# Development of Photo/Ultrasound Mediated Pathways with Metal-complexes for Anticancer and Antibacterial Therapy

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Currently, the market available cancer chemotherapeutics is facing major problems like drug resistance, off-target toxicity, and severe side effects due to their non-selective cell death mechanisms affecting both healthy and cancerous cells indiscriminately.[1] Thus, a new generation of cancer drugs that can overcome the drawbacks of chemotherapy with novel mechanisms of action is urgently needed to save the cancer-affected population of the globe. Importantly, metal complexes possess the largely unexplored potential to enhance the immunomodulatory effects of chemotherapeutic agents.[3] The design concepts for metallodrugs are in their infancy and need to be more widely explored. The core focus of our lab research is centered on the design and development of light-responsive metallodrugs (primarily Ir(III), Ru(II), Re(I), Os(II), etc.), integrating synthetic chemistry, photochemistry, and chemical biology.[4-13] Light-triggered cancer phototherapy has emerged as an alternative to chemotherapy with a novel mechanism of action and target site, and is being pursued by our group.[4-13] Cancer phototherapy provides spatiotemporal control over the activation of catalytic amounts of drugs at the target cancer site.[4-12] Ir(III)/Ru(II)/Re(I) complexes induced intracellular NADH/NAD(P)H photo-oxidation and ROS in cancer cells at catalytic concentrations to create an in-cell redox imbalance and metabolic disorder, which leads to cell death.[4-13] These complexes induce ROS-mediated oxidative stress and NADH/NAD(P)H photo-oxidation-mediated metabolic disruption, leading to impaired mitochondrial respiration, ATP depletion, and subsequent cancer cell death. Moreover, these Ir(III) and Ru(II)-based complexes were also able to overcome the hypoxia-related cancer drug resistance problems.[4-11] Lately, recognizing the limitations of light penetration in deep tissues, we extended our research to other external stimuli, particularly ultrasound. Our recent efforts focus on the development of ultrasound-responsive Re(I)/Mn(I) tricarbonyl complexes that function as sonosensitizers.[13,14] These agents integrate multiple therapeutic modalities within a single molecular scaffold, capable of controlled CO release, reactive oxygen species (ROS) generation, and cellular redox modulation upon ultrasound irradiation. This multimodal sonodynamic platform leverages the superior tissue-penetrating ability of ultrasound and introduces synergistic therapeutic pathways by coupling sonodynamic therapy (SDT) with gas therapy. Such systems are designed to target deeply buried tumors and achieve precise, non-invasive treatment outcomes.[13,14]

Parallel to our advances in cancer therapy, our group also focuses on metal-based strategies to combat antimicrobial resistance (AMR). We have developed a series of light-activated metallo-photoantibiotics based on Ru(II), Zn(II), Co(III), and Fe(III) complexes that demonstrate potent antibacterial activity against both Gram-positive and Gram-negative pathogens.[15-18] These photoactive agents employ ROS generation, NADH oxidation, and bacterial redox disruption as mechanisms of action, leading to effective biofilm eradication and wound healing. Crucially, these non-traditional, redox-based mechanisms bypass classical antibiotic resistance pathways, providing a sustainable approach to managing multidrug-resistant infections.[15-18] Together, our research establishes a unified platform of stimuli-responsive metallodrugs, driven by light or ultrasound, that can be rationally tuned for multimodal, multitarget therapeutic interventions for anticancer and antibacterial therapy. Through these efforts, we seek to advance the frontier of precision medicine by transforming fundamental inorganic chemistry into clinically translatable therapeutic innovation.

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