

Editorial

While cancer remains a major killer in the developed world, a broad spectrum of novel and exciting approaches are being developed and tested. The importance of metal compounds in medicine is undisputed, as can be judged by the use of many metal-based compounds in the treatment of various diseases. In terms of anti-tumour activity, a wide range of compounds of both transition metal and main group elements have been investigated for efficacy. The existence of a relationship between cancer and metals is widely acknowledged by researchers. Therefore, the aim of the theme issue "Metal-Containing Drugs and Novel Coordination Complexes in Therapeutic Anticancer Applications" of *Anti-Cancer Agents in Medicinal Chemistry* is to present an up-to date overview of this subject and to cover very recent developments in the field of metal-based anticancer agents.

Recent advances in medicinal inorganic chemistry demonstrate significant prospects for the utilization of metals and their coordination complexes as drugs, presenting a flourishing arena for inorganic chemistry. Significant progress in metal-based agents has been achieved. Nevertheless, there is an urgent need for new drugs to treat cancer, drugs with novel mechanisms of action. Metal complexes appear to provide a rich platform for the design of novel anticancer drugs. The metal, its oxidation state, the number and types of coordinated ligands, and the coordination geometry of the complexes can provide variety of properties. On the other side, the ligands can not only control the reactivity of the metal, but also play critical roles in determining the nature of interactions involved in the recognition of biological target sites, such as DNA, enzymes and protein receptors. These variables provide enormous potential diversity for the design of metallodrugs. They also introduce many challenges. Changes in composition are likely to be accompanied by changes in the respective biological activity. Hence it is important to identify the nature of the metal complex which exists in the biological medium and is undergoing the biological test, and ideally the species which reaches the target site. There is now no doubt that medicinal inorganic chemistry, and metal coordination chemistry in particular, is worthy of exploration for drug design. Developing metal complexes as drugs, however, is not an easy task. Accumulation of metal ions in the body can lead to deleterious effects. Thus biodistribution and clearance of the metal complexes as well as its pharmacological specificity are to be considered. Favourable physiological responses of candidate drugs need to be demonstrated by *in vitro* study with targeted biomolecules and tissues as well as *in vivo* investigation before they enter clinical trials. A mechanistic understanding of how metal complexes achieve their activities is crucial to their clinical success, as well as to the rational design of new compounds with improved potency.

In the first part of the Special Issue "Metal-Containing Drugs and Novel Coordination Complexes in Therapeutic Anticancer Applications" timely in-depth reviews are given. The first and this second part of the issue focused on recent advances in developing different metal-based anticancer agents, on recent efforts to prepare novel platinum, ruthenium, gold, titanium, selenium etc. complexes and reviewed some mechanistic insights into the pharmacological effects of these complexes. It is well known that for the perspective of metal-based drugs, some results are encouraging, but some others challenging. Firstly, the clinical success of a drug candidate depends not only on its bioactivity, but also on the absorption, distribution, elimination, metabolism and toxicity properties. These qualities are determined by the structure of the compound and also by external factors. The second difficulty is related to the activity/toxicity modulation. The next problem worth to be studied is the cell response to the metals. Differing from organic drugs, metals act on several key points in the life process. Thus they intervene with a pathological process from a number of targeting points. To this end, the scientists have to study the input and output relation and establish quantitative models to describe the effects of cell responses to different metals. It needs no discussion that the above-presented highlights and outlook about metal-based therapeutics provide fascinating new possibilities for research in the coming decades. It is generally appreciated that enormous progress has been made in the understanding of the mode of action of the most of metal-based agents. Application of this knowledge in drug design is close, and it is generally expected that in the next decades improved drugs will be developed based on this knowledge. The future development of medicinal inorganic chemistry of metals requires an understanding of the physiological processing of metal complexes, to provide a rational basis for the design of new metal-based drugs. Application of new methodologies such as combinatorial chemistry, extensively used in drug discovery, will be beneficial for the study of various metals and the development of their coordination complexes as therapeutics.

In the first review of the second part "Enzyme Inhibition as a Key Target for the Development of Novel Metal-Based Anti-Cancer Therapeutics" by Griffith, Parker and Marmion of the Royal College of Surgeons in Ireland, the authors report on the current knowledge about the enzyme inhibition by metal complexes. This review gives a very good overview of recent key advancements on enzyme inhibition as an important target for the development of novel metal-based anti-cancer therapeutics with a particular emphasis on metal complexes that inhibit protein and lipid kinases, matrix metalloproteases, telomerases, topoisomerases, glutathione-S-transferases and histone deacetylases. This thorough and exceptionally well written review covers almost all of the necessary aspects of the action of metal based drugs, as anti-cancer agents. A list of general strategies behind the development of such complexes is also highlighted. As demonstrated by the numerous examples of metal-based complexes with enzyme inhibitory activity cited in the review, fostering interest in medicinal inorganic chemistry and in particular, in this relatively new field, is entirely beneficial. With the expanding knowledge of the essential alterations in cell physiology that collectively dictate malignant growth, new opportunities are being presented for metal-based drugs that show high selectivity and low systemic toxicity. As a result of the latter advancements, clinical results and medicinal inorganic chemistry will only prosper with the now more plausible development of site-selective drugs with targets holding influence on cancer cell survival.

Next, the authors contribute a paper entitled "Recent Researches in Metal Supramolecular Complexes as Anticancer Agents" by Zhou *et al.* of the Southwest University, Chongqing, China. In this paper, the authors systematically review the recent progress of metal-based supramolecular complexes as anticancer agents mainly in 2009. It is known that numerous efforts have been directed toward metal supramolecular complexes as potential anticancer agents and the unprecedented progress has been made. This has opened up a wholly new and infinite space to create novel metal-based bioactive supermolecules. In view of the rapid progress in metal complex anticancer supermolecules with rich variation of structural types, this work thoroughly reviews the recent research and development of the whole range of metal-based supramolecular complexes as anticancer agents. This review with many references provides considerable valuable information for the related researchers. The perspectives of the foreseeable future and potential application of metal supramolecular complexes in cancer therapy are also presented. It is hoped that this review will serve as a stimulant for new thoughts in the quest for rational design of more active and less toxic metal supramolecular anticancer complexes. With the further expansion of organometallic supramolecular chemistry and its widespread extension in pharmaceutical sciences, as well as the ongoing progress of cell biology, molecular biology, pharmaceuticals, materials science, medicine and other disciplines, it is inevitable that more and more workers will engage in the research and development of metal-based supramolecular complexes as anticancer drugs. More and more metal supramolecular anticancer drugs with good efficacy, low toxicity and good pharmacokinetics properties will be used in clinic and make remarkable contributions for the protection of human health.

In the third paper, entitled "Fresh Platinum Complexes with Promising Antitumor Activity" by Xiaoyong Wang of the School of Life Sciences, Nanjing University, China, the author reviews the efforts made so far to develop new generations of platinum complexes which act as potent tumour inhibitors. This excellent and thorough review concentrates on the major development of novel platinum complexes in the last five years that have shown favourable properties for the improvement of platinum-based chemotherapy. Platinum-based anticancer agents have been in extensive use for many years to successfully treat many different types of cancer. However, the efficacy of these drugs is limited by serious side effects. The review highlights the complexes with DNA damage mode fundamentally different from that of cisplatin and thereby different profile and therapeutic index. Platinum complexes with DNA damage mode radically different from that of cisplatin may evade the cellular DNA repair machinery and inhibit tumour cells through different mechanisms. Special emphasis is put on the development of non-conventional complexes, such as monofunctional platinum(II) complexes, polynuclear platinum(II) complexes, *trans*-platinum(II) complexes and platinum(IV) complexes. All of these complexes display impressive antitumor activity and some of them show remarkable potentiality to circumvent the resistance to cisplatin. On the basis of these new facts, it can be concluded that structural modifications could substantially modulate the DNA binding mode and DNA damage process, and as a result largely improve the antitumor efficacy of platinum complexes. On the other side, the nature of the ligand is one of the key factors that affect the biological behaviour of platinum complexes. Tailored multifunctional ligands not only offer exciting possibilities to prepare more effective platinum complexes, but also play crucial roles in modulating the systemic toxicity of the complexes. Undoubtedly, rational design will become a standard means to develop platinum antitumor drugs. On this basis, further improvement in efficacy will prove to be a reachable expectation for platinum-based chemotherapy. This informative review gives a concise overview and strategies of the most recent preclinical developments in the field of antitumor platinum compounds. Even specialists in the field will find aspects they may have overlooked.

Another well known set of weapons in the fight against cancer are naturally occurring compounds and their metal complexes. The next article entitled "Progress in the TCM Metal-Based Antitumour Agents" by Zhen-Feng Chen and Hong Liang (Key Laboratory for the Chemistry and Molecular Engineering of Medicinal Resources of the Ministry of Education of China and Guangxi Normal University, Guilin, China) is a really interesting contribution to the field of anticancer drug design and development and gives a really concise information about this interesting subject. The paper describes the metal functionalization of traditional Chinese medicine (TCM)-derived biologically active compounds as a possible approach to designing potent anticancer agents. Traditional Chinese medicine has recently been recognized as a new source of anticancer drugs and new chemotherapy adjuvant to enhance the efficacy of chemotherapy and to diminish side effects and resistance of cancer chemotherapies. New coordination compounds based on traditional Chinese medicines (TCMs) provide a novel approach to potential pro-drugs. This review describes not only current chemical aspects of metal complexes of TCM but also historical view focusing on the synthesis, structure, antitumor activity and interactions with molecular targets of TCM based metal complexes. In this review, TCM alkaloids, flavonoids, cantharidin, coumarins, plumbagin, curcumin and camphoric acid metal-based antitumor agents have been covered. The future development of hybrid TCM-metal complexes as antitumor drugs has been also discussed. The pursuit of new TCM metal-based anticancer drugs and enhancement of modern TCM holds promise for overcoming multidrug resistance. The promising trends have been supported by great potential of TCM metal-based antitumour agents. This review is interesting and thorough approach summarizing the most recent research progress on metal-based traditional Chinese medicine and it may prove useful for researchers in the area of naturally occurring anticancer drugs and traditional Chinese medicine giving an exhaustive treatment of the subject.

Certainly, metal-based therapeutics has received an increasing amount of attention in the last decades. These days the chemical and medicinal aspects of metal-based compounds are indeed in focus and this group of compounds with anticancer activity forms one of the major fields of medicinal chemistry. Offering an authoritative and timely account by many internationally recognized experts, the hot-topic issue "Metal-Containing Drugs and Novel Coordination Complexes in Therapeutic Anticancer Applications" is exclusively devoted to the vital research area concerning metal complexes in cancer diagnosis and therapy and offers exciting opportunities for combinatorial approaches. Many insights gained in metal-based cancer therapy and also in other fields have been clearly shown and discussed. In this themed issue of *Anti-Cancer Agents in Medicinal Chemistry* seasonable reviews are gathered from leading well known research workers in the field. Their work illustrates that although great progress has been made in designing metal-based compounds for drug delivery, many improvements still need to be made before they can be considered for applications, and, as this themed issue demonstrates, the exciting challenges are likely to lead to rapid progress in the next few years and hopefully to discover some new clinically-useful anticancer drugs. At this point, I would like to thank the authors for providing such comprehensive overviews over their research despite their busy schedules and multiple engagements.

The Special Issue has been divided into two parts published one after the other. The seven reviews included in the issue (Part I) are followed by four other articles in Volume 10, Number 5 (Part II). I really feel delighted to have the privilege to edit this issue and it was a matter of great honour. I take this opportunity to express once again my own gratitude and appreciations for making this issue a reality thanks to everyone who has contributed excellent review articles. Their great knowledge and experience in this field will be very important, beneficial and valuable for the researchers involved in the topic. I am of firm belief that it would be helpful and purposeful issue that will stimulate the exchange of ideas to achieve effective solutions to the problems and to inspire and enhance the future mutual relations. Furthermore, I would like to thank the constructive learned reviewers for providing their valuable and speedy experts' reports. I feel happy to note that the groups that participated as authors and referees in this special issue are very distinguished and well respected among workers all over the world in the field of metal-based anticancer drugs. All this would make an important contribution to the field of drug development and could significantly help researchers being a good source of essential information to focus their further considerable research and investigations.

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