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Maria Contel
CUNY Brooklyn College

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Editorial

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María Contel [1,2,3,4]

[1] Department of Chemistry, Brooklyn College, The City University of New York, Brooklyn, NY 11210, USA; mariacontel@brooklyn.cuny.edu; Tel.: +1-718-951-5000 (ext. 2833)
[2] Biology PhD Program, The Graduate Center, The City University of New York, New York, NY 10016, USA
[3] Biochemistry PhD Program, The Graduate Center, The City University of New York, New York, NY 10016, USA
[4] Chemistry PhD Program, The Graduate Center, The City University of New York, New York, NY 10016, USA

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For the past 41 years, metal-based drugs have been widely used for the treatment of cancer. Cisplatin and follow-up drugs carboplatin (Paraplatin™) and oxaliplatin (Eloxatin™) have been the gold standard for metallodrugs as antineoplastic agents in clinical settings. Although effective, these drugs, either alone or in combination therapy, have faced a number of clinical challenges resulting from their limited spectrum of activity, high toxicity producing significant side effects, resistance, poor water solubility, low bioavailability, and short circulating time. In the past two decades, various unconventional non-platinum metal-based agents have emerged as potential alternatives for cancer treatment. These compounds are highly effective and selective in cancers resistant to cisplatin and other chemotherapeutic agents. Research in this area has recently intensified with a relevant number of patents and clinical trials, in addition to reports in scientific journals including some excellent reviews and books published in 2018–2019 [1–6]. Some recent highlights include ongoing clinical trials with gold auranofin for the treatment of small and non-small lung cancer and high-grade ovarian, fallopian tube, and peritoneal cancer [7,8], as well as upcoming clinical trials with copper derivatives in metastatic pancreas cancer [9], and phase II clinical trials with a ruthenium-based photodynamic compound (TLD-1433) for non-muscle invasive bladder cancer [10]. In parallel to the synthesis of coordination and organometallic compounds comprising different metals and unconventional platinum-based derivatives, researchers have also worked on optimizing the mechanistic and pharmacological features of promising drug candidates [1,2]. This Special Issue is devoted to some of the latest advances in anticancer metallodrugs with a focus on unconventional anticancer agents, as well as novel activation, targeting, and delivery strategies aimed at improving their pharmacological profile. Twelve medicinal inorganic chemistry groups from different countries have provided contributions to this Special Issue.

Three groups contributed with superb and well-organized reviews. In the area of unconventional anticancer agents, Romero-Canelón et al. completed an overview on key ruthenium drug candidates and the knowledge acquired during the past two decades with the aim of discussing ideas to optimize their chemical design by incorporating new concepts [11]. Tinoco et al. contributed a review on the significant roles that copper and iron play in the molecular pathways involved in cell proliferation and metastasis, and the evaluation of selected chelators for these metals showing promise as anticancer drugs [12]. Efforts to optimize the pharmacological profile (cellular delivery, efficacy, and tumor responsiveness) of these chelators as well as a description of analytical tools used to quantify the metal levels and to track the metals intracellularly are described [12]. Lastly, Mieszawska et al. contributed a timely comprehensive review on the use of nano-based systems and biomacromolecules as carriers to facilitate the in vivo application of metal-based drugs (solubility, bioavailability, and delivery to tumor tissues). This review focuses on complexes comprising platinum, ruthenium, copper, and iron [13].

This Special Issue also contains nine original research articles. Seven of these articles focus on unconventional metal-based agents with promising anticancer activity and/or their interactions with relevant cancer biomolecular targets. Komeda et al. report on dinuclear platinum(II) complexes containing ammonia and a bridge ligand between the platinum(II) centers consisting of a tetrazolate moiety with lipophilic substituents in the C5 position [14]. The authors describe the interactions of these complexes with β-cyclodextrin and its positive influence on the in vitro and in vivo activity of the dinuclear platinum(II) complexes in colorectal cancer cells and tumors [14]. Gómez-et al. describe the synthesis and cytotoxicity of new *trans*-platinum complexes containing iodido and amine ligands, and their chemical behavior in solution and reactivity towards biomolecules [15]. They found a beneficial effect (increased reactivity towards model nucleobase 5′-GMP) when exposed to UVA irradiation. Density functional theory (DFT) calculations for these compound, and comparisons of reactivity and biological activity with other iodide platinum(II) derivatives are also included in this article [15].

This Special Issue also collects reports on the synthesis and anticancer properties of compounds containing metals other than platinum [16–20]. Navarro et al. report cell viability assays on selected human cancer cell lines of cationic ruthenium(II) compounds based on *p*-cymene, triphenylphosphine, and biologically active clotrimazole and ketoconazole as ligands [16]. Preliminary studies on the cell cycle and mechanism of cell death as well as the promising anti-migration activity of a selected compound with clotrimazole on a triple negative breast tumor cancer cell line were reported [16]. Da Costa Ferreira et al. contributed to this issue with a report on new copper(II) and zinc(II) complexes containing new oxindolimine ligands [17]. The cytotoxicity of these compounds against hepatocellular carcinoma and neuroblastoma cancer cell lines, as well as their reactivity toward Calf Thymus DNA and human serum albumin, was investigated. The main conclusion is a confirmation of DNA as an important target for these compounds and an indication that oxidative damage is not the leading mechanism of cell death [17]. Three other leading medicinal inorganic chemistry groups contributed original articles on gold compounds [18–20]. Gimeno et al. describe the excellent cytotoxicity observed in several cancer cell lines by neutral gold(I) compounds containing biologically relevant thiolates and a new phosphine ligand bearing a thiophene molecule [18]. Farrell and Beaton report novel cationic gold(III) compounds containing the 1-methylcytosine ligand and chelating diamines for greater specificity toward biomolecules, with the ultimate goal of avoiding undesirable nonselective interactions and providing a better understanding of the speciation [19]. They describe the interactions of these compounds with models for the HIV nucleocapsid protein NCp7. More specifically, the authors report the affinity of the gold(III) complexes with the "essential" tryptophan of the C-terminal zinc finger motif of NCp7 by fluorescence and ^{1}H NMR spectroscopy, and included results on the specifics of this interaction by circular dichroism spectroscopy and electrospray-ionization mass spectrometry. A nearly immediate interaction with the apopeptide and indications of reactions via a charge transfer mechanism is described for the first time [19]. Casini et al. present findings on the synthesis and characterization of a series of cationic and neutral gold(III) compounds featuring a pyridine-benzimidazole scaffold [20]. The potent and selective inhibition of the membrane water and glycerol channels aquaporins (aquaglyceroporin, AQP3) in human red blood cells (hRBC) and a higher activity of the neutral compounds on melanoma A375 cells with marked membrane level expression of AQP3 are described. The potential of these compounds in the development of chemical probes to study the function of this protein isoform in biological systems is also highlighted [20].

This Special Issue contains a relevant research article by Meier-Menches et al. on the development and validation of liquid-chromatography-based methods to assess the lipophilicity of cytotoxic platinum(IV) complexes [21], which is of interest to the medicinal inorganic chemistry community due to: (1) the current availability of high-performance liquid chromatography (HPLC) instruments in research laboratories, and (2) the potential of obtaining chromatographic lipophilicity parameters (φ_0 that can be interconverted to Log P and Log Kw) for other metal-based compounds [21].

Lastly, Salassa et al. provide a contribution on functionalized upconverting nanoparticles (UCNPs) with bone-targeting phosphonate ligands for imaging purposes [22]. The authors report the synthesis and characterization of a new series of phosphonate-functionalized NaGdF4:YbmEr UCNPs that show affinity for hydroxyapatite, which is the inorganic constituent of bones, and discuss their potential as bone targeting multimodal (MRI/PET) imaging agents. In vivo biodistribution studies of ^{18}F-labbeled functionalized UCPNs in rats revealed the favored accumulation of nanoparticles in bones over time [22].

I truly hope that the readers find the open access format articles in this Special Issue timely and relevant, and that the Issue contributes to increasing awareness about the real potential of optimized metal-based drugs as competitive anticancer agents. The inorganic medicinal community has demonstrated that the assumption that all anticancer metallodrugs behave as cisplatin and related platinum-based compounds in terms of spectrum of activity and selectivity is no longer valid.

Finally, I want to thank all the authors for their excellent and diverse contributions to this Special Issue as well as the participating reviewers for their high quality suggestions and evaluations of the articles submitted. Lastly, this Special Issue would not have been possible without the constant dedication, support, and patience of the members of the editorial staff of *Inorganics* from the beginning to the end of the process. I am very grateful to them.

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