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Metal Anticancer Complexes – Activity, Mechanism of Action, Future Perspectives

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Cisplatin was first administered to a cancer patient in 1971 and obtained FDA approval for general oncology practice in 1978.[1] These events opened the way to the thriving of medicinal inorganic chemistry, a sub-discipline that traditionally – for historical reasons – has been mainly focused on cancer. This cluster issue of the *European Journal of Inorganic Chemistry*, with 30 contributions from scientist from all over the world, provides an excellent updated picture of the field. To the guest editors of this issue, who have been involved in anticancer metal compounds since the time they were fellow Ph D students in Italy more than 30 years ago, some general trends – the "future perspectives" explicitly mentioned in the title of the issue – appear very clearly. They are listed below, in an order that does not necessarily reflects their importance.

In general, we notice that there is an increasing number of examples – distributed in many review and research papers – concerning *structural metal compounds* that have anticancer activity (at least *in vitro*), i.e. compounds that are coordinatively saturated and inert. Structural compounds have no labile ligands that might open up coordination positions and thus the metal is not expected to bind directly to any biological target, be it DNA, a protein, a signaling pathway, an extracellular component, or else.[2] For decades, such compounds – in which the role of the metal is that of determining the 3D shape of the compound and/or to start an electron transfer process – had been regarded as useless for medicinal applications. Another important trend that is clearly emerging from this cluster issue concerns the increasing focus on molecularly targeted metal compounds, both for cancer treatment and diagnosis. Two review papers, presented by Ulrich Bierbach, Luca Ronconi and respective coworkers, and some contributions deal with this topic. These two trends are intimately connected and strictly related to the identification of new targets – aside from DNA – and new mechanisms of action that are peculiar to transition metal compounds. Remarkably, the essay paper by Peter Sadler and Pingyu Zhang that opens this issue, dedicated to redox-active metal anticancer pro-drugs, concerns exactly one of such new mechanistic approaches.

In terms of metals, we observe that there are very few contributions on the Pt(II) complexes that have dominated the scene for decades. In addition, they concern non-classical topics: see for example the review paper by Janice R. Aldrich-Wright and coworkers on Pt-intercalators (that are mainly structural compounds!), or the research paper on photo-activated Pt(II)-curcumin complexes. Indeed, the only paper dealing with cisplatin investigates its interaction with a non-classical target, i.e. the zinc-fingers. Most of the contributions on Pt compounds deal with Pt(IV) pro-drugs that – in principle – are expected to provide some sort of selectivity: in addition to three full papers, the state-of-the art of the field is nicely reviewed by Celine Marmion and coworkers. These observations clearly suggest that the field of Pt(II) compounds is now a mature topic and that the focus of research has shifted on Pt(IV).

Ruthenium attracted nearly as many contributions as platinum: aside from a critical review paper by Enzo Alessio on the antimetastatic Ru(III) coordination complex NAMI-A 30 years after its discovery, the other papers are mainly focused on half-sandwich Ru(II) organometallic compounds, still at the core of large research interest.

Another general trend is the increasing number of contributions on metals other than Pt and Ru, both exogenous and endogenous: Ir(III), Rh(III), Au(III), Ti(IV), V(V), Fe(III), Mn(II), Zn(II), and Cu(II). Some of them are presumably *functional compounds* (i.e. have labile ligands), others are structural compounds, thus no clear structure-activity relationship or trend can be detected yet. Nevertheless, in view of the wealth of new knowledge acquired in recent years on cancer cell metabolism as well as on the non-classical mechanisms available to metal compounds, the investigation of yet under-explored metals might lead to novel exciting findings.

However – and perhaps unexpectedly – the main actor of this issue is not a metal, but light! Indeed, an increasing number of scientists are focusing their research on the peculiar interactions that transition metal compounds have with visible light, trying to exploit them for therapy and/or diagnosis. Numerous contributions, in fact, concern light-activated metal compounds, mainly Ru(II), but also Ir(III), and Pt(II). The interaction of visible light with transition metal compounds is investigated – for therapeutic purposes – mainly with two aims, not necessarily self-exclusive: the catalytic generation of singlet oxygen (or other ROS) in the context of the photodynamic therapy (PDT) and/or the stoichiometric photo-induced release of ligands. This latter process can focus either on the activated metal fragment or on the released ligand when it is by itself a pharmacologically-active molecule (*photo-uncaging*). In this context, the review paper by Jin-Gang Liu and coworkers provides a detailed overview on the photo-induced release of NO from metal-nitrosyls. The 2015 approval by Health Canada of a phase Ib clinical trial application for evaluating a Ru(II)-polypyridyl compound (TLD-1433) as PDT agent in patients with bladder cancer is certainly giving great emphasis to this research topic.[3,4]

This cluster issue is perhaps also a good occasion for performing a critical analysis of the field of anticancer metal compounds nearly 50 years after its official start. We can have either an optimistic or a pessimistic view. On the bright side, we notice that

there is an increasing number of academic scientists contributing to this field, which is becoming more and more diverse in terms of metals, potential targets and mechanisms, with novel, non-classical concepts being explored.[5] Careful design and smart approaches are progressively replacing random synthesis and screening. However, it is fair to admit that many of the expectations induced by the development of cisplatin have not been fulfilled (yet). In the last 10 years this intense research activity has produced many proofs of principle but few concrete examples that might be close to application or even clinical development. As recently noticed by Stephen Lippard and coworkers, despite the widespread use of Pt drugs, no new platinum agent has received worldwide approval for over a decade.[6] The panorama is not much brighter for non-platinum compounds, with some noticeable exceptions: the already mentioned case of the potential Ru(II) PDT agent TLD-1433,[3,4] and the introduction into phase I clinical trials of a Cu(II) compound belonging to the Casiopeínas® family.[7] Among the many limits that affect this field we notice, among others: *i*) the general scarce interest/involvement of the pharmaceutical industry, *ii*) the lack of concreteness that characterizes many contributions of the chemists, often focused on compounds whose characteristics are not compatible with application;[8] *iii*) the general lack of simplicity: complicated constructs make nice proofs-of-principle and smart publications but are highly unlikely to ever become new drugs; *iv*) the underestimate by the academics of toxicity concerns; *v*) the lack of effective, reliable and easily accessible screening tests; *vi*) the lack of convincing mechanisms, identified targets and biomarkers for activity/toxicity.[9]

In conclusion, we anticipate that new advances are expected with the introduction of novel activation strategies and nano-platforms etc. which are crucial for the development of the field in the years to come. It appears that novel metal-based diagnostic and theranostic agents could potentially lead the field to a new altitude.

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