FRONTIERS IN THE USE OF METALS AS THERAPEUTIC AGENTS

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INTRODUCTION

The vast majority of therapeutic agents in the clinic are based on small, organic molecules used in stoichiometric quantities. Furthermore, over 75% of small molecule fragments used in screening libraries offer only two-dimensional structures, severely limiting their abilities to interact with the three-dimensional spaces of the body.[1] Owing to these limitations, an interest in metal-based therapeutics has emerged, initially inspired by the success of the blockbuster platinum drug, Cisplatin. Cisplatin, although an effective chemotherapeutic, leads to severe, deleterious side effects in most patients and has led to significant reluctance to develop new, metal-based therapeutics. New advances in the field, such as photoactivated or catalytic metallodrugs, and solid-lipid nanoparticle (SNL) delivery systems, offer opportunities to improve both the safety and efficacy of metallodrugs, and to dispel the pervasive myth of inherent toxicity.[2]

PHOTOACTIVATED METALLODRUGS

Photoactivated organic chemotherapeutics have been explored in the context of porphyrins and chlorins, for several years, but only three photosensitizers have been approved for therapy worldwide.[3] In recent years, photoactivated metallodrugs have begun to emerge as potential candidates for photodynamic therapy (PDT), photothermal therapy (PTT) and photoactivated chemotherapy (PACT) owing to their favorable targeting abilities, photophysical tunability, and ease of synthesis. This approach has led to three photoactivatable metallodrug candidates currently undergoing clinical trials: Ru^{II}-TLD1433 (Figure 1A), Lu^{III}-Lutrin®, and Au^{0}-Aurolase.[4] Further efforts to explore new ways to enable PDT, PTT, or PACT through metallodrugs are currently underway, as well as a standardization of the methods for measuring compound efficacy.[3]

CATALYTIC METALLODRUGS

Metallodrugs often suffer from in vivo toxicity and off-target effects owing to the high doses required for effective treatment. Catalytic metallodrugs offer the opportunity to reduce dosing regimens, as well as to offer unique mechanisms of action that are unreachable with small molecule therapeutics.[5] Some of these catalytic drugs are mimics of naturally occurring enzymes, such as AEOL-10150, a Mn-based superoxide dismutase mimic capable of reducing damage from a broad spectrum of oxidants.[6] However, beyond enzyme mimics, metallodrugs can also catalyze bioorthogonal processes in the body, such as the Pd-mediated cleavage of *N*-propargyl groups to release the anti-cancer drug 5-fluorouracil

(Figure 1B).[7] This technology has been further expanded to allow for asymmetric transfer hydrogenation in living cells, opening further avenues for cancer treatement.[8]

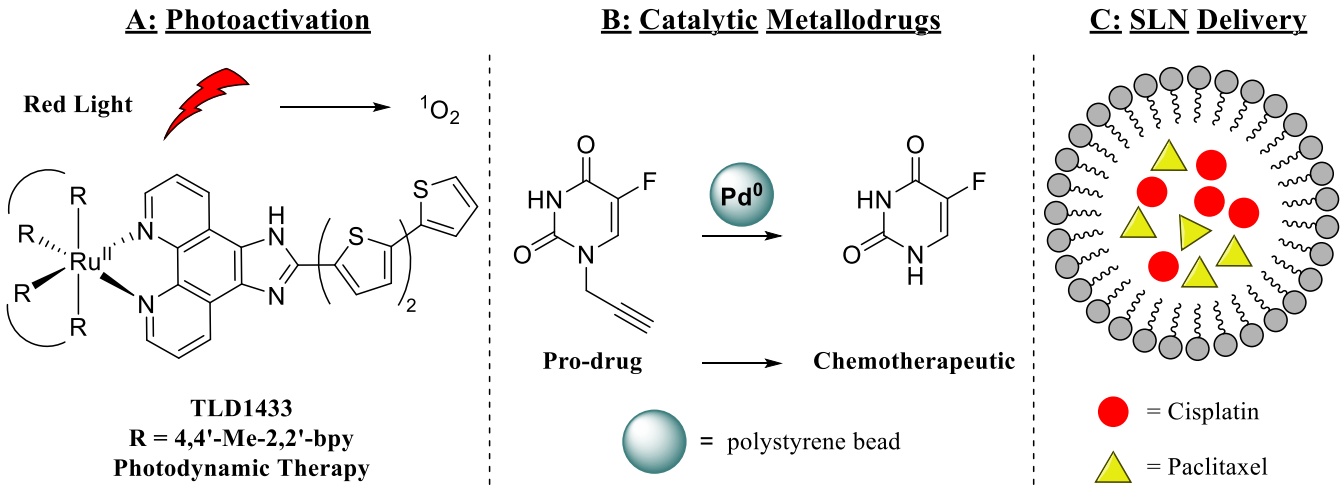

Figure 1. Representative examples of each therapeutic strategy.

SOLID LIPID NANOPARTICLE DRUG DELIVERY SYSTEMS FOR METALLODRUGS

Nanoparticle (NP) drug delivery systems (DDS) have been explored for the delivery of small molecules and other therapeutics to targeted sites in the body to reduce off-target effects and metabolic decomposition.[9] More recently, the use of solid-lipid nanoparticles (SLNs) has emerged as a biocompatible method for drug delivery that obviates the common toxicity problems of inorganic- and polymer-based nanoparticles.[10] In 2018, Jain and coworkers showed that folic-acid grafted SNLs were capable NP DDS for oxaliplatin, allowing for higher cytotoxicity against an HT-29 colorectal cancer cell line than free oxaliplatin.[11] SLNs also offer the ability to administer drug cocktails simultaneously and have been shown by Jiang and coworkers to be competent to deliver a cocktail of cisplatin and paclitaxel (Figure 1C).[12] The tunability of these NP DDS will allow for further treatment regimens that target other diseases safely and effectively.

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