Preface to Volume 18

Metallo-Drugs: Development and Action of Anticancer Agents

Platinum-based anticancer drugs are among the most widely used of all chemotherapeutic cancer treatments. Three FDA-approved platinum(II) anticancer drugs, i.e., cisplatin, carboplatin, and oxaliplatin, have been in the clinic for many years to treat testicular, ovarian, cervical, head and neck, colorectal, and other cancers. These breakthroughs are the result of the serendipitous discovery of the anticancer activity of cisplatin, cis-diamminodichloroplatinum(II), more than 50 years ago. Meanwhile an understanding of its medicinal properties has developed, allowing for improved treatment regimens reducing somewhat the side effects, including nephrotoxicity, myelosuppression, peripheral neuropathy, ototoxicity, and nausea. All this and more is covered in Chapter 1 which focuses on Cisplatin and Oxaliplatin.

Polynuclear Platinum Complexes (PPCs) were developed to combat cisplatin-resistant cancers. PPCs represent a discrete structural class of DNA-binding agents: The use of at least two platinum-coordinating units makes multifunctional binding modes possible. Proof of principle of this hypothesis was achieved by the advance to the clinic (Phase II trials) of triplatin, a charged trinuclear, bifunctional, DNA-binding agent with two terminal arms, –NH2-Pt(NH3)2Cl. Chapter 2 emphasizes the structural diversity and reactivity of PPCs.

Another approach to avoid resistance and side effects centers on octahedral and kinetically inert Pt(IV) Prodrugs (Chapter 3). They can be reduced in cancer cells to active square-planar Pt(II) complexes, e.g., by intracellular reducing agents such as glutathione or by photoexcitation. The additional axial ligands in Pt(IV) complexes, which are released on reduction, allow bioactive molecules to be delivered, which can act synergistically with the Pt(II) species in killing the cancer cells. Pt(IV) complexes are likely to be stable under the highly acidic conditions in the stomach and therefore suitable for oral administration.
Chapter 4 introduces the concept of **Metalloglycomics**, that is, the interaction of metal ions with biologically relevant oligosaccharides, in particular glycosaminoglycans (GAGs) such as heparin and heparan sulfate. Their structure and conformation and the role of various metal ions during their interaction with proteins and enzymes are reviewed. Cleavage of heparan sulfate proteoglycans by heparanase modulates tumor-related events. Heparan sulfate is identified as a ligand receptor for polynuclear platinum complexes defining a new mechanism of cellular accumulation.

The structure of the ruthenium(III) drug candidates KP1019 and NAMI-A is deceptively similar, i.e., trans-RuCl₄(X,Y)⁻, as discussed in Chapter 5, yet, surprisingly they have markedly different macroscopic pharmacological activities: KP1019 behaves rather as a classical antitumor compound (with the advantage of being active also against platinum(II)-resistant tumors), whereas NAMI-A has a more unconventional activity that affects metastases and not the primary tumor. The complicated *in vivo* chemistry (no clearly identified target) is affecting negatively their further clinical development after initial progress (Phase II).

Organometallic ruthenium-arene complexes (Chapter 6) have risen to prominence as a pharmacophore due to the success of other ruthenium drug candidates in clinical trials. Ru(arene) complexes are almost exclusively octahedral, low-spin d⁶ Ru(II) species. Mononuclear Ru(arene) complexes have therapeutic properties against cancer *in vitro* and *in vivo*, therefore researchers began exploiting these potentially therapeutic entities for higher-order multinuclear Ru(arene) complexes.

The *Medicinal Chemistry of Gold Anticancer Metallodrugs* is described in Chapter 7. Since ancient times gold and its complexes have been used as therapeutics against different diseases. In modern medicine gold drugs are applied for the treatment of rheumatoid arthritis, but recently they also serve as antiparasitic, antibacterial, and antiviral agents. The exciting findings on gold(I) and gold(III) complexes as antitumor agents are summarized and warrant the discussion of the relevant aspects of their modes of action.

Titanium(IV) complexes represent attractive alternatives to Pt(II)-based anticancer drugs because of their low toxicity (Chapter 8). The pioneering compounds titanocene dichloride and budotitane were the first to enter clinical trials. Yet, despite the high efficacy and low toxicity observed *in vivo*, they failed, mainly because of formulation complications, their rapid hydrolysis, the difficulty of isolating and identifying the particular active species and the precise cellular target. The following generation of phenolato-based complexes came three decades later and exhibited high activity and improved stability, with no signs of toxicity to the treated animals. The mechanistic insights gained so far include the interaction with DNA and the induction of apoptosis; hence, these Ti(IV) complexes are highly promising for future clinical development.

Vanadium compounds have been known for long to have beneficial therapeutic properties (Chapter 9), but it was not until 1965 when it was discovered that these effects could be extended to treating cancer due to the similarities in some metabolic pathways that are utilized by both diabetes and cancer. The links between these diseases emerged through epidemiological investigations which
suggest that the incidence of pancreatic, liver, and endometrial cancers are associated with diabetes though the links are not yet fully understood.

The antineoplastic activity of gallium nitrate, Ga(NO₃)₂, was recognized over three decades ago and several clinical trials (Phase I and II) have confirmed this in patients with lymphoma and bladder cancer (Chapter 10). Ga(III) shares chemical characteristics with Fe(III) and these enable it to interact with iron-binding proteins and to disrupt iron-dependent tumor cell growth. Beyond the first generation of gallium(III) salts (parenterally administered) a new generation of complexes such as tris(8-quinolinato)gallium(III) with oral bioavailability, has emerged and is now evaluated in the clinic while other ligands for Ga(III) are in preclinical development.

Non-covalent Metallo-Drugs: Using Shape to Target DNA and RNA Junctions and Other Nucleic Acid Structures is the title of Chapter 11. This shape specificity contrasts with the most effective class of anticancer drugs in clinical use, the Pt(II) agents, which act by binding to duplex B-DNA in a sequence-specific manner, but duplex B-DNA is not DNA in its active form. The chapter describes how large cationic metallo-supramolecular structures can be used to bind to less common, yet active, nucleic acid structures like Y-shaped forks and 4-way junctions, and thus, possibly display high cytotoxicity and inhibit cancer.

Chapter 12 deals with Nucleic Acid Quadruplexes and Metallo-Drugs. Guanine-rich sequences of DNA can readily fold into tetra-stranded helical assemblies, known as G-quadruplexes (G4). It has been proposed that these structures play important roles in transcription, translation, replication, and telomere maintenance. Therefore they receive attention as potential drug targets for small molecules including metal complexes. Indeed, G4s have been identified as potential drug targets, in particular for cancer.

Anticancer platinum-based drugs are widely used in the treatment of a variety of tumoric diseases. They target DNA and thereby induce apoptosis in cancer cells. Their reactivities with other biomolecules have often been associated with side effects during chemotherapy. The development of metal compounds that target proteins rather than DNA has the potential to overcome or to reduce these disadvantages. New compounds on track toward clinical application are highlighted in Chapter 13, Antitumor Metallodrugs that Target Proteins.

Chapter 14, entitled Metallointercalators and Metalloinsertors deals with their structural requirements for DNA recognition and anticancer activity. The focus is on the non-covalent recognition of the highly structured DNA surface by substitutionally inert metal complexes (mostly of Ru(II) and Rh(III) with low-spin 4d⁶) capable of either sliding in between the normal base pairs (metallointercalators) or flipping out thermodynamically destabilized mispaired nucleobases (metalloinsertors). New structural insights enable the development of novel DNA binding modes and thus, new anticancer drug candidates.

The last three chapters of this volume deal with essential metal ions. First, Iron and Its Role in Cancer Defence: A Double-Edged Sword is discussed (Chapter 15). Iron is vital for many biological functions including electron transport, DNA synthesis, detoxification, and erythropoiesis. Interactions between Fe(II/III) and O₂ can result in the generation of reactive oxygen species. Excess iron may cause
oxidative damage resulting in cell death, but DNA damage may also lead to permanent mutations. Hence, iron is carcinogenic and may initiate tumor formation and growth; however, Fe(II/III) can also contribute to cancer defense by initiating specific forms of cell death, which will benefit cancer treatment. Furthermore, Fe-binding and Fe-regulatory proteins, such as heme oxygenase-1, ferritin, and iron-sulfur clusters can display antitumor properties in certain cancer types. Consequently, very specific and selective drugs that target Fe metabolism in tumors are promising candidates for the prevention and therapy of cancer.

Copper is another essential micronutrient required for fundamental biological processes in all organisms (Chapter 16). It is a redox-active metal able to shift between reduced (Cu\(^+\)) and oxidized (Cu\(^{2+}\)) states. Free copper ions can generate highly reactive oxygen species (ROS) and damage lipids, proteins, nucleic acids, and other biomolecules. Hence, copper homeostasis is tightly regulated to ensure sufficient copper for cuproprotein biosynthesis, while limiting oxidative stress and toxicity. Over the last century copper complexes have been developed as antimicrobials and for treating special diseases which now also include cancer because copper has been recognized as a limiting factor for multiple aspects of cancer progression including growth, angiogenesis, and metastasis. Consequently, ‘old copper complexes’ (e.g., tetrathiomolybdate and clioquinol) have been repurposed for cancer therapy and have demonstrated anticancer activity \textit{in vitro} and in preclinical models. Likewise, with tailer-made copper complexes considerable progress has been made in understanding their pharmacological requirements and human clinical trials continue.

Zinc(II) is gaining momentum as a potential target for cancer therapy since it has been recognized as a second messenger (Chapter 17). It is able to activate many signalling pathways within a few minutes by an extracellular stimulus which leads to the release of zinc(II) from intracellular stores. This zinc(II) release inhibits tyrosine phosphatases preventing the inactivation of tyrosine kinases, etc. These signalling pathways are commonly considered the main driving force in aberrant cancer growth. These insights position zinc(II) signalling as a particularly important new target to prevent aggressive cancer growth.

To conclude, this volume, devoted to \textit{Metallo-Drugs: Development and Action of Anticancer Agents}, is rich on specific information. MILS-18 updates our knowledge not only on platinum(II) and related platinum complexes, but it provides also deep insights on the new research frontiers dealing with the next generation of anticancer drugs. It is a \textit{must} for all researchers working in medicinal chemistry and beyond as well as for teachers giving courses on this topic.

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