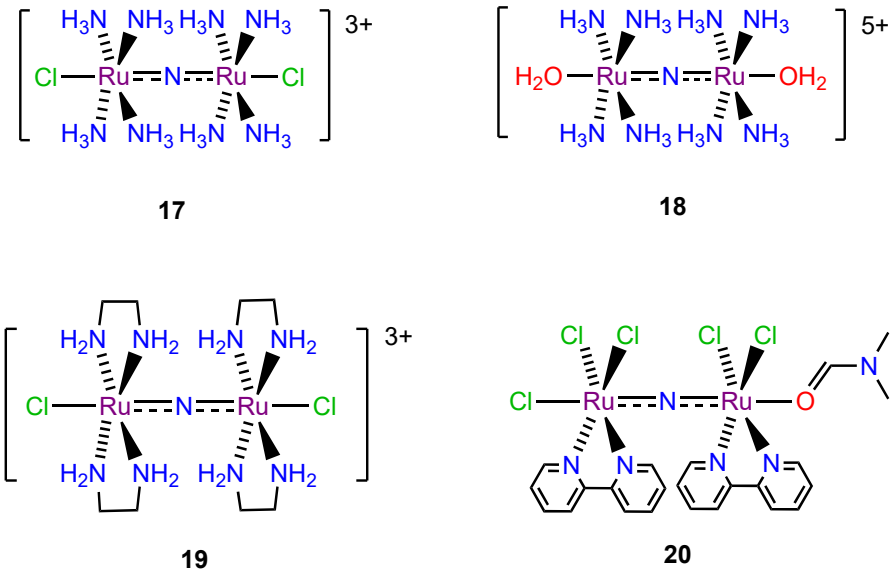


Chart 8. Structures of previously reported multinuclear oxo-bridged Ru MCU inhibitors.[186,189,198–200,204]

Given the high potency of **15**, analogues of this compound with improved stability and cell permeability were sought. The use of a bridging nitrido, rather than oxo, ligand afforded the compounds Ru265 (**17**, **Chart 9**)[185] and Ru265′ (**18**, **Chart 9**).[205] These analogues retained the nM potency for MCU inhibition observed for **15**. Unlike **15**, these compounds were also able to inhibit the MCU in intact, non-permeabilized cells. A series of studies were carried out to study the origin of the enhanced cell permeability of **17** compared to **15**. These results suggest that this property is a consequence of the greater redox stability of **17**. Compound **15** is reduced by common biological reductants like glutathione, affording products with no MCU-inhibitory properties.[205] By contrast, **17** remains intact in the presence of reducing agents. Thus, the current working model is that extracellular reduction and decomposition of **15** forms species that are not cell permeable nor active MCU inhibitors. Importantly, like **15**, **17** interacts with the DXXE motif of the MCU, as evidenced by site-directed mutagenesis studies[163,178] and molecular docking,[206] indicating that both compounds have the same molecular target and mechanism of action.



17 **18** **19** **20**

Chart 9. Structures of the dinuclear nitrido-bridged Ru MCU inhibitors.[185,205,207]

Given the better cell permeability and enhanced stability of **17**, it was demonstrated to be an effective protective agent in in vitro hypoxia-reoxygenation assays within both rat ventricular myocytes[185] and primary cortical neurons.[208] In addition to preserving cell viability, **17** also showed no negative effects on the mitochondrial integrity.[185] Furthermore, **17** was effective in vivo, substantially reducing the brain infract size within mice that had been subjected to a model of ischemic stroke (**Figure 9**).[208] In addition to **17**, the ethylenediamine (en) (**19**, **Chart 9**) and 2,2′-bipyridine (bpy) (**20**, **Chart 9**) analogues of these compounds were investigated. The en analogue **19** was a substantially less effective MCU inhibitor than **17** with poorer cell permeability,[185] and **20** with bpy ligands was completely inactive with respect to MCU inhibition.[207] These results indicate that the equatorial ammine ligands are important for the MCU-inhibitory properties of this compound class.

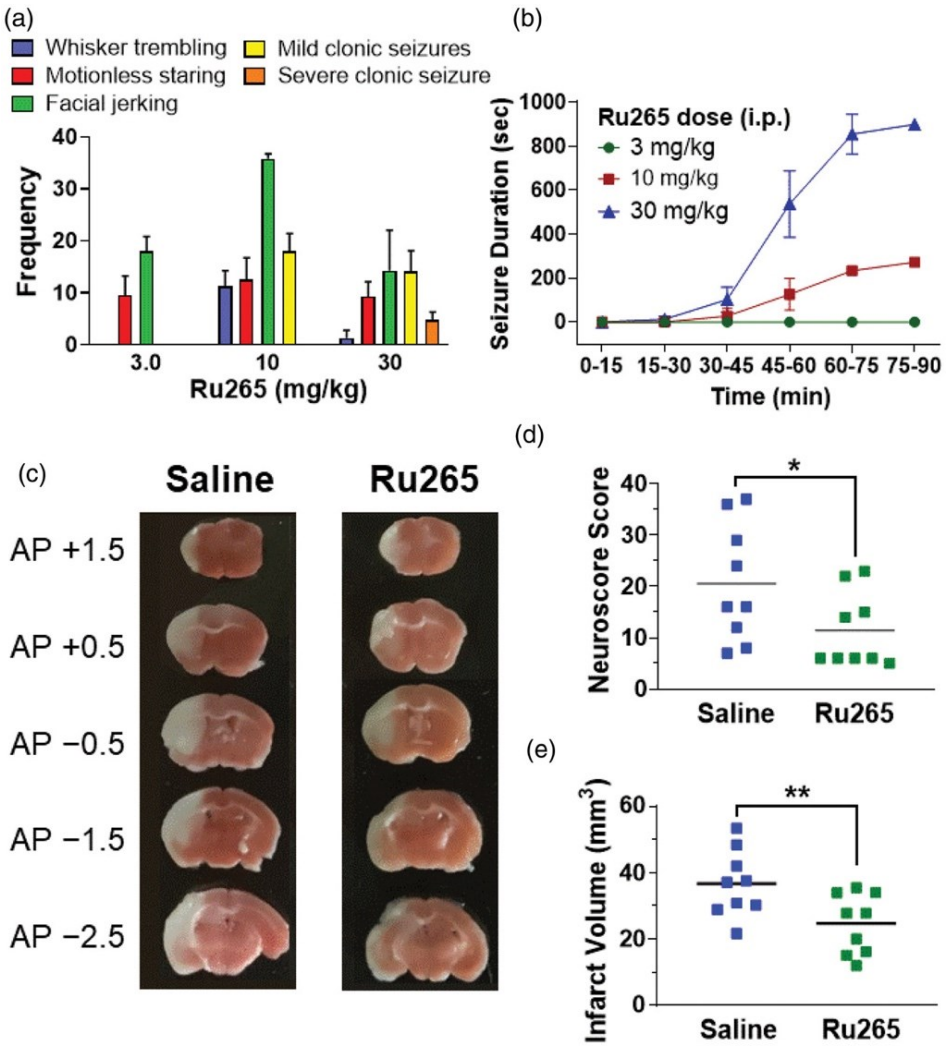
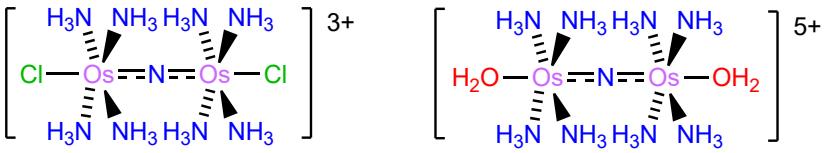


Figure 9. In vivo effects within mice treated with Ru265. (**17**) (a,b) Durations of seizures detected over 90 min after i.p. injection of Ru265 at varying concentration. (c) Representative TTC-stained brain sections after subjection to 24 h of hypoxic injury. (d, e) Neuroscores and infarct volumes in mice injected with saline or 3 mg kg^{-1} **17** after 24 h of IRI. Reproduced with permission from ref. 208. Copyright 2020 Sage Publications.

3.2. Dinuclear Osmium Complexes

Building upon the success of **17** as an MCU inhibitor, an analogue containing osmium (Os), instead of Ru, was investigated. The Os analogue, named Os245 (**21**, **Chart 10**), was also able to inhibit the MCU in intact cells and was stable towards biological reductants.[209] This

compound protected primary cortical neurons exposed to oxygen-glucose deprivation, an in vitro model for IRI, without causing any negative effects on mitochondrial function. A significant difference between **17** and **21** arises within their axial ligand aquation kinetics. For **17**, the chlorido ligands are displaced by water under physiologically relevant conditions with a half-life of only 2.3 min, whereas the half-life for this process for **21** is 700.1 min. Accordingly, the diaqua analogue of **21**, Os245′ (**22**, **Chart 10**), exhibits different MCU-inhibitory activity than its parent compound. Compound **22** is equipotent as **17** and **18**, and 100-fold more potent than **21**. These results suggest that the axial chlorido ligands, which remain bound to the Os centers on **21** for a substantial length of time, act to diminish the MCU-inhibitory activity of this compound class.[205] Molecular docking simulations support the higher potency of the diaqua compounds, as these coordinated water ligands are engaged in hydrogen-bonding interactions with acidic residues within the MCU pore entry.[206,209] Both of these nitrido-bridged Ru and Os dinuclear complexes are among the most potent MCU inhibitors reported to date, and their redox stability and cell permeability make them excellent therapeutic candidates for the prevention of IRI. Further functionalization of the axial sites of this compound class has also shown promise for the improvement of their delivery with added chemical functionalities,[210–212] suggesting that axial ligand modification is a viable pathway for identifying new lead compounds.



21 **22**

Chart 10. Structures of the dinuclear nitrido-bridged Os MCU inhibitors.[209]

The major limitation of this compound class is their relatively low in vivo therapeutic window, which when exceeded causes seizures in mice (**Figure 9**). The i.p. injection of **17** in adult male mice caused seizures at doses of 10 mg kg^{-1} or higher 45 min after treatment.[208] For **21**, the onset of seizures was observed at similar doses, but was delayed by nearly 30 min.[209] These side effects present challenges in the use of these compounds as therapeutic agents for IRI. Optimization of these compounds to increase their therapeutic windows is an important objective in using MCU inhibition as an approach for treating IRI.

4. ROS Scavengers

Ischemic cells and tissue are ill-equipped to handle the surge of oxygen that returns upon reperfusion. Consequently, ROS, which include hydrogen peroxide (H_2O_2), hydroxyl radical ($HO^{\bullet}$), and superoxide ($O_2^{\bullet-}$), are produced by the reduction of dioxygen as undesired side products of the mitochondrial respiratory chain,[213] and contribute to the cell damage and death that is characteristic of IRI.[214] Although it has recently been recognized that low levels of ROS play key roles in cellular regulatory and signaling processes, high concentrations of these species damage critical biomolecules and lead to cell death.[215] As such, cells have evolved sophisticated enzymes, like catalases and SODs, that can decompose these ROS to prevent cellular damage.[216,217] Inspired by nature, researchers have developed small molecules with similar catalytic properties and applied them as therapeutic agents to decompose ROS and protect against IRI.[218,219]

SODs catalyze the dismutation of $O_2^{\bullet-}$ into H_2O_2 and O_2,[220,221] whereas catalase facilitates the decomposition of H_2O_2 into O_2 and H_2O (**Figure 10**).[222] Mammals express three types of SOD: manganese SOD (MnSOD), found primarily in the mitochondria, copper/zinc SOD (CuZnSOD),

the major SOD in cells found within the nucleus and cytosol, and extracellular SOD (ECSOD), which has similar dinuclear Cu/Zn active sites as CuZnSOD.[223,224] Catalases in mammals are classified into three groups: monofunctional heme-containing catalases, heme-containing catalase peroxidases, and Mn-containing catalases.[225] The therapeutic potential of systems that can catalytically decompose ROS is evident in various studies that explored the effects of different expression profiles of SOD and catalase within animals. For example, overexpression of MnSOD within the hearts of transgenic mice rendered them substantially less susceptible to the damaging effects of myocardial IRI.[226] With respect to catalase, its deficiency has been linked to a wide variety of diseases and disorders, including neurological disorders, cancer, and certain metabolic disorders.[222] Accordingly, the overexpression of catalase confers protective effects against IRI in vivo.[227] These studies suggest that the use of small-molecule SOD and catalase mimics may be a therapeutically viable strategy for the management of IRI.

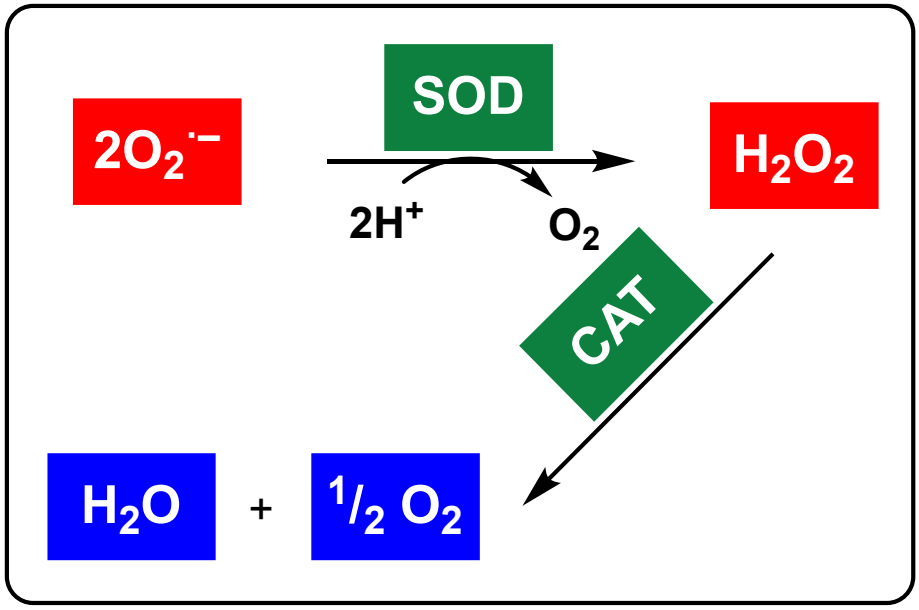


Figure 10. Mechanism of ROS dismutation by the enzymes SOD and catalase (CAT).

To design suitable small-molecule analogues, consideration of the metal-containing active sites of these enzymes is needed. With respect to SOD mimics, most efforts have focused on modeling MnSOD rather than CuZnSOD, due to the fact that the former provides simpler mononuclear active site. The active site of human MnSOD (**Figure 11a**) comprises a Mn center in a trigonal bipyramidal geometry coordinated by three histidine and one aspartate residues, as well as a labile water molecule.[228,229] Human catalases are tetrameric proteins (**Figure 11b**) with a heme-Fe active site. Unsurprisingly, the Fe center attains a five-coordinate, square pyramidal geometry, supported by the porphyrin donor atoms and an axial labile site occupied by water in the resting state.[230] As described below, small-molecule mimics of these enzymes have adopted similar primary coordination sphere features of their active sites.

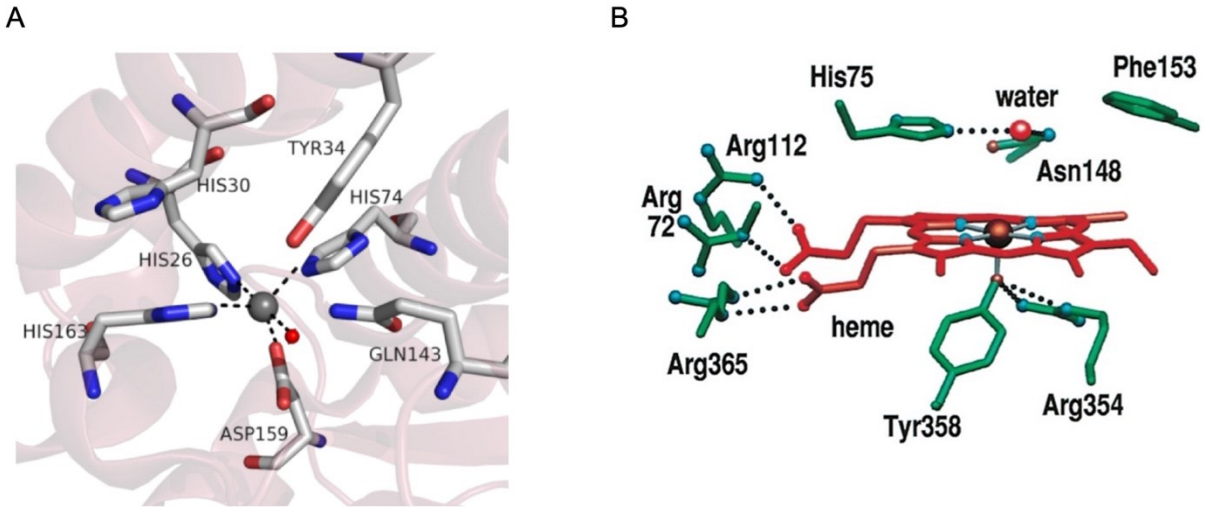


Figure 11. A. Active site of human MnSOD (PDB 1N0J, ref. 227). Adapted with permission from ref. [229]. Copyright 2010 Elsevier Inc. B. Active site of human catalase (PDB 1DGF, ref. 229). Adapted with permission from ref. 230. Copyright 2000 Elsevier Inc.

4.1. Mn(III) Porphyrins

A very common class of small-molecule SOD mimics are Mn(III) porphyrin complexes. The Mn(III) porphyrin, AEOL 10150 (**23**, **Chart 11**), was investigated in various clinical trials for

its application as a catalytic antioxidant, displaying both SOD and catalase activities.[231–235] Compound **23** was protective in an in vitro model of neuronal oxygen-glucose deprivation and was also able to decrease the brain infarct size in mice subjected to an ischemic stroke model.[236] Other Mn(III) porphyrins (**24**–**25**, **Chart 11**) were found to attenuate the infarct size of ischemic brain tissue of rats.[237] These protective effects correlated with decreased ROS levels in the brain, indicating that their catalase and SOD activities are responsible for ameliorating the effects of IRI. Notably, the administration of these complexes both before and after the reperfusion gave rise to protective effects, suggesting that depletion of ROS can be therapeutic even after the IRI event.

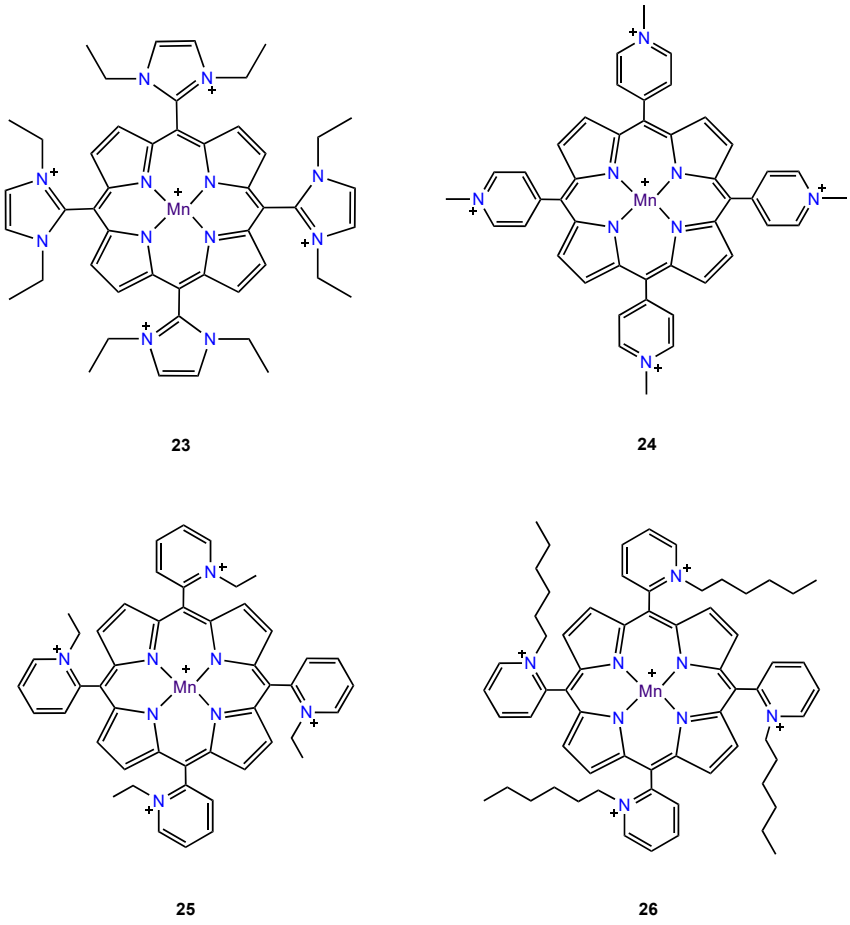


Chart 11. Structures of SOD/catalase mimics that showed attenuation of neuronal IRI.[236–239]

Modifying the substituents of the porphyrin provides a versatile means of altering and improving the catalytic activities and therapeutic potentials of their Mn(III) complexes. Adding *N*-hexylpyridinium substituents onto the porphyrin (**26**, **Chart 11**) led to the discovery of a MnSOD mimic that has a rate of $O_2^{\bullet-}$ dismutation on the same scale as native SOD enzymes.[240] This dramatic increase in rate compared to compounds **24** and **25** suggested that this complex afforded significant promise for IRI. Researchers thus investigated the ability of this complex to attenuate the effects of IRI ex vivo with primary renal tissue[238] and in vivo, examining the effects of IRI on the spinal cord, with adult female rats.[239] In the ex vivo model, a dose of 50 μg kg^{-1} of **26** for 30 min followed by a 40 min ischemic period and an 18 h reperfusion period showed minimal protection in renal tissue, but treatment with **26** for 24 h showed significant reduction in tissue damage (**Figure 12**).[238] Longer pretreatment periods of **26** afforded a greater attenuation of damage in the in vivo spinal cord model, indicating that the presence of this compound during the IRI event was vital. The measurement of ROS within the relevant tissues of the treated animals revealed them to be lower than those within untreated animals, supporting that the therapeutic activity of **25** is mediated by its antioxidant properties.

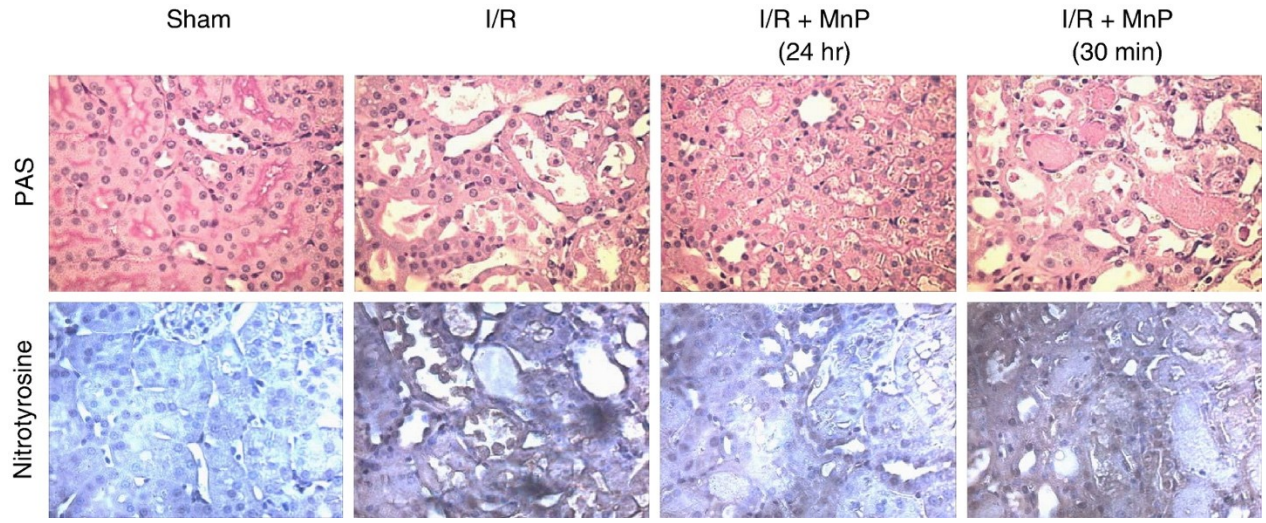
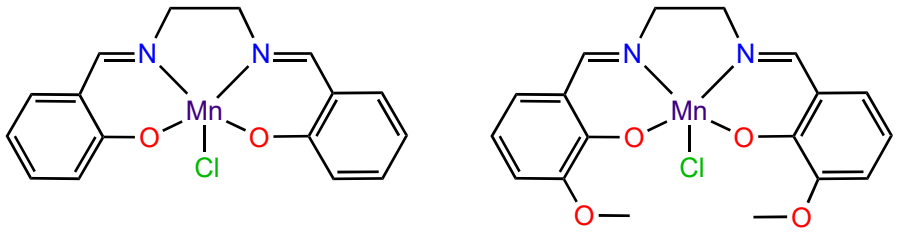


Figure 12. Renal tissue that has been stained with periodic acid-Schiff (PAS) and an anti-nitrotyrosine antibody after IRI (I/R) with and without pretreatment of **26** (MnP). Sham = No IRI. PAS staining demonstrates the presence of polysaccharides in tissue and was used to examine histopathological changes. The anti-nitrotyrosine antibody staining detects nitrotyrosine, a metabolite of tyrosine that arises from oxidative nitration (dark staining surrounding damaged white space within tissue). In both cases, the even distribution of the PAS stain is characteristic of undamaged tissue, whereas white regions indicate significant morphological damage. Furthermore, the lower intensity of the nitrotyrosine staining within the treated mice indicate less oxidative nitration occurred. Reproduced with permission from ref. 238. Copyright 2007 Elsevier Inc.

4.2. Salen and Macrocyclic Complexes

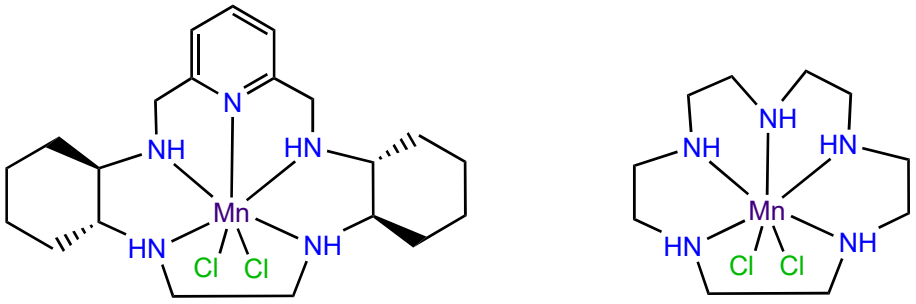
The well-known tetradentate Schiff base salen ligands afford metal complexes with SOD and catalase activities.[241,242] Two such Mn(III) salen complexes, EUK-8 (**27**, **Chart 12**) and EUK-134 (**28**, **Chart 12**), possess exceptional SOD and catalase activities[243,244] that have been leveraged for a variety of biological applications.[245–247] Notably, these compounds have been applied for the management of IRI in various models and conditions.[248–253] Compound **27** was found to preserve normal cardiac and mitochondrial function in rats subjected to IRI.[249] Compound **28** was able to decrease the size of the brain infarct size in rats subjected to an ischemic stroke more effectively than compound **27**, indicating that the methoxy groups improved the therapeutic potential, presumably due to the higher catalase activity of **28** compared to **27**.[250]



27 **28**

Chart 12. Structures of EUK-8 (**27**) and EUK-134 (**28**), salen Mn(III) complexes that can attenuate the effects of IRI.[249,250]

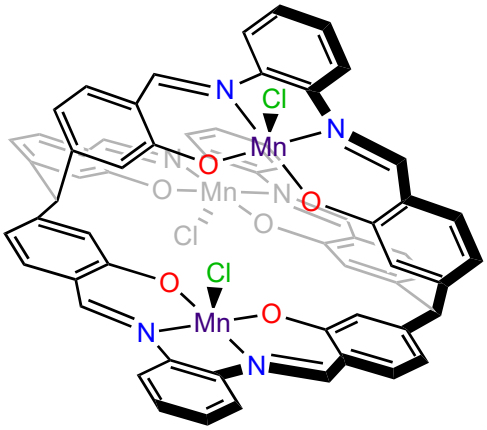
A series of pentaazamacrocyclic complexes of Mn(II) are also effective SOD mimics.[254,255] Most notably, the compound M40403 (**29**, **Chart 13**)[256,257] has progressed to clinical trials for the treatment of various pathological conditions related to elevated levels of ROS.[258–261] This complex has specifically demonstrated protective effects against models of IRI. Treatment of rats exposed to ischemia and sequential reperfusion periods with compound **29** led to smaller myocardial infarct sizes at concentrations of 1 mg kg^{-1} or higher.[262] In addition, the compound SC-52608 (**30**, **Chart 13**)[263] has shown a significant protective effect against IRI in both isolated rabbit hearts[264] and an in vivo model of myocardial IRI within dogs.[265] In both models, the myocardial infarct sizes were significantly smaller within those treated with **30** compared to the control.



29 **30**

Chart 13. Structures of M40403 (**29**) and SC-52608 (**30**), macrocyclic Mn(II) mimics of SOD/catalase that protect against IRI.[256,257,263]

A general limitation of many SOD mimics arises from their production of H_2O_2. If their catalase activity is not sufficiently fast to further decompose H_2O_2, this ROS can undergo redox chemistry with intracellular Fe, which catalyzes the Fenton reaction and produces highly toxic $HO^{\bullet}$.[266,267] Avoiding the production of $HO^{\bullet}$ can be achieved by a more rapid succession of catalase activity, a feature that is lacking in the some of the prior Mn complexes discussed, limiting their therapeutic potentials.[268] A recent study described a trinuclear Mn(III) salen complex, supported by a cryptand-like ligand (**31**, **Chart 14**).[269] This complex showed catalase activity and was able to decrease H_2O_2 levels in vitro without producing $HO^{\bullet}$. Based on these promising results, this complex was evaluated in an in vivo ischemic stroke model. In rats treated with **31** via intracerebroventricular injection, the size of the brain infarct, as measured by postmortem TTC staining and in vivo ^{18}F-fludeoxygluclose ([^{18}F]FDG) positron emission tomography (PET), was significantly smaller than that in the untreated rats (**Figure 13**). Additionally, the large magnetic moment of the trinuclear compound **31** enabled its use as a MRI contrast agent. Compound **31** could be directly detected via MRI and was shown to be present throughout the brain with this imaging technique. The dual antioxidant and imaging properties of **31** could render it valuable as a theranostic agents and further highlights the value of Mn complexes as MRI contrast agents.[270,271]



31

Chart 14. Structure of a salen-based, tri-Mn metallocryptand (**31**) with protective effects against ischemic stroke.[269]

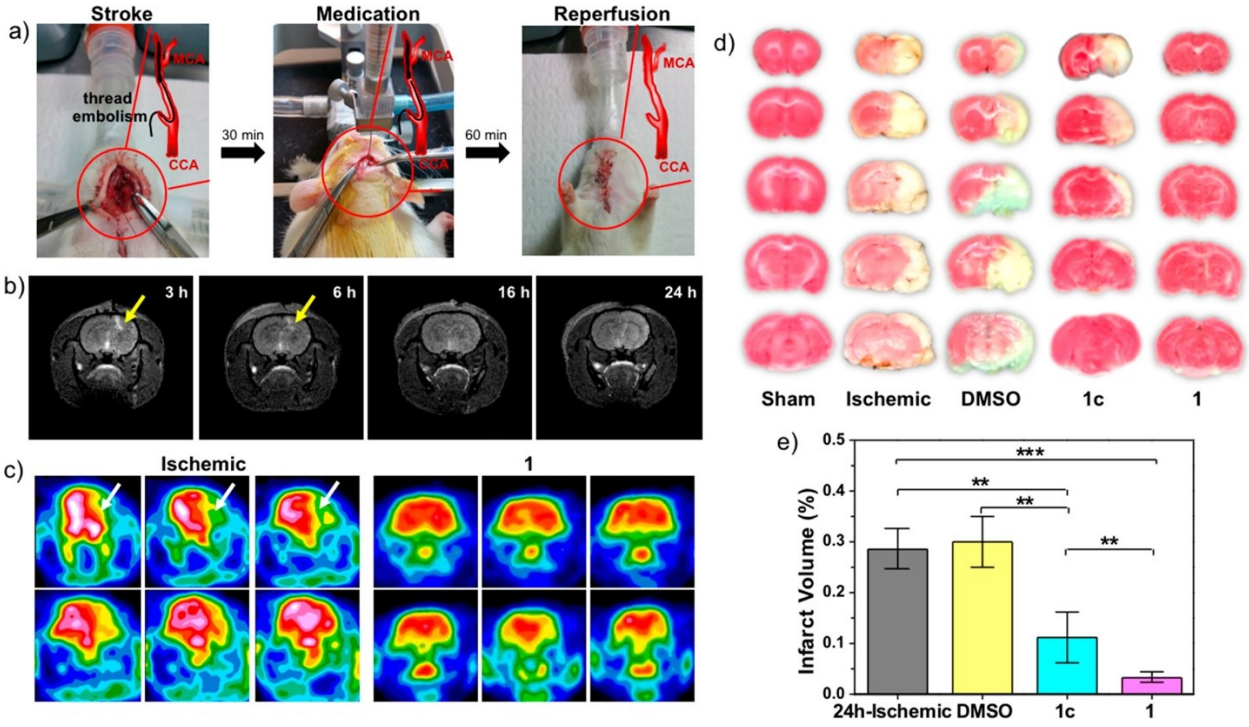


Figure 13. a) Schematic of the operation and procedure of ischemic stroke and intracerebroventricular injection (2 mM). b) Biodistribution of compound **31** (shown as **1** in the figure) by MRI after surgery. c) PET images of rat brain following tail vein injection of [^{18}F]FDG after treatment with **31**. d) Coronal brain sections of rats stained with TTC in the absence of IRI, with IRI, no treatment (DMSO), and treatment of compound **31** (**1**) and a mononuclear Mn-salen (**1c**). e) Calculated brain infarct volumes under conditions described in (d). Reproduced with permission from ref. 269. Copyright 2020 American Chemical Society.

5. Conclusions

In this Perspective, we examined the potential of metal coordination complexes as therapeutic agents for IRI. Given the current lack of clinically approved preventative measures for this condition, bioinorganic chemists can play an important role in this area by targeting the well-defined therapeutic strategies discussed in this manuscript. An important commonality between these three therapeutic approaches is that metal coordination complexes have unique properties that make them amenable for these applications. The release of CO, H_2S, and NO from metal coordination complexes is a well validated strategy to deliver these compounds in biological settings because of the strong ligating properties of these gasotransmitters. Furthermore, stopping $_{m}Ca^{2+}$ overload, another therapeutic approach for the prevention of IRI, is accomplished by blocking the MCU. In this context, the best inhibitors for the MCU are multi-metallic Ru and Os complexes, and these have been demonstrated to successfully prevent cell death caused by IRI. Various MCU inhibitors have been developed,[272] but not very many of these have been tested in models of IRI. Examining these complexes and others not yet reported can continue to expand this area. Finally, ROS scavengers have shown significant promise as therapeutic agents against IRI. In this case, metal complexes are uniquely suited for this application based on their ability to reversibly cycle through different oxidation states to catalytically decompose ROS.

The complexes all described within this Perspective exhibit protective effects against different models of IRI. The majority of these drug candidates have only yet been tested in vitro, with several key examples of compounds that have been evaluated in vivo and even in humans. Obviously, complexes in these latter categories have substantially more promise for further clinical advancement. Compound **12** has been used clinically for the management of blood pressure[273–276]

and has recently been explored clinically for the treatment of IRI.[159] This study, although promising towards the treatment of IRI, did not show a consistent outcome in patients, indicating that further clinical studies need to be performed. The Mn SOD mimics **23**[231–235] and **29**[258–261] have been investigated in clinical trials for a wide range of conditions, but have not yet been tested clinically for IRI. The strategy of MCU inhibition is the only approach presented in this manuscript that has not yet been applied in humans. The lack of work in this area may arise as a consequence of the fact that the MCU was only conclusively identified in 2011,[163,164] and as such it represents a relatively new drug target. In addition, as noted in Section 3, a major hurdle for the metal-based MCU inhibitors that must be overcome before human trials can be considered arises from their dose-limiting seizure-inducing activities within mouse models. Because ongoing studies suggest that this property arises from off-target effects,[277] efforts are required to improve their selectivity for the MCU in order to minimize their abilities to induce seizures. Therefore, like any drug candidate, improving the therapeutic window is an important objective for their advancement to clinical trials. In any case, this Perspective has shown that the groundwork for preventative strategies against IRI has been laid, and metal complexes have an important role in the management of this condition moving forward.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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REFERENCES

(1) Cohen, S. M.; Lippard, S. J. Cisplatin: From DNA Damage to Cancer Chemotherapy. *Prog. Nucleic Acid Res. Mol. Biol.* **2001**, *67*, 93–130.
(2) Graham, J.; Muhsin, M.; Kirkpatrick, P. Fresh from the Pipeline: Oxaliplatin. *Nat. Rev. Drug Discovery* **2004**, *3*, 11–12.
(3) Canetta, R.; Rozencweig, M.; Carter, S. K. Carboplatin: The Clinical Spectrum to Date. *Cancer Treat. Rev.* **1985**, *12*, 125–136.
(4) Brabec, V.; Hrabina, O.; Kasparkova, J. Cytotoxic Platinum Coordination Compounds. DNA Binding Agents. *Coord. Chem. Rev.* **2017**, *351*, 2–31.
(5) Johnstone, T. C.; Suntharalingam, K.; Lippard, S. J. The Next Generation of Platinum Drugs: Targeted Pt(II) Agents, Nanoparticle Delivery, and Pt(IV) Prodrugs. *Chem. Rev.* **2016**, *116*, 3436–3486.
(6) Ndagi, U.; Mhlongo, N.; Soliman, M. E. Metal Complexes in Cancer Therapy – an Update from Drug Design Perspective. *Drug Des., Dev. Ther.* **2017**, *11*, 599–616.
(7) Konkankit, C. C.; Marker, S. C.; Knopf, K. M.; Wilson, J. J. Anticancer Activity of Complexes of the Third Row Transition Metals, Rhenium, Osmium, and Iridium. *Dalton Trans.* **2018**, *47*, 9934–9974.
(8) Caravan, P.; Ellison, J. J.; McMurry, T. J.; Lauffer, R. B. Gadolinium(III) Chelates as MRI Contrast Agents: Structure, Dynamics, and Applications. *Chem. Rev.* **1999**, *99*, 2293–2352.
(9) Riley, D. P. Functional Mimics of Superoxide Dismutase Enzymes as Therapeutic Agents. *Chem. Rev.* **1999**, *99*, 2573–2587.
(10) Batinic-Harberle, I.; Reboucas, J. S.; Spasojevic, I. Superoxide Dismutase Mimics: Chemistry, Pharmacology, and Therapeutic Potential. *Antioxid. Redox Signaling* **2010**, *13*, 721–949.
(11) Bonetta, R. Potential Therapeutic Applications of MnSODs and SOD-Mimetics. *Chem. - Eur. J.* **2018**, *24*, 5032–5041.
(12) Borgstahl, G. E. O.; Oberley-Deegan, R. E. Superoxide Dismutases (SODs) and SOD Mimetics. *Antioxidants* **2018**, *7*, 156.
(13) Wu, M.-Y.; Yiang, G.-T.; Liao, W.-T.; Tsai, A. P.-Y.; Cheng, Y.-L.; Cheng, P.-W.; Li, C.-Y.; Li, C.-J. Current Mechanistic Concepts in Ischemia and Reperfusion Injury. *Cell.*

Physiol. Biochem. **2018**, *46*, 1650–1667.
(14) Hausenloy, D. J.; Yellon, D. M. Myocardial Ischemia-Reperfusion Injury: A Neglected Therapeutic Target. *J. Clin. Invest.* **2013**, *123*, 92–100.
(15) Tsao, C. W.; Aday, A. W.; Almarzooq, Z. I.; Alonso, A.; Beaton, A. Z.; Bittencourt, M. S.; Boehme, A. K.; Buxton, A. E.; Carson, A. P.; Commodore-Mensah, Y.; Elkind, M. S. V.; Evenson, K. R.; Eze-Nliam, C.; Ferguson, J. F.; Generoso, G.; Ho, J. E.; Kalani, R.; Khan, S. S.; et al. *Heart Disease and Stroke Statistics-2022 Update: A Report from the American Heart Association*; 2022; Vol. 145.
(16) Kalogeris, T.; Baines, C. P.; Krenz, M.; Korthuis, R. J. Cell Biology of Ischemia/Reperfusion Injury. *Int. Rev. Cell Mol. Biol.* **2012**, *298*, 229–317.
(17) Piper, H. M.; Meuter, K.; Schäfer, C. Cellular Mechanisms of Ischemia-Reperfusion Injury. *Ann. Thorac. Surg.* **2003**, *75*, S644–S648.
(18) Shintani-Ishida, K.; Inui, M.; Yoshida, K. Ischemia-Reperfusion Induces Myocardial Infarction through Mitochondrial Ca^{2+} Overload. *J. Mol. Cell. Cardiol.* **2012**, *53*, 233–239.
(19) Halestrap, A. R.; Connern, C. R.; Griffiths, E. J.; Kerr, P. M. Cyclosporin A Binding to Mitochondrial Cyclophilin Inhibits the Permeability Transition Pore and Protects Hearts from Ischaemia/Reperfusion Injury. *Mol. Cell. Biochem.* **1997**, *174*, 167–172.
(20) Nighoghossian, N.; Ovize, M.; Mewton, N.; Ong, E.; Cho, T.-H. Cyclosporine A, a Potential Therapy of Ischemic Reperfusion Injury. A Common History for Heart and Brain. *Cerebrovasc. Dis.* **2016**, *42*, 309–318.
(21) Tedesco, D.; Haragsim, L. Cyclosporine: A Review. *J. Transplant.* **2012**, *2012*, 230386.
(22) Yang, G.; Sener, A.; Ji, Y.; Pei, Y.; Pluth, M. D. Gasotransmitters in Biology and Medicine: Molecular Mechanisms and Drug Targets. *Oxid. Med. Cell. Longevity* **2016**, *2016*, 4627308.
(23) Moody, B. F.; Calvert, J. W. Emergent Role of Gasotransmitters in Ischemia-Reperfusion Injury. *Med. Gas Res.* **2011**, *1*, 3.
(24) Goldbaum, L. R.; Orellano, T.; Dergal, E. Mechanism of the Toxic Action of Carbon Monoxide. *Ann. Clin. Lab. Sci.* **1976**, *6*, 372–376.
(25) Kim, H. P.; Ryter, S. W.; Choi, A. M. K. CO as a Cellular Signaling Molecule. *Annu. Rev. Pharmacol. Toxicol.* **2006**, *46*, 411–449.
(26) Wilkinson, W. J.; Kemp, P. J. Carbon Monoxide: An Emerging Regulator of Ion Channels. *J. Physiol.* **2011**, *589*, 3055–3062.
(27) Mann, B. E. Carbon Monoxide: An Essential Signalling Molecule. *Top. Organomet. Chem.* **2010**, *32*, 247–285.
(28) Kwong, A. M.; Luke, P. P. W.; Bhattacharjee, R. N. Carbon Monoxide Mechanism of Protection against Renal Ischemia and Reperfusion Injury. *Biochem. Pharmacol.* **2022**, *202*, 115156.
(29) Chung, S. W.; Liu, X.; Macias, A. A.; Baron, R. M.; Perrella, M. A. Heme Oxygenase-1-Derived Carbon Monoxide Enhances the Host Defense Response to Microbial Sepsis in Mice. *J. Clin. Invest.* **2008**, *118*, 239–247.
(30) Chen, B.; Guo, L.; Fan, C.; Bolisetty, S.; Joseph, R.; Wright, M. M.; Agarwal, A.; George, J. F. Carbon Monoxide Rescues Heme Oxygenase-1-Deficient Mice from Arterial Thrombosis in Allogeneic Aortic Transplantation. *Am. J. Pathol.* **2009**, *175*, 422–429.
(31) Motterlini, R.; Otterbein, L. E. The Therapeutic Potential of Carbon Monoxide. *Nat. Rev. Drug Discovery* **2010**, *9*, 728–743.
(32) Romão, C. C.; Blättler, W. A.; Seixas, J. D.; Bernardes, G. J. L. Developing Drug Molecules for Therapy with Carbon Monoxide. *Chem. Soc. Rev.* **2012**, *41*, 3571–3583.

(33) Wegiel, B.; Hanto, D. W.; Otterbein, L. E. The Social Network of Carbon Monoxide in Medicine. *Trends Mol. Med.* **2013**, *19*, 3–11.
(34) Amersi, F.; Shen, X.-D.; Anselmo, D.; Melinek, J.; Iyer, S.; Southard, D. J.; Katori, M.; Volk, H.-D.; Busuttil, R. W.; Buelow, R.; Kupiec-Weglinski, J. W. Ex Vivo Exposure to Carbon Monoxide Prevents Hepatic Ischemia/Reperfusion Injury through P38 MAP Kinase Pathway. *Hepatology* **2002**, *35*, 815–823.
(35) Akamatsu, Y.; Haga, M.; Tyagi, S.; Yamashita, K.; Graça-Souza, A. V.; Ollinger, R.; Czismadia, E.; May, G. A.; Ifedigbo, E.; Otterbein, L. E.; Bach, F. H.; Soares, M. P. Heme Oxygenase-1-Derived Carbon Monoxide Protects Hearts from Transplant Associated Ischemia Reperfusion Injury. *FASEB J.* **2004**, *18*, 771–772.
(36) Fujimoto, H.; Ohno, M.; Ayabe, S.; Kobayashi, H.; Ishizaka, N.; Kimura, H.; Yoshida, K.; Nagai, R. Carbon Monoxide Protects Against Cardiac Ischemia–Reperfusion Injury In Vivo via MAPK and Akt– ENOS Pathways. *Arterioscler., Thromb., Vasc. Biol.* **2004**, *24*, 1848–1853.
(37) Neto, J. S.; Nakao, A.; Kimizuka, K.; Romanosky, A. J.; Stolz, D. B.; Uchiyama, T.; Nalesnik, M. A.; Otterbein, L. E.; Murase, N. Protection of Transplant-Induced Renal Ischemia-Reperfusion Injury with Carbon Monoxide. *Am. J. Physiol. Ren. Physiol.* **2004**, *287*, F979–F989.
(38) Kohmoto, J.; Nakao, A.; Kaizu, T.; Tsung, A.; Ikeda, A.; Tomiyama, K.; Billiar, T. R.; Choi, A. M. K.; Murase, N.; McCurry, K. R. Low-Dose Carbon Monoxide Inhalation Prevents Ischemia/Reperfusion Injury of Transplanted Rat Lung Grafts. *Surgery* **2006**, *140*, 179–185.
(39) Nakao, A.; Choi, A. M. K.; Murase, N. Protective Effect of Carbon Monoxide in Transplantation. *J. Cell. Mol. Med.* **2006**, *10*, 650–671.
(40) Nakao, A.; Toyokawa, H.; Tsung, A.; Nalesnik, M. A.; Stolz, D. B.; Kohmoto, J.; Ikeda, A.; Tomiyama, K.; Harada, T.; Takahashi, T.; Yang, R.; Fink, M. P.; Morita, K.; Choi, A. M. K.; Murase, N. *Ex Vivo* Application of Carbon Monoxide in University of Wisconsin Solution to Prevent Intestinal Cold Ischemia/Reperfusion Injury. *Am. J. Transplant.* **2006**, *6*, 2243–2255.
(41) Nakao, A.; Faleo, G.; Shimizu, H.; Nakahira, K.; Kohmoto, J.; Sugimoto, R.; Choi, A. M. K.; McCurry, K. R.; Takahashi, T.; Murase, N. *Ex Vivo* Carbon Monoxide Prevents Cytochrome P450 Degradation and Ischemia/Reperfusion Injury of Kidney Grafts. *Kidney Int.* **2008**, *74*, 1009–1016.
(42) Nakao, A.; Kaczorowski, D. J.; Sugimoto, R.; Billiar, T. R.; McCurry, K. R. Application of Heme Oxygenase-1, Carbon Monoxide and Biliverdin for the Prevention of Intestinal Ischemia/Reperfusion Injury. *J. Clin. Biochem. Nutr.* **2008**, *42*, 78–88.
(43) Ling, K.; Men, F.; Wang, W.-C.; Zhou, Y.-Q.; Zhang, H.-W.; Ye, D.-W. Carbon Monoxide and Its Controlled Release: Therapeutic Application, Detection, and Development of Carbon Monoxide Releasing Molecules (CORMs). *J. Med. Chem.* **2018**, *61*, 2611–2635.
(44) Boczkowski, J.; Poderoso, J. J.; Motterlini, R. CO-Metal Interaction: Vital Signaling from a Lethal Gas. *Trends Biochem. Sci.* **2006**, *31*, 614–621.
(45) Herrmann, W. A. 100 Years of Metal Carbonyls: A Serendipitous Chemical Discovery of Major Scientific and Industrial Impact. *J. Organomet. Chem.* **1990**, *383*, 21–44.
(46) Motterlini, R.; Clark, J. E.; Foresti, R.; Sarathchandra, P.; Mann, B. E.; Green, C. J. Carbon Monoxide-Releasing Molecules. *Circ. Res.* **2002**, *90*, e17–e24.
(47) Clark, J. E.; Naughton, P.; Shurey, S.; Green, C. J.; Johnson, T. R.; Mann, B. E.; Foresti,

R.; Motterlini, R. Cardioprotective Actions by a Water-Soluble Carbon Monoxide-Releasing Molecule. *Circ. Res.* **2003**, *93*, e2–e8.
(48) Cepinskas, G.; Katada, K.; Bihari, A.; Potter, R. F. Carbon Monoxide Liberated from Carbon Monoxide-Releasing Molecule CORM-2 Attenuates Inflammation in the Liver of Septic Mice. *Am. J. Physiol. Gastrointest. Liver Physiol.* **2007**, *294*, 184–191.
(49) Sun, B.; Sun, Z.; Jin, Q.; Chen, X. CO-Releasing Molecules (CORM-2)-Liberated CO Attenuates Leukocytes Infiltration in the Renal Tissue of Thermally Injured Mice. *Int. J. Biol. Sci.* **2008**, *4*, 176–183.
(50) Katada, K.; Bihari, A.; Mizuguchi, S.; Yoshida, N.; Yoshikawa, T.; Fraser, D. D.; Potter, R. F.; Cepinskas, G. Carbon Monoxide Liberated from Co-Releasing Molecule (CORM-2) Attenuates Ischemia/Reperfusion (I/R)-Induced Inflammation in the Small Intestine. *Inflammation* **2010**, *33*, 92–100.
(51) Wei, Y.; Chen, P.; de Bruyn, M.; Zhang, W.; Bremer, E.; Helfrich, W. Carbon Monoxide-Releasing Molecule-2 (CORM-2) Attenuates Acute Hepatic Ischemia Reperfusion Injury in Rats. *BMC Gastroenterol.* **2010**, *10*, 42.
(52) Caumartin, Y.; Stephen, J.; Deng, J. P.; Lian, D.; Lan, Z.; Liu, W.; Garcia, B.; Jevnikar, A. M.; Wang, H.; Cepinskas, G.; Luke, P. P. W. Carbon Monoxide-Releasing Molecules Protect against Ischemia-Reperfusion Injury during Kidney Transplantation. *Kidney Int.* **2011**, *79*, 1080–1089.
(53) Ruan, Y.; Wang, L.; Zhao, Y.; Yao, Y.; Chen, S.; Li, J.; Guo, H.; Ming, C.; Chen, S.; Gong, F.; Chen, G. Carbon Monoxide Potently Prevents Ischemia-Induced High-Mobility Group Box 1 Translocation and Release and Protects against Lethal Renal Ischemia-Reperfusion Injury. *Kidney Int.* **2014**, *86*, 525–537.
(54) Zhao, S.; Lin, Q.; Li, H.; He, Y.; Fang, X.; Chen, F.; Chen, C.; Huang, Z. Carbon Monoxide Releasing Molecule-2 Attenuated Ischemia/Reperfusion-Induced Apoptosis in Cardiomyocytes via a Mitochondrial Pathway. *Mol. Med. Rep.* **2014**, *9*, 754–762.
(55) Kumar, A.; Boovarahan, S. R.; Prem, P. N.; Ramanathan, M.; Chellappan, D. R.; Kurian, G. A. Evaluating the Effects of Carbon Monoxide Releasing Molecule-2 against Myocardial Ischemia–Reperfusion Injury in Ovariectomized Female Rats. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **2021**, *394*, 2103–2115.
(56) Guo, Y.; Stein, A. B.; Wu, W.-J.; Tan, W.; Zhu, X.; Li, Q.-H.; Dawn, B.; Motterlini, R.; Bolli, R. Administration of a CO-Releasing Molecule at the Time of Reperfusion Reduces Infarct Size in Vivo. *Am. J. Physiol. Heart Circ. Physiol.* **2004**, *286*, 1649–1653.
(57) Stein, A. B.; Guo, Y.; Tan, W.; Wu, W.-J.; Zhu, X.; Li, Q.; Luo, C.; Dawn, B.; Johnson, T. R.; Motterlini, R.; Bolli, R. Administration of a CO-Releasing Molecule Induces Late Preconditioning against Myocardial Infarction. *J. Mol. Cell. Cardiol.* **2005**, *38*, 127–134.
(58) Varadi, J.; Lekli, I.; Juhasz, B.; Bacskay, I.; Szabo, G.; Gesztelyi, R.; Szendrei, L.; Varga, E.; Bak, I.; Foresti, R.; Motterlini, R.; Tosaki, A. Beneficial Effects of Carbon Monoxide-Releasing Molecules on Post-Ischemic Myocardial Recovery. *Life Sci.* **2007**, *80*, 1619–1626.
(59) Marques, A. R.; Kromer, L.; Gallo, D. J.; Penacho, N.; Rodrigues, S. S.; Seixas, J. D.; Bernardes, G. J. L.; Reis, P. M.; Otterbein, S. L.; Ruggieri, R. A.; Gonçalves, A. S. G.; Gonçalves, A. M. L.; Matos, M. N. D.; Bento, I.; Otterbein, L. E.; Blättler, W. A.; Romão, C. C. Generation of Carbon Monoxide Releasing Molecules (CO-RMs) as Drug Candidates for the Treatment of Acute Liver Injury: Targeting of CO-RMs to the Liver. *Organometallics* **2012**, *31*, 5810–5822.

(60) Wang, J.; Zhang, D.; Fu, X.; Yu, L.; Lu, Z.; Gao, Y.; Liu, X.; Man, J.; Li, S.; Li, N.; Chen, X.; Hong, M.; Yang, Q.; Wang, J. Carbon Monoxide-Releasing Molecule-3 Protects against Ischemic Stroke by Suppressing Neuroinflammation and Alleviating Blood-Brain Barrier Disruption. *J. Neuroinflammation* **2018**, *15*, 188.

(61) Obara, T.; Yamamoto, H.; Aokage, T.; Igawa, T.; Nojima, T.; Hirayama, T.; Seya, M.; Ishikawa-Aoyama, M.; Nakao, A.; Motterlini, R.; Naito, H. Luminal Administration of a Water-Soluble Carbon Monoxide-Releasing Molecule (CORM-3) Mitigates Ischemia/Reperfusion Injury in Rats Following Intestinal Transplantation. *Transplantation* **2022**, *106*, 1365–1375.

(62) Johnson, T. R.; Mann, B. E.; Teasdale, I. P.; Adams, H.; Foresti, R.; Green, C. J.; Motterlini, R. Metal Carbonyls as Pharmaceuticals? [$Ru(CO)_3Cl$(Glycinate)], a CO-Releasing Molecule with an Extensive Aqueous Solution Chemistry. *Dalton Trans.* **2007**, *15*, 1500–1508.

(63) Southam, H. M.; Smith, T. W.; Lyon, R. L.; Liao, C.; Trevitt, C. R.; Middlemiss, L. A.; Cox, F. L.; Chapman, J. A.; El-Khamisy, S. F.; Hippler, M.; Williamson, M. P.; Henderson, P. J. F.; Poole, R. K. A Thiol-Reactive Ru(II) Ion, Not CO Release, Underlies the Potent Antimicrobial and Cytotoxic Properties of CO-Releasing Molecule-3. *Redox Biol.* **2018**, *18*, 114–123.

(64) Stucki, D.; Krahl, H.; Walter, M.; Steinhausen, J.; Hommel, K.; Brenneisen, P.; Stahl, W. Effects of Frequently Applied Carbon Monoxide Releasing Molecules (CORMs) in Typical CO-Sensitive Model Systems – A Comparative *in Vitro* Study. *Arch. Biochem. Biophys.* **2020**, *687*, 108383.

(65) Southam, H. M.; Williamson, M. P.; Chapman, J. A.; Lyon, R. L.; Trevitt, C. R.; Henderson, P. J. F.; Poole, R. K. 'Carbon-Monoxide-Releasing Molecule-2 (CORM-2)' Is a Misnomer: Ruthenium Toxicity, Not CO Release, Accounts for Its Antimicrobial Effects. *Antioxidants* **2021**, *10*, 915.

(66) Yuan, Z.; Yang, X. Redox and Catalase-like Activities of Four Widely Used Carbon Monoxide Releasing Molecules (CORMs). *Chem. Sci.* **2021**, *12*, 13013–13020.

(67) Heinemann, S. H.; Hoshi, T.; Westerhausen, M.; Schiller, A. Carbon Monoxide - Physiology, Detection, and Controlled Release. *Chem. Commun.* **2014**, *50*, 3644–3660.

(68) Lazarus, L. S.; Benningho, A. D.; Berreau, L. M. Development of Triggerable, Trackable, and Targetable Carbon Monoxide Releasing Molecules. *Acc. Chem. Res.* **2020**, *53*, 2273–2285.

(69) Min, Q.; Ji, X. Strategies toward Metal-Free Carbon Monoxide Prodrugs: An Update. *ChemMedChem* **2022**, *2022*, e202200500.

(70) Crook, S. H.; Mann, B. E.; Meijer, A. J. H. M.; Adams, H.; Sawle, P.; Scapens, D.; Motterlini, R. [$Mn(CO)_4\{S_2CNMe(CH_2CO_2H)\}$], a New Water-Soluble CO-Releasing Molecule. *Dalton Trans.* **2011**, *40*, 4230–4235.

(71) Fayad-Kobeissi, S.; Wilson, J. L.; Michel, B.; Dubois-Randé, J.-L.; Motterlini, R.; Foresti, R. Pharmacological Activities of CORM-401, a Redox Sensitive Carbon Monoxide-Releasing Molecule, in H9C2 Cardiomyocytes. *Arch. Cardiovasc. Dis., Suppl.* **2014**, *6*, 15–17.

(72) Bhattacharjee, R. N.; Richard-Mohamed, M.; Sun, Q.; Haig, A.; Aboalsamh, G.; Barrett, P.; Mayer, R.; Alhasan, I.; Pineda-Solis, K.; Jiang, L.; Alharbi, H.; Saha, M.; Patterson, E.; Sener, A.; Cepinskas, G.; Jevnikar, A. M.; Luke, P. P. W. CORM-401 Reduces Ischemia Reperfusion Injury in an Ex Vivo Renal Porcine Model of the Donation after Circulatory

Death. *Transplantation* **2018**, *102*, 1066–1074.
(73) Bauer, E. B.; Haase, A. A.; Reich, R. M.; Crans, D. C.; Kühn, F. E. Organometallic and Coordination Rhenium Compounds and Their Potential in Cancer Therapy. *Coord. Chem. Rev.* **2019**, *393*, 79–117.
(74) Wilson, J. J. Leveraging the Photophysical Properties of Rhenium(I) Tricarbonyl Complexes for Biomedical Applications. In *Advances in Inorganic Chemistry*; Elsevier Inc., 2022; Vol. 80, pp 1–33.
(75) Pierri, A. E.; Pallaoro, A.; Wu, G.; Ford, P. C. A Luminescent and Biocompatible PhotoCORM. *J. Am. Chem. Soc.* **2012**, *134*, 18197–18200.
(76) Chakraborty, I.; Jimenez, J.; Sameera, W. M. C.; Kato, M.; Mascharak, P. K. Luminescent Re(I) Carbonyl Complexes as Trackable PhotoCORMs for CO Delivery to Cellular Targets. *Inorg. Chem.* **2017**, *56*, 2863–2873.
(77) Hostachy, S.; Policar, C.; Delsuc, N. Re(I) Carbonyl Complexes: Multimodal Platforms for Inorganic Chemical Biology. *Coord. Chem. Rev.* **2017**, *351*, 172–188.
(78) Marker, S. C.; MacMillan, S. N.; Zipfel, W. R.; Li, Z.; Ford, P. C.; Wilson, J. J. Photoactivated in Vitro Anticancer Activity of Rhenium(I) Tricarbonyl Complexes Bearing Water-Soluble Phosphines. *Inorg. Chem.* **2018**, *57*, 1311–1331.
(79) Zobi, F.; Degonda, A.; Schaub, M. C.; Bogdanova, A. Y. CO Releasing Properties and Cytoprotective Effect of Cis-Trans-$[Re^{II}(CO)_2Br_2L_2]^n$ Complexes. *Inorg. Chem.* **2010**, *49*, 7313–7322.
(80) Pettenuzzo, A.; Pigot, R.; Ronconi, L. Vitamin B_{12} – Metal Conjugates for Targeted Chemotherapy and Diagnosis: Current Status and Future Prospects. *Eur. J. Inorg. Chem.* **2017**, *2017*, 1625–1638.
(81) Huang, Z.; Wilson, J. J. Therapeutic and Diagnostic Applications of Multimetallic Rhenium(I) Tricarbonyl Complexes. *Eur. J. Inorg. Chem.* **2021**, *2021*, 1312–1324.
(82) Zobi, F.; Blacque, O.; Jacobs, R. A.; Schaub, M. C.; Bogdanova, A. Y. 17 e^- Rhenium Dicarbonyl CO-Releasing Molecules on a Cobalamin Scaffold for Biological Application. *Dalton Trans.* **2012**, *41*, 370–378.
(83) Santoro, G.; Beltrami, R.; Kottelat, E.; Blacque, O.; Bogdanova, A. Y.; Zobi, F. *N*-Nitrosamine-{*Cis*-$Re[CO]_2\}^{2+}$ Cobalamin Conjugates as Mixed CO/NO-Releasing Molecules. *Dalton Trans.* **2016**, *45*, 1504–1513.
(84) Paul, B. D.; Snyder, S. H. H_2S: A Novel Gasotransmitter That Signals by Sulfhydration. *Trends Biochem. Sci.* **2015**, *40*, 687–700.
(85) Woods, J. J.; Wilson, J. J. Bioinorganic Chemistry of Hydrogen Sulfide: Detection, Delivery, and Interactions with Metalloproteins. In *Encyclopedia of Inorganic and Bioinorganic Chemistry*; Scott, R. A., Ed.; John Wiley & Sons, Ltd.: Chichester, UK, 2021. DOI: 10.1002/9781119951438.eibc2764
(86) Filipovic, M. R.; Zivanovic, J.; Alvarez, B.; Banerjee, R. Chemical Biology of H_2S Signaling through Persulfidation. *Chem. Rev.* **2018**, *118*, 1253–1337.
(87) Lee, Z.-W.; Deng, L.-W. Role of H_2S Donors in Cancer Biology. *Handb. Exp. Pharmacol.* **2015**, *230*, 243–265.
(88) Fu, M.; Zhang, W.; Wu, L.; Yang, G.; Li, H.; Wang, R. Hydrogen Sulfide (H_2S) Metabolism in Mitochondria and Its Regulatory Role in Energy Production. *Proc. Natl. Acad. Sci. U.S.A.* **2012**, *109*, 2943–2948.
(89) Kimura, H. Physiological Role of Hydrogen Sulfide and Polysulfide in the Central Nervous System. *Neurochem. Int.* **2013**, *63*, 492–497.

(90) Kimura, H. Signaling by Hydrogen Sulfide (H_2S) and Polysulfides (H_2S_n) in the Central Nervous System. *Neurochem. Int.* **2019**, *126*, 118–125.
(91) Ryazantseva, N. V.; Novitsky, V. V.; Starikova, E. G.; Kleptsova, L. A.; Jakushina, V. D.; Kaigorodova, E. V. Role of Hydrogen Sulfide in the Regulation of Cell Apoptosis. *Bull. Exp. Biol. Med.* **2011**, *151*, 702–704.
(92) Liu, Y.-H.; Lu, M.; Hu, L.-F.; Wong, P. T.-H.; Webb, G. D.; Bian, J.-S. Hydrogen Sulfide in the Mammalian Cardiovascular System. *Antioxid. Redox Signaling* **2012**, *17*, 141–185.
(93) Andreadou, I.; Iliodromitis, E. K.; Rassaf, T.; Schulz, R.; Papapetropoulos, A.; Ferdinandy, P. The Role of Gasotransmitters NO, H_2S and CO in Myocardial Ischaemia/Reperfusion Injury and Cardioprotection by Preconditioning, Postconditioning and Remote Conditioning. *Br. J. Pharmacol.* **2015**, *172*, 1587–1606.
(94) Szabõ, C. Hydrogen Sulphide and Its Therapeutic Potential. *Nat. Rev. Drug Discovery* **2007**, *6*, 917–935.
(95) Wallace, J. L.; Wang, R. Hydrogen Sulfide-Based Therapeutics: Exploiting a Unique but Ubiquitous Gasotransmitter. *Nat. Rev. Drug Discovery* **2015**, *14*, 329–345.
(96) Chan, S. J.; Wong, P. T.-H. Reprint of: Hydrogen Sulfide in Stroke: Protective or Deleterious? *Neurochem. Int.* **2017**, *107*, 78–87.
(97) Nicholson, C. K.; Calvert, J. W. Hydrogen Sulfide and Ischemia-Reperfusion Injury. *Pharm. Res.* **2010**, *62*, 289–297.
(98) Lefer, D. J. A New Gaseous Signaling Molecule Emerges: Cardioprotective Role of Hydrogen Sulfide. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 17907–17908.
(99) Bliksøen, M.; Kaljusto, M.-L.; Vaage, J.; Stensløkken, K.-O. Effects of Hydrogen Sulphide on Ischaemia-Reperfusion Injury and Ischaemic Preconditioning in the Isolated, Perfused Rat Heart. *Eur. J. Cardio-Thoracic Surg.* **2008**, *34*, 344–349.
(100) Elrod, J. W.; Calvert, J. W.; Morrison, J.; Doeller, J. E.; Kraus, D. W.; Tao, L.; Jiao, X.; Scalia, R.; Kiss, L.; Szabo, C.; Kimura, H.; Chow, C. W.; Lefer, D. J. Hydrogen Sulfide Attenuates Myocardial Ischemia-Reperfusion Injury by Preservation of Mitochondrial Function. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 15560–15565.
(101) Qu, K.; Chen, C. P. L. H.; Halliwell, B.; Moore, P. K.; Wong, P. T.-H. Hydrogen Sulfide Is a Mediator of Cerebral Ischemic Damage. *Stroke* **2006**, *37*, 889–893.
(102) Jang, H.; Oh, M.; Kim, Y.; Choi, I.; Yang, H.; Ryu, W.; Lee, S.; Yoon, B. Hydrogen Sulfide Treatment Induces Angiogenesis After Cerebral Ischemia. *J. Neurosci. Res.* **2014**, *92*, 1520–1528.
(103) Zhang, X.; Bian, J.-S. Hydrogen Sulfide: A Neuromodulator and Neuroprotectant in the Central Nervous System. *ACS Chem. Neurosci.* **2014**, *5*, 876–883.
(104) Dou, Y.; Wang, Z.; Chen, G. The Role of Hydrogen Sulfide in Stroke. *Med. Gas Res.* **2016**, *6*, 79–84.
(105) Narne, P.; Pandey, V.; Phanithi, P. B. Role of Nitric Oxide and Hydrogen Sulfide in Ischemic Stroke and the Emergent Epigenetic Underpinnings. *Mol. Neurobiol.* **2019**, *56*, 1749–1769.
(106) Song, Y.-J.; Shi, Y.; Cui, M.-M.; Li, M.; Wen, X.-R.; Zhou, X.-Y.; Lou, H.-Q.; Wang, Y.-L.; Qi, D.-S.; Tang, M.; Zhang, X.-B. H_2S Attenuates Injury after Ischemic Stroke by Diminishing the Assembly of CaMKII with ASK1-MKK3-P38 Signaling Module. *Behav. Brain Res.* **2020**, *384*, 112520.
(107) Zhao, W.; Zhang, J.; Lu, Y.; Wang, R. The Vasorelaxant Effect of H_2S as a Novel Endogenous Gaseous K_{ATP} Channel Opener. *EMBO J.* **2001**, *20*, 6008–6016.

(108) Hill, B. C.; Woon, T.-C.; Nicholls, P.; Peterson, J.; Greenwood, C.; Thomson, A. J. Interactions of Sulphide and Other Ligands with Cytochrome *c* Oxidase. *Biochem. J.* **1984**, *224*, 591–600.
(109) Hüttemann, M.; Helling, S.; Sanderson, T. H.; Sinkler, C.; Samavati, L.; Mahapatra, G.; Varughese, A.; Lu, G.; Liu, J.; Ramzan, R.; Vogt, S.; Grossman, L. I.; Doan, J. W.; Marcus, K.; Lee, I. Regulation of Mitochondrial Respiration and Apoptosis through Cell Signaling: Cytochrome *c* Oxidase and Cytochrome *c* in Ischemia/Reperfusion Injury and Inflammation. *Biochim. Biophys. Acta* **2012**, *1817*, 598–609.
(110) Hu, Y.; Chen, X.; Pan, T.-T.; Neo, K. L.; Lee, S. W.; Sandar, E.; Khin, W.; Moore, P. K.; Bian, J.-S. Cardioprotection Induced by Hydrogen Sulfide Preconditioning Involves Activation of ERK and PI3K/Akt Pathways. *Pflügers Arch. Eur. J. Physiol.* **2008**, *455*, 607–616.
(111) Devarie-Baez, N. O.; Bagdon, P. E.; Peng, B.; Zhao, Y.; Park, C.-M.; Xian, M. Light-Induced Hydrogen Sulfide Released from "Caged" *Gem*-Dithiols. *Org. Lett.* **2013**, *15*, 2786–2789.
(112) Fukushima, N.; Ieda, N.; Sasakura, K.; Nagano, T.; Hanaoka, K.; Suzuki, T.; Miyata, N.; Nakagawa, H. Synthesis of a Photocontrollable Hydrogen Sulfide Donor Using Ketoprofenate Photocages. *Chem. Commun.* **2014**, *50*, 587–589.
(113) Fukushima, N.; Ieda, N.; Kawaguchi, M.; Sasakura, K.; Nagano, T.; Hanaoka, K.; Miyata, N.; Nakagawa, H. Development of Photo-Controllable Hydrogen Sulfide Donor Applicable in Live Cells. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 175–178.
(114) Sharma, A. K.; Nair, M.; Chauhan, P.; Gupta, K.; Saini, D. K.; Chakrapani, H. Visible-Light-Triggered Uncaging of Carbonyl Sulfide for Hydrogen Sulfide (H_2S) Release. *Org. Lett.* **2017**, *19*, 4822–4825.
(115) Yi, S. Y.; Moon, Y. K.; Kim, S.; Kim, S.; Park, G.; Kim, J. J.; You, Y. Visible Light-Driven Photogeneration of Hydrogen Sulfide. *Chem. Commun.* **2017**, *53*, 11830–11833.
(116) Zhao, Y.; Bolton, S. G.; Pluth, M. D. Light-Activated COS/H_2S Donation from Photocaged Thiocarbamates. *Org. Lett.* **2017**, *19*, 2278–2281.
(117) Venkatesh, Y.; Das, J.; Chaudhuri, A.; Karmakar, A.; Maiti, T. K.; Singh, N. D. P. Light Triggered Uncaging of Hydrogen Sulfide (H_2S) with Real-Time Monitoring. *Chem. Commun.* **2018**, *54*, 3106–3109.
(118) Bera, M.; Maji, S.; Paul, A.; Ray, S.; Maiti, T. K.; Singh, N. D. P. A Water Soluble Light Activated Hydrogen Sulfide Donor Induced by an Excited State Meta Effect. *Org. Biomol. Chem.* **2019**, *17*, 9059–9064.
(119) Chaudhuri, A.; Singha, T.; Jena, B. C.; Shee, M.; Datta, P. K.; Mandal, M.; Singh, N. D. P. A Two-Photon Responsive Hydroxyphenylquinazolinone (HPQ)-Based Fluorescent Organic Nanoprodrug for H_2S Release against Oxidative Stress. *Chem. Commun.* **2023**, *53*, 1177–1180.
(120) Zhao, Y.; Pluth, M. D. Hydrogen Sulfide Donors Activated by Reactive Oxygen Species. *Angew. Chem., Int. Ed.* **2016**, *55*, 14638–14642.
(121) Zhao, Y.; Henthorn, H. A.; Pluth, M. D. Kinetic Insights into Hydrogen Sulfide Delivery from Caged-Carbonyl Sulfide Isomeric Donor Platforms. *J. Am. Chem. Soc.* **2017**, *139*, 16365–16376.
(122) Zhao, Y.; Bhushan, S.; Yang, C.; Otsuka, H.; Stein, J. D.; Pacheco, A.; Peng, B.; Devarie-baez, N. O.; Aguilar, H. C.; Lefer, D. J.; Xian, M. Controllable Hydrogen Sulfide Donors and Their Activity against Myocardial Ischemia-Reperfusion Injury. *ACS Chem. Biol.* **2013**,

8, 1283–12900.
(123) Foster, J. C.; Radzinski, S. C.; Zou, X.; Finkielstein, C. V.; Matson, J. B. H_2S - Releasing Polymer Micelles for Studying Selective Cell Toxicity. *Mol. Pharmaceutics* **2017**, *14*, 1300–1306.
(124) Zhao, Y.; Steiger, A. K.; Pluth, M. D. Cysteine-Activated Hydrogen Sulfide (H_2S) Delivery through Caged Carbonyl Sulfide (COS) Donor Motifs. *Chem. Commun.* **2018**, *54*, 4951–4954.
(125) Chauhan, P.; Bora, P.; Ravikumar, G.; Jos, S.; Chakrapani, H. Esterase Activated Carbonyl Sulfide/Hydrogen Sulfide (H_2S) Donors. *Org. Lett.* **2017**, *19*, 62–65.
(126) Steiger, A. K.; Marcatti, M.; Szabo, C.; Szczesny, B.; Pluth, M. D. Inhibition of Mitochondrial Bioenergetics by Esterase-Triggered COS/H_2S Donors. *ACS Chem. Biol.* **2017**, *12*, 2117–2123.
(127) Kang, J.; Li, Z.; Organ, C. L.; Park, C.-M.; Yang, C.; Pacheco, A.; Wang, D.; Lefer, D. J.; Xian, M. PH-Controlled Hydrogen Sulfide Release for Myocardial Ischemia-Reperfusion Injury. *J. Am. Chem. Soc.* **2016**, *138*, 6336–6339.
(128) Li, L.; Whiteman, M.; Guan, Y. Y.; Neo, K. L.; Cheng, Y.; Lee, S. W.; Zhao, Y.; Baskar, R.; Tan, C.-H.; Moore, P. K. Characterization of a Novel, Water-Soluble Hydrogen Sulfide-Releasing Molecule (GYY4137). *Circulation* **2008**, *117*, 2351–2360.
(129) Alexander, B. E.; Coles, S. J.; Fox, B. C.; Khan, T. F.; Maliszewski, J.; Perry, A.; Pitak, M. B.; Whiteman, M.; Wood, M. E. Investigating the Generation of Hydrogen Sulfide from the Phosphonamidodithioate Slow-Release Donor GYY4137. *Med. Chem. Commun.* **2015**, *6*, 1649–1655.
(130) Rose, P.; Dymock, B. W.; Moore, P. K. GYY4137, a Novel Water-Soluble H_2S-Releasing Molecule. *Methods Enzymol.* **2015**, *554*, 143–167.
(131) Meng, G.; Wang, J.; Xiao, Y.; Bai, W.; Xie, L.; Shan, L.; Moore, P. K.; Ji, Y. GYY4137 Protects against Myocardial Ischemia and Reperfusion Injury by Attenuating Oxidative Stress and Apoptosis in Rats. *J. Biomed. Res.* **2015**, *29*, 203–213.
(132) Woods, J. J.; Cao, J.; Lippert, A. R.; Wilson, J. J. Characterization and Biological Activity of a Hydrogen Sulfide-Releasing Red Light-Activated Ruthenium(II) Complex. *J. Am. Chem. Soc.* **2018**, *140*, 12383–12387.
(133) Brulet, C. R.; Isied, S. S.; Taube, H. Disulfur Binuclear Ruthenium Ammines. *J. Am. Chem. Soc.* **1973**, *95*, 4758–4759.
(134) Woods, J. J.; Wilson, J. J. A Dinuclear Persulfide-Bridged Ruthenium Compound Is a Hypoxia-Selective Hydrogen Sulfide (H_2S) Donor. *Angew. Chem., Int. Ed.* **2021**, *60*, 1588–1592.
(135) Lundberg, J. O.; Weitzberg, E. Nitric Oxide Signaling in Health and Disease. *Cell* **2022**, *185*, 2853–2878.
(136) Kobayashi, H.; Nonami, T.; Kurokawa, T.; Takeuchi, Y.; Harada, A.; Nakao, A.; Takagi, H. Role of Endogenous Nitric Oxide in Ischemia-Reperfusion Injury in Rat Liver. *J. Surg. Res.* **1995**, *59*, 772–779.
(137) Nonami, Y. The Role of Nitric Oxide in Cardiac Ischemia-Reperfusion Injury. *Jpn. Circ. J.* **1997**, *61*, 119–132.
(138) Shimamura, T.; Zhu, Y.; Zhang, S.; Jin, M. B.; Ishizaki, N.; Urakami, A.; Totsuka, E.; Kishida, A.; Lee, R.; Subbotin, V.; Furukawa, H.; Starzl, T. E.; Todo, S. Protective Role of Nitric Oxide in Ischemia and Reperfusion Injury in the Liver. *J. Am. Coll. Surg.* **1999**, *188*, 43–52.

(139) Peralta, C.; Rull, R.; Rimola, A.; Deulofeu, R.; Roselló-Catafau, J.; Gelpí, E.; Rodés, J. Endogenous Nitric Oxide and Exogenous Nitric Oxide Supplementation in Hepatic Ischemia-Reperfusion Injury in the Rat. *Transplantation* **2001**, *71*, 529–536.
(140) Hines, I. N.; Kawachi, S.; Harada, H.; Pavlick, K. P.; Hoffman, J. M.; Bharwani, S.; Wolf, R. E.; Grisham, M. B. Role of Nitric Oxide in Liver Ischemia and Reperfusion Injury. *Mol. Cell. Biochem.* **2002**, *234*, 229–237.
(141) Ferdinandy, P.; Schulz, R. Nitric Oxide, Superoxide, and Peroxynitrite in Myocardial Ischaemia-Reperfusion Injury and Preconditioning. *Br. J. Pharmacol.* **2003**, *138*, 532–543.
(142) Schulz, R.; Kelm, M.; Heusch, G. Nitric Oxide in Myocardial Ischemia/Reperfusion Injury. *Cardiovasc. Res.* **2004**, *61*, 402–413.
(143) Webb, A.; Bond, R.; McLean, P.; Uppal, R.; Benjamin, N.; Ahluwalia, A. Reduction of Nitrite to Nitric Oxide during Ischemia Protects against Myocardial Ischemia-Reperfusion Damage. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 13683–13688.
(144) Hataishi, R.; Rodrigues, A. C.; Neilan, T. G.; Morgan, J. G.; Buys, E.; Shiva, S.; Tambouret, R.; Jassal, D. S.; Raher, M. J.; Furutani, E.; Ichinose, F.; Gladwin, M. T.; Rosenzweig, A.; Zapol, W. M.; Picard, M. H.; Bloch, K. D.; Scherrer-Crosbie, M. Inhaled Nitric Oxide Decreases Infarction Size and Improves Left Ventricular Function in a Murine Model of Myocardial Ischemia-Reperfusion Injury. *Am. J. Physiol. Heart Circ. Physiol.* **2006**, *291*, H379–H384.
(145) Botha, P.; Jeyakanthan, M.; Rao, J. N.; Fisher, A. J.; Prabhu, M.; Dark, J. H.; Clark, S. C. Inhaled Nitric Oxide for Modulation of Ischemia-Reperfusion Injury in Lung Transplantation. *J. Heart Lung Transplant.* **2007**, *26*, 1199–1205.
(146) Nagasaka, Y.; Fernandez, B. O.; Garcia-Saura, M. F.; Petersen, B.; Ichinose, F.; Bloch, K. D.; Feelisch, M.; Zapol, W. M. Brief Periods of Nitric Oxide Inhalation Protect against Myocardial Ischemia-Reperfusion Injury. *Anesthesiology* **2008**, *109*, 675–682.
(147) Jones, S. P.; Bolli, R. The Ubiquitous Role of Nitric Oxide in Cardioprotection. *J. Mol. Cell. Cardiol.* **2006**, *40*, 16–23.
(148) Phillips, L.; Toledo, A. H.; Lopez-Neblina, F.; Anaya-Prado, R.; Toledo-Pereyra, L. H. Nitric Oxide Mechanism of Protection in Ischemia and Reperfusion Injury. *J. Invest. Surg.* **2009**, *22*, 46–55.
(149) Enemark, J. H.; Feltham, R. D. Principles of Structure, Bonding, and Reactivity for Metal Nitrosyl Complexes. *Coord. Chem. Rev.* **1974**, *13*, 339–406.
(150) Michael, D.; Mingos, P.; Sherman, D. J. Transition Metal Nitrosyl Complexes. *Adv. Inorg. Chem.* **1989**, *34*, 293–377.
(151) Fry, N. L.; Mascharak, P. K. Photoactive Ruthenium Nitrosyls as NO Donors: How To Sensitize Them toward Visible Light. *Acc. Chem. Res.* **2011**, *44*, 289–298.
(152) Ford, P. C. Metal Complex Strategies for Photo-Uncaging the Small Molecule Bioregulators Nitric Oxide and Carbon Monoxide. *Coord. Chem. Rev.* **2018**, *376*, 548–564.
(153) King, R. C.; Binns, O. A. R.; Kanithanon, R. C.; Cope, J. T.; Chun, R. L.; Shockey, K. S.; Tribble, C. G.; Kron, I. L. Low-Dose Sodium Nitroprusside Reduces Pulmonary Reperfusion Injury. *Ann. Thorac. Surg.* **1997**, *63*, 1398–1404.
(154) Benz, S.; Schanbel, R.; Weber, H.; Pfeffer, F.; Wiesner, R.; von Breitenbuch, P.; Nizze, H.; Schareck, W.; Hopt, U. T. The Nitric Oxide Donor Sodium Nitroprusside Is Protective in Ischemia/Reperfusion Injury of the Pancreas. *Transplantation* **1998**, *66*, 994–999.
(155) Madesh, M.; Ramachandran, A.; Pulimood, A.; Vadranam, M.; Balasubramanian, K. A. Attenuation of Intestinal Ischemia/Reperfusion Injury with Sodium Nitroprusside: Studies

on Mitochondrial Function and Lipid Changes. *Biochim. Biophys. Acta* **2000**, *1500*, 204–216.
(156) Dobashi, K.; Singh, I.; Orak, J. K.; Asayama, K.; Singh, A. K. Combination Therapy of N-Acetylcysteine, Sodium Nitroprusside and Phosphoramidon Attenuates Ischemia-Reperfusion Injury in Rat Kidney. *Mol. Cell. Biochem.* **2002**, *240*, 9–17.
(157) Akin, M.; Kurukahvecioglu, O.; Gulbahar, O.; Isikgonul, I.; Taneri, F.; Tezel, E.; Onuk, E. Comparison of the Effects of Sodium Nitroprusside and L-Carnitine in Experimental Ischemia-Reperfusion Injury in Rats. *Transplant. Proc.* **2007**, *39*, 2997–3001.
(158) Grossi, L.; D'Angelo, S. Sodium Nitroprusside: Mechanism of NO Release Mediated by Sulfhydryl-Containing Molecules. *J. Med. Chem.* **2005**, *48*, 2622–2626.
(159) Ghosh, R.; Ray, U.; Jana, P.; Bhattacharya, R.; Banerjee, D.; Sinha, A. Reduction of Death Rate Due to Acute Myocardial Infarction in Subjects with Cancers through Systemic Restoration of Impaired Nitric Oxide. *PLoS One* **2014**, *9*, e88639.
(160) da Silva, R. S.; de Lima, R. G.; de Paula Machado, S. Design, Reactivity, and Biological Activity of Ruthenium Nitrosyl Complexes. *Adv. Inorg. Chem.* **2015**, *67*, 265–294.
(161) Campelo, M. W. S.; Oriá, R. B.; de França Lopes, L. G.; de Castro Brito, G. A.; dos Santos, A. A.; de Vasconcelos, R. C.; da Silva, F. O. N.; Nobrega, B. N.; Bento-Silva, M. T.; de Vasconcelos, P. R. L. Preconditioning with a Novel Metallopharmaceutical NO Donor in Anesthetized Rats Subjected to Brain Ischemia/Reperfusion. *Neurochem. Res.* **2012**, *37*, 749–758.
(162) Kirichok, Y.; Krapivinsky, G.; Clapham, D. E. The Mitochondrial Calcium Uniporter Is a Highly Selective Ion Channel. *Nature* **2004**, *427*, 360–364.
(163) Baughman, J. M.; Perocchi, F.; Girgis, H. S.; Plovanich, M.; Belcher-Timme, C. A.; Sancak, Y.; Bao, X. R.; Strittmatter, L.; Goldberger, O.; Bogorad, R. L.; Koteliansky, V.; Mootha, V. K. Integrative Genomics Identifies MCU as an Essential Component of the Mitochondrial Calcium Uniporter. *Nature* **2011**, *476*, 341–345.
(164) De Stefani, D.; Raffaello, A.; Teardo, E.; Szabó, I.; Rizzuto, R. A Forty-Kilodalton Protein of the Inner Membrane Is the Mitochondrial Calcium Uniporter. *Nature* **2011**, *476*, 336–340.
(165) Kamer, K. J.; Mootha, V. K. The Molecular Era of the Mitochondrial Calcium Uniporter. *Nat. Rev. Mol. Cell Biol.* **2015**, *16*, 545–553.
(166) Nemani, N.; Shanmughapriya, S.; Madesh, M. Molecular Regulation of MCU: Implications in Physiology and Disease. *Cell Calcium* **2018**, *74*, 86–93.
(167) Baradaran, R.; Wang, C.; Siliciano, A. F.; Long, S. B. Cryo-EM Structures of Fungal and Metazoan Mitochondrial Calcium Uniporters. *Nature* **2018**, *559*, 580–584.
(168) Fan, C.; Fan, M.; Orlando, B. J.; Fastman, N. M.; Zhang, J.; Xu, Y.; Chambers, M. G.; Xu, X.; Perry, K.; Liao, M.; Feng, L. X-Ray and Cryo-EM Structures of the Mitochondrial Calcium Uniporter. *Nature* **2018**, *559*, 575–579.
(169) Nguyen, N. X.; Armache, J.-P.; Lee, C.; Yang, Y.; Zeng, W.; Mootha, V. K.; Cheng, Y.; Bai, X.-C.; Jiang, Y. Cryo-EM Structure of a Fungal Mitochondrial Calcium Uniporter. *Nature* **2018**, *559*, 570–574.
(170) Yoo, J.; Wu, M.; Yin, Y.; Herzik, M. A.; Lander, G. C.; Lee, S.-Y. Cryo-EM Structure of a Mitochondrial Calcium Uniporter. *Science* **2018**, *361*, 506–511.
(171) Wang, Y.; Nguyen, N. X.; She, J.; Zeng, W.; Yang, Y.; Bai, X.-C.; Jiang, Y. Structural Mechanism of EMRE-Dependent Gating of the Human Mitochondrial Calcium Uniporter. *Cell* **2019**, *177*, 1252–1261.

(172) Kamer, K. J.; Sancak, Y.; Fomina, Y.; Meisel, J. D.; Chaudhuri, D.; Grabarek, Z.; Mootha, V. K. MICU1 Imparts the Mitochondrial Uniporter with the Ability to Discriminate between Ca^{2+} and Mn^{2+}. *Proc. Natl. Acad. Sci. U.S.A.* **2018**, *115*, E7960–E7969.
(173) Kamer, K. J.; Jiang, W.; Kaushik, V. K.; Mootha, V. K.; Grabarek, Z. Crystal Structure of MICU2 and Comparison with MICU1 Reveal Insights into the Uniporter Gating Mechanism. *Proc. Natl. Acad. Sci. U.S.A.* **2019**, *116*, 3546–3555.
(174) Paillard, M.; Csordás, G.; Huang, K. T.; Várnai, P.; Joseph, S. K.; Hajnóczky, G. MICU1 Interacts with the D-Ring of the MCU Pore to Control Its Ca2+ Flux and Sensitivity to Ru360. *Mol. Cell* **2018**, *72*, 778–785.
(175) Xing, Y.; Wang, M.; Wang, J.; Nie, Z.; Wu, G.; Yang, X.; Shen, Y. Dimerization of MICU Proteins Controls Ca2+ Influx through the Mitochondrial Ca2+ Uniporter. *Cell Rep.* **2019**, *26*, 1203–1212.
(176) Phillips, C. B.; Tsai, C.-W.; Tsai, M.-F. The Conserved Aspartate Ring of MCU Mediates MICU1 Binding and Regulation in the Mitochondrial Calcium Uniporter Complex. *Elife* **2019**, *8*, e41112.
(177) Oxenoid, K.; Dong, Y.; Cao, C.; Cui, T.; Sancak, Y.; Markhard, A. L.; Grabarek, Z.; Kong, L.; Liu, Z.; Ouyang, B.; Cong, Y.; Mootha, V. K.; Chou, J. J. Architecture of the Mitochondrial Calcium Uniporter. *Nature* **2016**, *533*, 269–273.
(178) Cao, C.; Wang, S.; Cui, T.; Su, X.-C.; Chou, J. J. Ion and Inhibitor Binding of the Double-Ring Ion Selectivity Filter of the Mitochondrial Calcium Uniporter. *Proc. Natl. Acad. Sci. U.S.A.* **2017**, *114*, E2846–E2851.
(179) Kon, N.; Murakoshi, M.; Isobe, A.; Kagechika, K.; Miyoshi, N.; Nagayama, T. DS16570511 Is a Small-Molecule Inhibitor of the Mitochondrial Calcium Uniporter. *Cell Death Discovery* **2017**, *3*, 17045.
(180) Arduino, D. M.; Wettmarshausen, J.; Vais, H.; Navas-Navarro, P.; Cheng, Y.; Leimpek, A.; Ma, Z.; Delrio-Lorenzo, A.; Giordano, A.; Garcia-Perez, C.; Médard, G.; Kuster, B.; García-Sancho, J.; Mokranjac, D.; Foskett, J. K.; Alonso, M. T.; Perocchi, F. Systematic Identification of MCU Modulators by Orthogonal Interspecies Chemical Screening. *Mol. Cell* **2017**, *67*, 711–723.
(181) Schwartz, J.; Holmuhamedov, E.; Zhang, X.; Lovelace, G. L.; Smith, C. D.; Lemasters, J. J. Minocycline and Doxycycline, but Not Other Tetracycline-Derived Compounds, Protect Liver Cells from Chemical Hypoxia and Ischemia/Reperfusion Injury by Inhibition of the Mitochondrial Calcium Uniporter. *Toxicol. Appl. Pharmacol.* **2013**, *273*, 172–179.
(182) Di Marco, G.; Vallese, F.; Jourde, B.; Bergsdorf, C.; Sturlese, M.; De Mario, A.; Techer-Etienne, V.; Haasen, D.; Oberhauser, B.; Schleeger, S.; Minetti, G.; Moro, S.; Rizzuto, R.; De Stefani, D.; Fornaro, M.; Mammucari, C. A High-Throughput Screening Identifies MICU1 Targeting Compounds. *Cell Rep.* **2020**, *30*, 2321–2331.
(183) Thu, V. T.; Kim, H.-K.; Long, L. T.; Lee, S.-R.; Hanh, T. M.; Ko, T. H.; Heo, H.-J.; Kim, N.; Kim, S. H.; Ko, K. S.; Rhee, B. D.; Han, J. NecroX-5 Prevents Hypoxia/Reoxygenation Injury by Inhibiting the Mitochondrial Calcium Uniporter. *Cardiovasc. Res.* **2012**, *94*, 342–350.
(184) Santo-Domingo, J.; Vay, L.; Hernández-SanMiguel, E.; Lobatón, C. D.; Moreno, A.; Montero, M.; Alvarez, J. The Plasma Membrane Na^{+}/Ca^{2+} Exchange Inhibitor KB-R7943 Is Also a Potent Inhibitor of the Mitochondrial Ca^{2+} Uniporter. *Br. J. Pharmacol.* **2007**, *151*, 647–654.
(185) Woods, J. J.; Nemani, N.; Shanmughapriya, S.; Kumar, A.; Zhang, M.; Nathan, S. R.;

Thomas, M.; Carvalho, E.; Ramachandran, K.; Srikantan, S.; Stathopulos, P. B.; Wilson, J. J.; Madesh, M. A Selective and Cell-Permeable Mitochondrial Calcium Uniporter (MCU) Inhibitor Preserves Mitochondrial Bioenergetics after Hypoxia/Reoxygenation Injury. *ACS Cent. Sci.* **2019**, *5*, 153–166.

(186) Fletcher, J. M.; Greenfield, B. F.; Hardy, C. J.; Scargill, D.; Woodhead, J. L. Ruthenium Red. *J. Chem. Soc.* **1961**, 2000–2006.

(187) Luft, J. H. Ruthenium Red and Violet. I. Chemistry, Purification, Methods of Use for Electron Microscopy and Mechanism of Action. *Anat. Rec.* **1971**, *171*, 347–368.

(188) Moore, C. L. Specific Inhibition of Mitochondrial Ca^{++} Transport by Ruthenium Red. *Biochem. Biophys. Res. Commun.* **1971**, *42*, 298–305.

(189) Luft, J. H. Ruthenium Red and Violet. II. Fine Structural Localization in Animal Tissues. *Anat. Rec.* **1971**, *171*, 369–416.

(190) Vasington, F. D.; Gazzotti, P.; Tiozzo, R.; Carafoli, E. The Effect of Ruthenium Red on Ca2+ Transport and Respiration in Rat Liver Mitochondria. *Biochim. Biophys. Acta* **1972**, *256*, 43–54.

(191) Rossi, C. S.; Vasington, F. D.; Carafoli, E. The Effect of Ruthenium Red on the Uptake and Release of Ca^{2+} by Mitochondria. *Biochem. Biophys. Res. Commun.* **1973**, *50*, 846–852.

(192) Griffiths, E. J. Use of Ruthenium Red as an Inhibitor of Mitochondrial Ca^{2+} Uptake in Single Rat Cardiomyocytes. *FEBS Lett.* **2000**, *486*, 257–260.

(193) Grover, G. J.; Dzwonczyk, S.; Sleph, P. G. Ruthenium Red Improves Postischemic Contractile Function in Isolated Rat Hearts. *J. Cardiovasc. Pharmacol.* **1990**, *16*, 783–789.

(194) Hochman, J. H.; Partridge, B.; Miller-Ferguson, S. An Effective Electron Donor to Cytochrome Oxidase: Purification, Identification, and Kinetic Characterization of a Contaminant of Ruthenium Red, Hexaammineruthenium II/III. *J. Biol. Chem.* **1981**, *256*, 8693–8698.

(195) Kehrer, J. P.; Park, Y. Purity of Ruthenium Red Used in Pharmacological Research. *J. Pharmacol. Methods* **1991**, *25*, 179–183.

(196) Leperre, A.; Millart, H.; Prevost, A.; Trenque, T.; Kantelip, J. P.; Keppler, B. K. Compared Effects of Ruthenium Red and Cis $[Ru(NH_3)_4Cl_2]Cl$ on the Isolated Ischaemic-Reperfused Rat Heart. *Fundam. Clin. Pharmacol.* **1995**, *9*, 545–553.

(197) Broekemeier, K. M.; Krebsbach, R. J.; Pfeiffer, D. R. Inhibition of the Mitochondrial Ca^{2+} Uniporter by Pure and Impure Ruthenium Red. *Mol. Cell. Biochem.* **1994**, *139*, 33–40.

(198) Ying, W.-L.; Emerson, J.; Clarke, M. J.; Sanadi, D. R. Inhibition of Mitochondrial Calcium Ion Transport by an Oxo-Bridged Dinuclear Ruthenium Ammine Complex. *Biochemistry* **1991**, *30*, 4949–4952.

(199) Emerson, J.; Clarke, M. J.; Ying, W.-L.; Sanadi, D. R. The Component of "Ruthenium Red" Responsible for Inhibition of Mitochondrial Calcium Ion Transport. Spectra, Electrochemistry, and Aquation Kinetics. Crystal Structure of μ-O-$[(HCO_2)(NH_3)_4Ru]_2Cl_3$. *J. Am. Chem. Soc.* **1993**, *115*, 11799–11805.

(200) Matlib, M. A.; Zhou, Z.; Knight, S.; Ahmed, S.; Choi, K. M.; Krause-Bauer, J.; Phillips, R.; Altschuld, R.; Katsube, Y.; Sperelakis, N.; Bers, D. M. Oxygen-Bridged Dinuclear Ruthenium Amine Complex Specifically Inhibits Ca^{2+} Uptake into Mitochondria *in Vitro* and *in Situ* in Single Cardiac Myocytes. *J. Biol. Chem.* **1998**, *273*, 10223–10231.

(201) García-Rivas, G. D. J.; Guerrero-Hernández, A.; Guerrero-Serna, G.; Rodríguez-Zavala, J. S.; Zazueta, C. Inhibition of the Mitochondrial Calcium Uniporter by the Oxo-Bridged Dinuclear Ruthenium Amine Complex (Ru360) Prevents from Irreversible Injury in

Postischemic Rat Heart. *FEBS J.* **2005**, *272*, 3477–3488.
(202) García-Rivas, G. de J.; Carvajal, K.; Correa, F.; Zazueta, C. Ru360, a Specific Mitochondrial Calcium Uptake Inhibitor, Improves Cardiac Post-Ischaemic Functional Recovery in Rats *in Vivo*. *Br. J. Pharmacol.* **2006**, *149*, 829–837.
(203) Hajnóczky, G.; Csordás, G.; Das, S.; Garcia-Perez, C.; Saotome, M.; Sinha Roy, S.; Yi, M. Mitochondrial Calcium Signalling and Cell Death: Approaches for Assessing the Role of Mitochondrial Ca^{2+} Uptake in Apoptosis. *Cell Calcium* **2006**, *40*, 553–560.
(204) Nathan, S. R.; Pino, N. W.; Arduino, D. M.; Perocchi, F.; MacMillan, S. N.; Wilson, J. J. Synthetic Methods for the Preparation of a Functional Analogue of Ru360, a Potent Inhibitor of Mitochondrial Calcium Uptake. *Inorg. Chem.* **2017**, *56*, 3123–3126.
(205) Woods, J. J.; Lovett, J.; Lai, B.; Harris, H. H.; Wilson, J. J. Redox Stability Controls the Cellular Uptake and Activity of Ruthenium-Based Inhibitors of the Mitochondrial Calcium Uniporter (MCU). *Angew. Chem., Int. Ed.* **2020**, *59*, 6482–6491.
(206) Woods, J. J.; Rodriguez, M. X.; Tsai, C.-W.; Tsai, M.-F.; Wilson, J. J. Cobalt Amine Complexes and Ru265 Interact with the DIME Region of the Mitochondrial Calcium Uniporter. *Chem. Commun.* **2021**, *57*, 6161–6164.
(207) Urgiles, J.; Nathan, S. R.; MacMillan, S. N.; Wilson, J. J. Dinuclear Nitrido-Bridged Ruthenium Complexes Bearing Diimine Ligands. *Dalton Trans.* **2017**, *46*, 14256–14263.
(208) Novorolsky, R. J.; Nichols, M.; Kim, J. S.; Pavlov, E. V.; Woods, J. J.; Wilson, J. J.; Robertson, G. S. The Cell-Permeable Mitochondrial Calcium Uniporter Inhibitor Ru265 Preserves Cortical Neuron Respiration after Lethal Oxygen Glucose Deprivation and Reduces Hypoxic/Ischemic Brain Injury. *J. Cereb. Blood Flow Metab.* **2020**, *40*, 1172–1181.
(209) Woods, J. J.; Novorolsky, R. J.; Bigham, N. P.; Robertson, G. S.; Wilson, J. J. Dinuclear Nitrido-Bridged Osmium Complexes Inhibit the Mitochondrial Calcium Uniporter and Protect Cortical Neurons against Lethal Oxygen–Glucose Deprivation. *RSC Chem. Biol.* **2023**, *4*, 84–93.
(210) Bigham, N. P.; Huang, Z.; Spivey, J. A.; Woods, J. J.; MacMillan, S. N.; Wilson, J. J. Carboxylate-Capped Analogues of Ru265 Are MCU Inhibitor Prodrugs. *Inorg. Chem.* **2022**, *61*, 17299–17312.
(211) Huang, Z.; Spivey, J. A.; Macmillan, S. N.; Wilson, J. J. A Ferrocene-Containing Analogue of the MCU Inhibitor Ru265 with Increased Cell Permeability. *Inorg. Chem. Front.* **2023**, *10*, 591–599.
(212) Huang, Z.; Macmillan, S. N.; Wilson, J. J. A Fluorogenic Inhibitor of the Mitochondrial Calcium Uniporter. *Angew. Chem., Int. Ed.* **2023**, *62*, e202214920.
(213) Jassem, W.; Fuggle, S. V.; Rela, M.; Koo, D. D. H.; Heaton, N. D. The Role of Mitochondria in Ischemia/Reperfusion Injury. *Transplantation* **2002**, *73*, 493–499.
(214) Zhang, W.; Wang, M.; Xie, H. Y.; Zhou, L.; Meng, X. Q.; Shi, J.; Zheng, S. Role of Reactive Oxygen Species in Mediating Hepatic Ischemia-Reperfusion Injury and Its Therapeutic Applications in Liver Transplantation. *Transplant. Proc.* **2007**, *39*, 1332–1337.
(215) Dröge, W. Free Radicals in the Physiological Control of Cell Function. *Physiol. Rev.* **2002**, *82*, 47–95.
(216) Heck, D. E.; Shakarjian, M.; Kim, H. D.; Laskin, J. D.; Vetrano, A. M. Mechanisms of Oxidant Generation by Catalase. *Ann. N. Y. Acad. Sci.* **2010**, *1203*, 120–125.
(217) Wang, Y.; Branicky, R.; Noë, A.; Hekimi, S. Superoxide Dismutases: Dual Roles in Controlling ROS Damage and Regulating ROS Signaling. *J. Cell Biol.* **2018**, *217*, 1915–

1928.
(218) Jaeschke, H.; Woolbright, B. L. Current Strategies to Minimize Hepatic Ischemia-Reperfusion Injury by Targeting Reactive Oxygen Species. *Transplant. Rev.* **2012**, *26*, 103–114.
(219) Wu, L.; Xiong, X.; Wu, X.; Ye, Y.; Jian, Z.; Zhi, Z.; Gu, L. Targeting Oxidative Stress and Inflammation to Prevent Ischemia-Reperfusion Injury. *Front. Mol. Neurosci.* **2020**, *13*, 28.
(220) Fridovich, I. Superoxide Dismutases. *Annu. Rev. Biochem.* **1975**, *44*, 147–159.
(221) Fukai, T.; Ushio-Fukai, M. Superoxide Dismutases: Role in Redox Signaling, Vascular Function, and Disease. *Antioxid. Redox Signaling* **2011**, *15*, 1583–1606.
(222) Nandi, A.; Yan, L.-J.; Jana, C. K.; Das, N. Role of Catalase in Oxidative Stress- And Age-Associated Degenerative Diseases. *Oxid. Med. Cell. Longevity* **2019**, *2019*, 9613090.
(223) Weisiger, R. A.; Fridovich, I. Superoxide Dismutase: Organelle Specificity. *J. Biol. Chem.* **1973**, *248*, 3582–3592.
(224) Marklund, S. L. Human Copper-Containing Superoxide Dismutase of High Molecular Weight. *Proc. Natl. Acad. Sci. U.S.A.* **1982**, *79*, 7634–7638.
(225) Zamocky, M.; Furtmüller, P. G.; Obinger, C. Evolution of Catalases from Bacteria to Humans. *Antioxid. Redox Signaling* **2010**, *10*, 1527–1548.
(226) Chen, Z.; Siu, B.; Ho, Y.-S.; Vincent, R.; Chua, C. C.; Hamdy, R. C.; Chua, B. H. L. Overexpression of MnSOD Protects against Myocardial Ischemia/Reperfusion Injury in Transgenic Mice. *J. Mol. Cell. Cardiol.* **1998**, *30*, 2281–2289.
(227) Li, G.; Chen, Y.; Saari, J. T.; Kang, Y. J. Catalase-Overexpressing Transgenic Is Resistant to Ischemia-Reperfusion Mouse Heart Injury. *Am. J. Physiol. Heart Circ. Physiol.* **1997**, *273*, H1090–H1095.
(228) Borgstahl, G. E.; Parge, H. E.; Hickey, M. J.; Beyer, W. F.; Hallewell, R. A.; Tainer, J. A. The Structure of Human Mitochondrial Manganese Superoxide Dismutase Reveals a Novel Tetrameric Interface of Two 4-Helix Bundles. *Cell* **1992**, *71*, 107–118.
(229) Abreu, I. A.; Cabelli, D. E. Superoxide Dismutases-a Review of the Metal-Associated Mechanistic Variations. *Biochim. Biophys. Acta* **2010**, *1804*, 263–274.
(230) Putnam, C. D.; Arvai, A. S.; Bourne, Y.; Tainer, J. A. Active and Inhibited Human Catalase Structures: Ligand and NADPH Binding and Catalytic Mechanism. *J. Mol. Biol.* **2000**, *296*, 295–309.
(231) Crow, J. P.; Calingasan, N. Y.; Chen, J.; Hill, J. L.; Beal, M. F. Manganese Porphyrin Given at Symptom Onset Markedly Extends Survival of ALS Mice. *Ann. Neurol.* **2005**, *58*, 258–265.
(232) Orrell, R. W. AEOL-10150 (Aeolus). *Curr. Opin. Investig. Drugs* **2006**, *7*, 70–80.
(233) Bhatt, J. M.; Gordon, P. H. Current Clinical Trials in Amyotrophic Lateral Sclerosis Current Clinical Trials in Amyotrophic Lateral Sclerosis. *Expert Opin. Invest. Drugs* **2007**, *16*, 1197–1207.
(234) O'Neill, H. C.; White, C. W.; Veress, L. A.; Hendry-Hofer, T. B.; Loader, J. E.; Min, E.; Huang, J.; Rancourt, R. C.; Day, B. J. Treatment with the Catalytic Metalloporphyrin AEOL 10150 Reduces Inflammation and Oxidative Stress Due to Inhalation of the Sulfur Mustard Analog 2-Chloroethyl Ethyl Sulfide. *Free Radical Biol. Med.* **2010**, *48*, 1188–1196.
(235) Cui, W.; Zhang, P.; Hankey, K. G.; Xiao, M.; Farese, A. M.; MacVittie, T. J. AEOL 10150 Alleviates Radiation-Induced Innate Immune Responses in Non-Human Primate Lung Tissue. *Health Phys.* **2021**, *121*, 331–344.
(236) Sheng, H.; Enghild, J. J.; Bowler, R.; Patel, M.; Batinić-Haberle, I.; Calvi, C. L.; Day, B.

J.; Pearlstein, R. D.; Crapo, J. D.; Warner, D. S. Effects of Metalloporphyrin Catalytic Antioxidants in Experimental Brain Ischemia. *Free Radical Biol. Med.* **2002**, *33*, 947–961.
(237) Mackensen, G. B.; Patel, M.; Sheng, H.; Calvi, C. L.; Batinić-Haberle, I.; Day, B. J.; Liang, L. P.; Fridovich, I.; Crapo, J. D.; Pearlstein, R. D.; Warner, D. S. Neuroprotection from Delayed Postischemic Administration of a Metalloporphyrin Catalytic Antioxidant. *J. Neurosci.* **2001**, *21*, 4582–4592.
(238) Saba, H.; Batinic-Haberle, I.; Munusamy, S.; Mitchell, T.; Lichti, C.; Megyesi, J.; MacMillan-Crow, L. A. Manganese Porphyrin Reduces Renal Injury and Mitochondrial Damage during Ischemia/Reperfusion. *Free Radical Biol. Med.* **2007**, *42*, 1571–1578.
(239) Celic, T.; Španjol, J.; Bobinac, M.; Tovmasyan, A.; Vukelic, I.; Reboucas, J. S.; Batinic-Haberle, I.; Bobinac, D. Mn Porphyrin-Based SOD Mimic, MnTnHex-2-PyP^{5+}, and Non-SOD Mimic, MnTBAP^{3-}, Suppressed Rat Spinal Cord Ischemia/Reperfusion Injury via NF-KB Pathways. *Free Radical Res.* **2014**, *48*, 1426–1442.
(240) Batinić-Haberle, I.; Spasojević, I.; Stevens, R. D.; Hambright, P.; Neta, P.; Okado-Matsumoto, A.; Fridovich, I. New Class of Potent Catalysts of $O2^{\cdot-}$ Dismutation. Mn(III) Ortho-Methyoxyethylpyridyl- and Di-Ortho-Methoxyethyl-Imidazolylporphyrins. *Dalton Trans.* **2004**, *11*, 1696–1702.
(241) Huffman, K.; Marcus, C. B.; Baudryt, M.; Malfroy, B. Salen-Manganese Complexes: Combined Superoxide Dismutase/Catalase Mimics with Broad Pharmacological Efficacy. *Adv. Pharmacol.* **1996**, *38*, 247–269.
(242) Erxleben, A. Transition Metal Salen Complexes in Bioinorganic and Medicinal Chemistry. *Inorg. Chim. Acta* **2018**, *472*, 40–57.
(243) Baudry, M.; Etienne, S.; Bruce, A.; Palucki, M.; Jacobsen, E.; Malfroy, B. Salen-Manganese Complexes Are Superoxide Dismutase-Mimics. *Biochem. Biophys. Res. Commun.* **1993**, *192*, 964–968.
(244) Doctrow, S. R.; Huffman, K.; Marcus, C. B.; Tocco, G.; Malfroy, E.; Adinolfi, C. A.; Kruk, H.; Baker, K.; Lazarowych, N.; Mascarenhas, J.; Malfroy, B. Salen-Manganese Complexes as Catalytic Scavengers of Hydrogen Peroxide and Cytoprotective Agents: Structure-Activity Relationship Studies. *J. Med. Chem.* **2002**, *45*, 4549–4558.
(245) Rong, Y.; Doctrow, S. R.; Tocco, G.; Baudry, M. EUK-134, a Synthetic Superoxide Dismutase and Catalase Mimetic, Prevents Oxidative Stress and Attenuates Kainate-Induced Neuropathology. *Proc. Natl. Acad. Sci. U.S.A.* **1999**, *96*, 9897–9902.
(246) Pong, K.; Doctrow, S. R.; Baudry, M. Prevention of 1-Methyl-4-Phenylpyridinium- and 6-Hydroxydopamine-Induced Nitration of Tyrosine Hydroxylase and Neurotoxicity by EUK-134, a Superoxide Dismutase and Catalase Mimetic, in Cultured Dopaminergic Neurons. *Brain Res.* **2000**, *881*, 182–189.
(247) Howard, M. D.; Greineder, C. F.; Hood, E. D.; Muzykantov, V. R. Endothelial Targeting of Liposomes Encapsulating SOD/Catalase Mimetic EUK-134 Alleviates Acute Pulmonary Inflammation. *J. Controlled Release* **2014**, *177*, 34–41.
(248) Gianello, P.; Saliez, A.; Bufkens, X.; Pettinger, R.; Misseleyn, D.; Hori, S.; Malfroy, B. EUK-134, a Synthetic Superoxide Dismutase and Catalase Mimetic, Protects Rat Kidneys from Ischemia-Reperfusion-Induced Damage. *Transplantation* **1996**, *62*, 1664–1666.
(249) Pucheu, S.; Boucher, F.; Sulpice, T. EUK-8 a Synthetic Catalytic Scavenger of Reactive Oxygen Species Protects Isolated Iron-Overloaded Rat Heart from Functional and Structural Damage Induced by Ischemia / Reperfusion. *Cardiovasc. Drugs Ther.* **1996**, *10*, 331–339.

(250) Baker, K.; Marcus, C. B.; Huffman, K.; Kruk, H.; Malfroy, B.; Doctrow, S. R. Synthetic Combined Superoxide Dismutase/Catalase Mimetics Are Protective as a Delayed Treatment in a Rat Stroke Model: A Key Role for Reactive Oxygen Species in Ischemic Brain Injury. *J. Pharmacol. Exp. Ther.* **1998**, *284*, 215–221.
(251) Izumi, M.; McDonald, M. C.; Sharpe, M. A.; Chatterjee, P. K.; Thiemermann, C. Superoxide Dismutase Mimetics with Catalase Activity Reduce the Organ Injury in Hemorrhagic Shock. *Shock* **2002**, *18*, 230–235.
(252) Chen, S.; Dehart, D. B.; Sulik, K. K. Protection from Ethanol-induced Limb Malformations by the Superoxide Dismutase/Catalase Mimetic, EUK-134. *FASEB J.* **2004**, *18*, 1234–1236.
(253) Ni, X.; Yang, Z.-J.; Carter, E. L.; Martin, L. J.; Koehler, R. C. Striatal Neuroprotection from Neonatal Hypoxia-Ischemia in Piglets by Antioxidant Treatment with EUK-134 or Edaravone. *Dev. Neurosci.* **2011**, *33*, 299–311.
(254) Riley, D. P.; Schall, O. F. Structure-Activity Studies and the Design of Synthetic Superoxide Dismutase (SOD) Mimetics as Therapeutics. *Adv. Inorg. Chem.* **2006**, *59*, 233–263.
(255) Policar, C.; Bouvet, J.; Bertrand, H. C.; Delsuc, N. SOD Mimics: From the Tool Box of the Chemists to Cellular Studies. *Curr. Opin. Chem. Biol.* **2022**, *67*, 102109.
(256) Salvemini, D.; Riley, D. P. M40403: Superoxide Dismutase Mimetic. *Drugs Future* **2000**, *25*, 1027–1033.
(257) Aston, K.; Rath, N.; Naik, A.; Slomczynska, U.; Schall, O. F.; Riley, D. P. Computer-Aided Design (CAD) of Mn(II) Complexes: Superoxide Dismutase Mimetics with Catalytic Activity Exceeding the Native Enzyme. *Inorg. Chem.* **2001**, *40*, 1779–1789.
(258) Salvemini, D.; Wang, Z.; Zweier, J. L.; Samouilov, A.; Macarthur, H.; Misko, T. P.; Currie, M. G.; Cuzzocrea, S.; Sikorski, J. A.; Riley, D. P. A Nonpeptidyl Mimic of Superoxide Dismutase with Therapeutic Activity in Rats. *Science* **1999**, *286*, 40403–40405.
(259) Samlowski, W. E.; Petersen, R.; Cuzzocrea, S.; Macarthur, H.; Burton, D.; McGregor, J. R.; Salvemini, D. A Nonpeptidyl Mimic of Superoxide Dismutase, M40403, Inhibits Dose-Limiting Hypotension Associated with Interleukin-2 and Increases Its Antitumor Effects. *Nat. Med.* **2003**, *9*, 750–755.
(260) Thompson, J. S.; Chu, Y.; Glass, J.; Tapp, A. A.; Brown, S. A. The Manganese Superoxide Dismutase Mimetic, M40403, Protects Adult Mice from Lethal Total Body Irradiation. *Free Radical Res.* **2010**, *44*, 529–540.
(261) Filograna, R.; Godena, V. K.; Sanchez-Martinez, A.; Ferrari, E.; Casella, L.; Beltramini, M.; Bubacco, L.; Whitworth, A. J.; Bisaglia, M. Superoxide Dismutase (SOD)-Mimetic M40403 Is Protective in Cell and Fly Models of Paraquat Toxicity. *J. Biol. Chem.* **2016**, *291*, 9257–9267.
(262) Masini, E.; Cuzzocrea, S.; Mazzon, E.; Marzocca, C.; Mannaioni, P. F.; Salvemini, D. Protective Effects of M40403, a Selective Superoxide Dismutase Mimetic, in Myocardial Ischaemia and Reperfusion Injury *in Vivo*. *Br. J. Pharmacol.* **2002**, *136*, 905–917.
(263) Riley, D. P.; Weiss, R. H. Manganese Macrocyclic Ligand Complexes as Mimics of Superoxide Dismutase. *J. Am. Chem. Soc.* **1994**, *116*, 387–388.
(264) Kilgore, K. S.; Friedrichs, G. S.; Johnson, C. R.; Schasteen, C. S.; Riley, D. P.; Weiss, R. H.; Ryan, U.; Lucchesi, B. R. Protective Effects of the SOD-Mimetic SC-52608 against Ischemia/Reperfusion Damage in the Rabbit Isolated Heart. *J. Mol. Cell. Cardiol.* **1994**, *26*, 995–1006.
(265) Black, S. C.; Schasteen, C. S.; Weiss, R. H.; Riley, D. P.; Driscoll, E. M.; Lucchesi, B. R. Inhibition of In Vivo Myocardial Ischemic and Reperlusion Injury by a Synthetic

Manganese-Based Superoxide Dismutase Mimetic. *J. Pharmacol. Exp. Ther.* **1994**, *280*, 1208–1215.
(266) Gradys, J. K.; Chens, Y.; Chasteen, N. D.; Harris, D. C. Hydroxyl Radical Production during Oxidative Deposition of Iron in Ferritin. *J. Biol. Chem.* **1989**, *264*, 20224–20229.
(267) Burkitt, M. J.; Masont, R. P. Direct Evidence for *in Vivo* Hydroxyl-Radical Generation in Experimental Iron Overload: An ESR Spin-Trapping Investigation. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 8440–8444.
(268) Cheton, P. L.; Archibald, F. S. Manganese Complexes and the Generation and Scavenging of Hydroxyl Free Radicals. *Free Radical Biol. Med.* **1988**, *5*, 325–333.
(269) Ning, Y.; Huo, Y.; Xue, H.; Du, Y.; Yao, Y.; Sedgwick, A. C.; Lin, H.; Li, C.; Jiang, S. Da; Wang, B. W.; Gao, S.; Gao, S.; Kang, L.; Sessler, J. L.; Zhang, J. L. Tri-Manganese(III) Salen-Based Cryptands: A Metal Cooperative Antioxidant Strategy That Overcomes Ischemic Stroke Damage *in Vivo*. *J. Am. Chem. Soc.* **2020**, *142*, 10219–10227.
(270) Pan, D.; Schmieder, A. H.; Wickline, S. A.; Lanza, G. M. Manganese-Based MRI Contrast Agents: Past, Present, and Future. *Tetrahedron* **2011**, *67*, 8431–8444.
(271) Drahos, B.; Lukes, I.; Tóth, É. Manganese (II) Complexes as Potential Contrast Agents for MRI. *Eur. J. Inorg. Chem.* **2012**, *2012*, 1975–1986.
(272) Woods, J. J.; Wilson, J. J. Inhibitors of the Mitochondrial Calcium Uniporter for the Treatment of Disease. *Curr. Opin. Chem. Biol.* **2020**, *55*, 9–18.
(273) Erstad, B. L.; Barletta, J. F. Treatment of Hypertension in the Perioperative Patient. *Ann. Pharmacother.* **2000**, *34*, 66–79.
(274) Varon, J. Treatment of Acute Severe Hypertension: Current and Newer Agents. *Drugs* **2008**, *68*, 283–297.
(275) Yancy, C. W.; Jessup, M.; Bozkurt, B.; Butler, J.; Casey, D. E.; Drazner, M. H.; Fonarow, G. C.; Geraci, S. A.; Horwich, T.; Januzzi, J. L.; Johnson, M. R.; Kasper, E. K.; Levy, W. C.; Masoudi, F. A.; McBride, P. E.; McMurray, J. J. V; Mitchell, J. E.; Peterson, P. N.; et al. 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* **2013**, *128*, e240-327.
(276) Nishimura, R. A.; Otto, C. M.; Bonow, R. O.; Carabello, B. A.; Erwin, J. P.; Guyton, R. A.; O'Gara, P. T.; Ruiz, C. E.; Skubas, N. J.; Sorajja, P.; Sundt, T. M.; Thomas, J. D. 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* **2014**, *129*, 2440–2492.
(277) Xu, P.; Novorolsky, R. J.; Woods, J. J.; Huang, Z.; Wilson, J. J.; Robertson, G. S.; Renden, R. B. "A cell-permeable mitochondrial calcium uniporter inhibitor elicits asynchronous transmission at synapses." Presented in part at *Neuroscience 2021 – Society for Neuroscience 50th Annual Meeting*. (P128.07), November, 2021.

FOR TABLE OF CONTENTS ONLY

SYNOPSIS

Metal coordination complexes can be leveraged as therapeutic tools against ischemia-reperfusion injury through the mechanism of three unique strategies: gasotransmitter delivery, mitochondrial calcium overload prevention, and the scavenging of reactive oxygen species.