Is the next cisplatin already in our laboratory?

Damiano Cirri[a], Lorenzo Chiaverini[b], Alessandro Pratesi*[a] and Tiziano Marzo*[b]

[a] Department of Chemistry and Industrial Chemistry, University of Pisa, Via G. Moruzzi, 13, 56124 Pisa, Italy. E-mail: **alessandro.pratesi@unipi.it**

[b] Department of Pharmacy, University of Pisa. Via Bonanno Pisano, 6, 56126, Pisa, Italy. E-mail: **tiziano.marzo@unipi.it**

ABSTRACT. Since the serendipitous discovery of cisplatin, thousands of inorganic molecules have been synthesised in search of new drugs endowed with powerful anticancer activity and safe profile. As matter of fact, this "magic" and desired combination to date remains unmet. On the other side, after cisplatin, only two additional platinum-based drugs - that have been substantially designed as cisplatin-like molecules- have been approved at the global level i.e., carboplatin and oxaliplatin. Accordingly, here, we try to summarize and highlight some relevant reasons for this "lack" of newly approved molecules. Also, we try to rationalize what are the critical steps in the discovery process (and approval) of new ameliorated anticancer metallodrugs contributing to stimulate an open and critical scientific debate.

Keywords: Inorganic Drug Development; Metallodrugs; Drug Discovery; Clinical Trials; Cancer.

1. Inorganic chemistry and cancer: the challenge to find the next cisplatin

The use of metals and metalloids in medicine can be traced back to very ancient times being their use documented since thousands of years and throughout the history of humanity. For instance, it is possible to find traces of the application of gold against several diseases.[1] More recent examples come with the advent of modern medicine. Indeed, in the 19th century, the complex dicyanoaurate(I) ($K[Au(CN)_2]$) was proposed by Koch to treat tubercle bacillus infections. Similarly, As(III) (marketed as Salvarsan and Neosalvarsan) was proposed by Paul Ehrlich against syphilis.[2] Also, Hg(II) compounds have been exploited up to the 20th century as a chemotherapeutic for the treatment of infections.[3] At least one organomercury compound (Thimerosal) survived in clinical applications up to the present day (Figure 1). More precisely, Thimerosal was extensively employed as a preservative in vaccine and immunoglobulins preparation due to its antiseptic properties. Despite the growing scepticism about thimerosal utilization,[4] a clear and definitive scientific evidence on the toxicity related to its clinical employment is still lacking.[5]

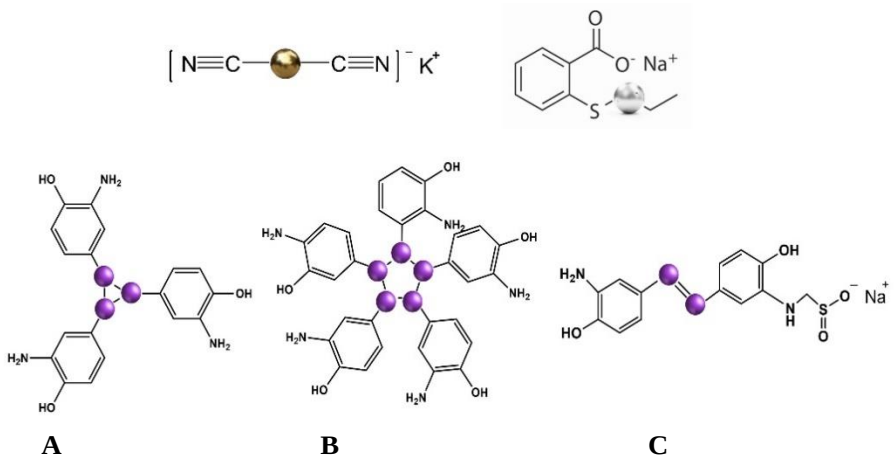

Fig. 1. Chemical structures of the gold-based compound potassium dicyanoaurate(I) (top left); the Hg(II)-based complex thimerosal, (top right). Structures **A** and **B** represent the composition of the As(III)-based mixture known as Salvarsan while **C** represents the structure of Neosalvarsan. Gold sphere = Au; grey = Hg; purple = As.

Beyond these examples, is the modern clinical experience that tells us inorganic drugs represent an essential resource for medicine, and -in particular- against cancer. The proof supporting this affirmation is the success of cisplatin.[6] Cisplatin (together with its second- and third-generation analogues carboplatin and oxaliplatin) has indeed represented a cornerstone in anticancer chemotherapy, making possible to cure or improve the prognosis for various kinds of cancer e.g. testicular cancer (Figure 2).[7, 8]

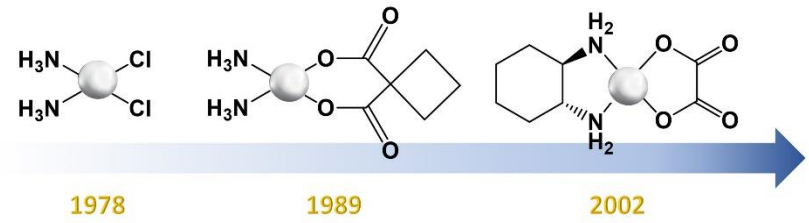

Fig. 2. Chemical structures of the platinum-based anticancer drugs approved at the global level. Cisplatin (left); carboplatin (middle) and oxaliplatin (right). The timeline reports the year of FDA approval.

If these evidences are well known, on the other side, though in the last decades the scientific community devoted huge efforts to the design and synthesis of novel and improved inorganic drugs, their impact on the clinical practice remains quite disappointing.[9, 10] Overall, since 1978 (the year of the FDA approval of cisplatin), an average approval rate (at the global level) of roughly one inorganic anticancer compound every eleven years emerges (including in this count As_2O_3, Trisenox®).[11, 12] It is undeniable that this low approval rate of novel molecules, strongly depends on the inherent complexity of cancer disease. In fact, it does not consist of a single condition, but rather of a series of diseases featured by high variability and common determinants. Accordingly, the old concept of the so-called "magic bullet" is outdated and has been replaced with the new concepts of personalized and combinatory therapy, being this the approach driving modern cancer research and clinical practice.[13] However, beyond these observations, it is necessary to consider other independent -but still relevant- aspects to understand the difficulties in the clinical development of new inorganic anticancer drugs. Herein, we aim to summarize some that, in our opinion, are particularly relevant. Importantly, these considerations (that aren't exclusive) that pertain specifically to metallodrugs, and more in general to inorganic drugs, can be potentially extended -at least in part- to organic ones as well as to other bioactive substances.[14] Indeed, in the World Health Organization's List of Essential Medicines for cancer treatment, only 3 out of 68 are metal-based drugs.[15] At the same time, it is not possible to overlook the evidence that the three included (cisplatin, oxaliplatin and carboplatin) have a huge impact on the clinical practice, clearly indicating that metals represent a potentially very important source for the development of drugs.
Considering these premises, we want to propose some arguments related to the discovery process of new metallodrugs with the aim to promote an honest and constructive reflection inside the chemists' community about this topic. Importantly, we are aware that the object of the discussion is extremely complex and multifaceted and cannot be settled here.

2. Some thoughts on the discovery process of inorganic anticancer drugs

The description of the reasons behind the difficulties in the development and approval of new anticancer metallodrugs is not trivial. As stated above, we must start considering the high complexity of the disease. In fact, even limiting our observations only to this aspect, the approval of a new anticancer molecule would be already extremely challenging; however, this is obviously an unalterable fact. Certainly, modern investigation techniques, including omics approaches, may provide increasing information at the molecular level allowing a growing understanding of the cancer cellular mechanisms and features. This is fundamental for drug design and development. However, it is also true that scientists can act on some further aspects with a key role in the drug development process. Specifically, we would like to focus the attention on those aspects that are sometimes "taken for granted" or reputed -scientifically speaking- almost like "physiologically unalterable limitations of research" to live with.

A substantial diffidence towards metals and metalloids as an important source of novel agents for medicinal applications is still common. Despite metal-based compounds have been used for centuries in the treatment of several diseases, they have been progressively abandoned mainly because of claims of toxicity.[16, 17]
However, it is not black or white, and it should be considered that this "bad reputation" rises from an empirical use, dating back to the period before the advent of modern medicine. In fact, several metal- and metalloid-based drugs are nowadays included in clinical protocols for both therapy and diagnosis, representing an essential resource (e.g. gold and platinum in the treatment of arthritis and solid cancers, arsenic for promyelocytic leukaemia, technetium and gadolinium in PET and MRI imaging techniques). This is possible owing to the advanced knowledge of the chemical profiles and of the interactions and transformations that unfold in the biological milieu, that in turn allow the use of specific ligands or administration protocols capable to manage drawbacks.[2] For instance, the case of gadolinium is emblematic to observe and demonstrate how, the use of appropriate ligands, allows the exploitation of metals in medicine (including the non-essential ones), limiting or abolishing the potential toxic effects. Gadolinium is extremely toxic as a free ion, but when administered in its chelated form (contrast agent) is safe, allowing to increase the quality of the MRI images and thus diagnosis.[18, 19] Accordingly, this "false myth" on the absolute toxicity of exogenous metals is detrimental and should be reappraised.

As highlighted by Casini and co-workers in the preface of the book "Metal-based Anticancer Agents",[20] despite the success of approved metal-based anticancer drugs, discovery programs remain almost exclusively academic. There is a sort of "perceived risks and challenges" associated with their development. Indeed, if on the one hand it cannot be denied that metal-based anticancer drugs are capable of multiple reactions, and their high reactivity implies complex patterns of speciation; on the other hand, these features are certainly extremely important for their application in medicine, contributing to the positive pharmacological effects. Nevertheless, this reactivity makes metal complexes more "difficult to control". Overall, this may contribute to the general preconception on metallodrugs -and more in general metals- as toxic.[20]

Through the choice of proper ligands, the information available on the speciation patterns and the transformation that inorganic drugs undergo in the biological environment, we have the chance and the tools to limit the eventual toxicity associated with metals, conveniently exploiting them for medicinal applications. We should devote efforts to debunking preconceptions, highlighting the importance of the use of inorganic compounds in medicine owing to their chemical versatility and the peculiar features of metals and metalloids, which are not reproducible or replaceable by organic molecules.[2, 11]

In our laboratories, we have hundreds of complexes synthesised as potential anticancer, antiparasitic, and antiviral agents that most probably have been subjected to preliminary assessments and then published. However, for most of them, even if endowed with promising biological profiles, the evaluation has been likely terminated with the first stage. This is the result of a few concomitant factors. Firstly, for all of us, an important goal is to publish our research and thus this event becomes a sort of "endpoint". Also, it is often difficult to select the best candidates based on routine cell studies. The questions are: what is the best/most convenient method to select the most promising complex? What is the reliability and how predictive are *in vitro* experiments? Answering these questions is rather difficult and a single answer is unlikely to exist. Moreover, it is also impossible to initiate all the compounds for animal testing due to both ethical and economic issues.

Additionally, animal experiments are subjected to different legislations in different countries that sometimes are strict and sometimes too permissive. This fragmentation, even provided that the *in vitro* methods are adequate to carefully select the best drug candidates, makes the situations sometimes hard to manage. In some countries, it can take months (or even years) to access *in vivo* tests. This means that -on average- there is a substantial lack of compromise between the necessary (and important) protection of animals and the possibility of conducting experiments that are essential to reach the goal of effectively cure cancer, with benefit for patients.

Moreover, animal experiments are expensive and the diffuse lack of funds and investments, together with the systematic difficulties in updating technologies and equipment, represent further issues.

Owing to these reasons, most of the novel compounds, after the preliminary studies are not subjected to further evaluation, which, nevertheless, might unveil valuable pharmacological properties. Keeping this idea in mind, one might assume that -in this context- even Barnett Rosenberg and Loretta VanCamp might not have discovered the cisplatin's properties. Certainly, this is an impressive consideration in light of the clinical role of this drug.

Also, it should be noted that, based on the current standards required for the development of modern anticancer therapies, and more in general, for all new drugs, cisplatin -most probably- would never be deeply studied due to its *in vitro* performances (e.g. poor selectivity index) and, consequently, never approved from FDA.[21] For sake of clarity, we do not

intend to deprecate the strict body of rules that have been developed over the years in order to ensure safe and effective pharmacological profiles. We would just highlight as those rules, jointly to profoundly mutated attention to the safety and harmlessness of drugs, have led to reduced development of new clinically approved metal-based drugs. Consequently, the result is that the efforts in the synthesis and design of new molecules may have no practical effects, remaining pure exercises in style rather than concrete attempts to solve a global problem. In any case, it is important to point out that, these synthetic efforts are -scientifically speaking- fascinating, stimulating, and fundamental. Accordingly, as chemists, we should be always on the target trying to maximize the practical impact of our work. Creating a chemically beautiful panel of metallodrugs should be not the final aim, rather, the development and selection of effective drugs to be subjected to advanced preclinical and clinical trials should be the final goal.

The combination of all these factors produces a situation in which for thousands of molecules synthesized, only a minimal or even an infinitesimal part is evaluated effectively. Most of them remain in our laboratories, and at best they can be used to publish another paper.

Furthermore, we should always consider that the development of novel drugs expresses in diverse ways and, as well attested by the cases of cisplatin and As_2O_3 (Trisenox®), the aim to be effective against cancer (but even against other diseases) could be reached with structurally and synthetically simple molecules. Also, an easy synthesis may represent an advantage even to attract the interest of pharma companies thus supporting the translation in the clinical practice. In fact, the industry plays a crucial role in the development and marketing of new anticancer drugs. However, production and investment choices of the pharma industries are also related to business reasons that, in most cases, make the economic effort to produce a new drug not appealing if the ameliorations of the pharmacological outcomes are not “outstanding”. To reach this goal, a more efficient development process of metal-based drugs should never forget to move towards patient-oriented treatments. It is nowadays feasible -and maybe mandatory- to consider and integrate the development of a drug in a more extended context combining and connecting the chemical and pharmacological properties with the increasing knowledge on tumour biomarkers, smart drug carriers and so on, for the achievement of an innovative “Personalised Therapy”.[22]

2.1 Metal-based nanostructures for innovative anticancer therapy

Metals can be also exploited for the synthesis of nanostructures for innovative anticancer entities. It is indeed widely recognised the importance of metal-based nanotechnologies in cancer research, as attested by the impact that gold nanoparticles (NPs)-based photothermal therapy (PTT) may have in clinical practice.[23, 24] This approach offers a reliable alternative to conventional chemotherapy and radiotherapy. The pioneering work carried out in this field by Prof. Mostafa A. El-Sayed as well as by several other international groups, have provided the proof of concept that (NPs)-based photothermal therapy may potentially ensure a significant advantage because of the specificity of the treatment itself capable to target the tumour site inducing the cancer cells death through exposure to heat-generating near-infrared (NIR) light.[24] Since the first evidence of the potential suitability of PTT against cancer, advancement in the synthesis of NPs as well as in controlling their shape and size, have represented a further valuable tool in promoting the use of NPs in medicine.[25] Thus, the potential of metallic NPs is exploitable in several fields including drug delivery, imaging, and diagnostics but also against diseases different from cancer.[26] Accordingly, silver NPs are promising to treat bacterial infections even in the case of multidrug resistance,[27, 28] while various metal-based NPs have been developed as antiviral agents;[29] interestingly, in this context, copper-based NPs have been tested as surface coating agent owing to the antiviral properties of this metal against SARS-CoV-2, eventually confirming the role that metals may have against viruses.[30–32]

2.2 Future directions and perspectives

Several metallodrugs are currently administered to patients for both therapy and diagnostic purposes, with remarkable results. The approval of cisplatin in 1978, despite its undeniable success, triggered enormous efforts in search of improved metallodrugs in cancer treatment (Figure 3).

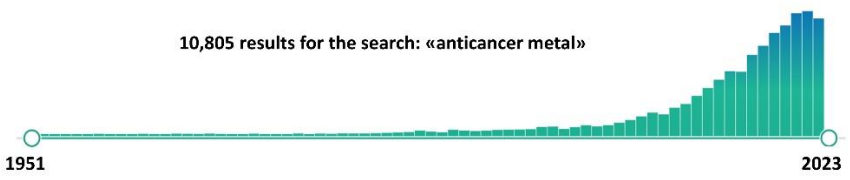

Fig. 3. Results of PubMed.gov search for “anticancer metal”. The graph clearly shows the exponential increase of the interest on development of anticancer metallodrugs, specifically from 1978, the year of approval of cisplatin.

Importantly, these numbers highlight as the success of cisplatin (renewed with the approval of carboplatin, oxaliplatin and Trisenox), did not blocked the search for new inorganic drugs, but rather -as already pointed out- has stimulated new interest. The point of arrival has therefore become a new starting point producing new positive results. This evidence should be the driving force for our future objectives. Emerging needs are higher selectivity and lower side effects. These claims from the clinic should be addressed through the application of the innovative approaches/strategies available. In this context, and towards the strategies reported above, it is also desirable to attain improvement in the networks, contacts and partnerships between universities and pharma companies en route to supporting the common aim of new, more effective/faster drug approval protocols.[33] Overall, this point of view wants to stimulate the debate on the above relevant aspects on which we can act to improve the discovery process of inorganic anticancer drugs. This may help to limit the risk to add insult to injury that, the "new cisplatin", is already waiting for us, ready and characterized, in some of our laboratories... without our knowledge.

3. Point/Counterpoint Commentary

3.1 The challenge to find new anticancer candidates, both inorganic and organic molecules. Common features and divergences

Point. We have outlined numerous factors that have contributed to prevent the approval of new inorganic drugs at a faster pace in the last decades. In fact, though the thousands of new complexes that have been synthesized worldwide, and despite a significant number of them showed promising preclinical activity profiles, the approval of new entities is still a very slow process. However, it could be pointed out that, these concepts, might be largely applicable also to purely organic compounds. Accordingly, drug development could be a long road in all cases and most of the attempts do not produce clinical impact.

Counterpoint. Basically, chemists (either organic or inorganic) face similar difficulties in developing inorganic and organic drugs. In other words, translation into the clinics is always a hard and time-consuming challenge implying enormous economic and scientific efforts. However, it is particularly important to consider numbers. Sadler et al., have recently estimated that less than 50 inorganic therapeutic drugs are currently approved worldwide for different indications,[34] and only three out of them are anticancer metallodrugs (i.e. cisplatin, carboplatin and oxaliplatin). The list can be expanded up to four if we include the As-based antileukemic agent Trisenox (this count excluding radioactive therapeutic metallodrugs, *vide infra*). The same authors also pointed out that overall, the total number of approved metallodrugs corresponds about to 50% of that of kinase inhibitors, i.e. a single class of organic drugs.[34] This simple statistic is representative of a substantial gap, in fact a remarkable difference between the number of commercially available inorganic and organic drugs does exist. Hence, looking at the FDA new molecular entities approved for application in oncology in the period 2010-2019, the situation is even clearer. In this period, a total of 65 new molecules was approved, and the only metal-based compound approved was radium-223 dichloride which is intravenously administered in prostate cancer patients.[35] This means that inorganic drugs represent the 1.5% of new molecular entities approved, while pure organic molecules account for >98% of the total. It follows that, for metallodrugs, there are some aspects making the entire process of development and subsequent approval more difficult. The reasons behind this evidence are not necessarily independent and in part have been outlined in this manuscript. Among them, the intrinsic high reactivity of metals/metalloid and the consequent existence of multiple interactions with various biological substrates that needs to be investigated for drug optimization. In turn, this, over the years, has perhaps contributed to consider the metals as intrinsically toxic independently on the administered form/formulation. Furthermore, another key point to bear in mind is that, although Lipinski's rules are helpful to identify active and bioavailable organic drugs,[36, 37] these rules, include specific requirements such as a molecular weight <500 Da, that cannot be straightforwardly applied to metallodrugs. However, beyond the non-exhaustive (neither exclusive) hypothesis here provided, it is desirable deeper and more careful debate and discussion within the inorganic chemists' community.

3.2 Some inorganic drugs clinically used in the past have been supplanted completely or in part in favour of organic molecules

Point. Among various examples to which we can refer, the cases of auranofin and As-based compounds are certainly indicative. Auranofin itself, despite still in clinic, is no longer a first-line choice to treat rheumatoid arthritis owing to some adverse effects that have been reported. In fact, the first-line treatment is nowadays usually represented by methotrexate.[38] Analogously, since decades the treatment of syphilis is based on the use of penicillin being arsenic compounds supplanted in clinical practice.

Counterpoint. Certainly, the story of medicine tells us that a very toxic molecule is far less toxic (and even effective against a disease!) when managed in the proper manner. In some way, we can state that this is substantially implicit in

the drug development process itself. The two-fold requirement of effectiveness and reasonable tolerability is indeed essential and only when these two aspects converge, we obtain “the drug”. This is the case of cisplatin that before the approval by FDA has requested the development of strict hyperhydration regimens to overcome its nephrotoxicity.[39–41] Furthermore, the cisplatin cytotoxicity has been “controlled” over time through the development of its analogues carboplatin and oxaliplatin that has substantially been designed as cisplatin-like molecules.[42, 43] From this point of view, the optimization, exclusively regards structural modifications of the parent molecule. The point is -maybe- that the most notable factor making a molecule synthesised in our laboratory an anticancer metallodrug is the real value, i.e. the cost-benefit balance. The contingency situations can be favourable or not. Again, the story of cisplatin approval teaches us that was the perseverance of Dr Cvitkovic and colleagues in developing the first hydration protocol for preventing renal failure that literally allowed the clinical use of the drug.[41] Nowadays, we know that, in this latter case ,the cost-benefit balance has been extremely positive. Moving from platinum to gold-based substance, the paradigm is auranofin (Figure 4).

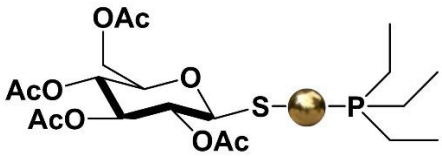

Fig. 4. Chemical structures of auranofin. The gold sphere represents the Au(I) atom linearly coordinated to the phosphine and thioglucose tetraacetate ligands.

This drug entered several clinical trials as an anticancer agent (see clinicaltrials.gov website) for the treatment of ovarian and lung cancer or Chronic Lymphocytic Leukemia (CLL). Thus, despite auranofin has been largely replaced by other and more effective and tolerable organic drugs in the treatment of arthritis, yet, as anticancer agent, the cost-benefit balance could be far better compared with other tested drugs. In fact, we know that in comparison with several approved inorganic or organic antineoplastic agents, it is far more tolerable. Additionally, it is orally administrable, and furthermore, the clinical experience gained may allow to prevent several of the potential drawbacks when administered in cancer patients.[44] Thus, auranofin reprofiling programs may have a huge impact and they are worthy of deep consideration because the cost-benefit balance might be very advantageous. Last but not least, it is important to observe that -as stated above- arsenic has been withdrawn from the clinic in favour of penicillin for treating syphilis, owing to its high toxic profile; nevertheless, As(III) in the form of the corresponding oxide has been approved in 2000 for the treatment (even as first-line drug) in the treatment of acute promyelocytic leukemia (APL). Its approval had an impact for which the cost-benefit balance is uncountable.[45] The key aspect of the use of As is overall the capability of managing the administered form, to limit the drawbacks and benefiting from its anticancer effects.

Author Contributions

DC, AP and TM conceived the idea of writing this paper, however, this work is the result of discussions and reflections by all the authors. All the authors contributed to the writing and revision.

Conflicts of interest

There are no conflicts to declare.

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