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Development of trackable metal-based drugs: new generation of therapeutic agents

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Benoît Bertrand,[a, b, §] Pierre-Emmanuel Doulain,[a, §] Christine Goze,*[, a] and Ewen Bodio*[, a]

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In medicinal chemistry, the aim is not only to conceive ever more efficient molecules, but also to understand their mechanism of action. In very recent years, a new promising strategy was developed to tackle this issue: the conception of trackable therapeutic agents. Metal-based drugs are ideally to exploit this expanding area of research.

Introduction

Metal-based compounds have a long tradition in medicine. Gold has been reported in medical use in the written history of many cultures, as well as silver for its antimicrobial properties. Numerous archaeological records indicate that gold's medicinal history dates back far into pre-history.[1] The field of medicinal metal-based chemistry started at the beginning of the 20th century with arsenic-based compound Salvarsan for the treatment of syphilis.[2] Since then, this research area has developed, with metal-based compounds now widely used as treatments for several diseases such as stomach ulcers (bismuth),[3] diabetes (vanadium),[4] rheumatoid arthritis (gold),[5] cancer (platinum)[6]… Presently, cisplatin and platinum derivatives are still used in more than 50% of anticancer chemotherapeutic cocktails.[7] Nevertheless, drugs which are currently used in clinic are often not ideal: they present heavy side effects and/or a lack of efficiency, and can induce some resistance phenomena.

Researchers have tried to overcome these problems by increasing the development of novel metal complexes, leading to some promising results, particularly with gold and ruthenium derivatives.[8] However, most of these new complexes did not passed clinical trial due to their low efficiency *in vivo* and lack of understanding of their mechanism of action. This last issue could be tackled by accumulating data from numerous biological experiments, but one more elegant method is to facilitate tracking of the therapeutic compounds. This consists of tethering an imaging probe to the therapeutic moiety, which in turn results in a new class of compounds. These are commonly called "theranostics" or "theragnostic,[9] whichthe definition is in constant evolution. The Funkhouser's original theranostic definition focused on imaging tools which help to establish a diagnosis.[10] Then, it evolved to include radionuclides matched pairs, aconcept originating more than twenty years ago with the seminal work of Maecke and coworkers.[10] It consists of using two nuclides of the same element, one for imaging, the other one for therapy.[11,12] Several matched pairs have been proposed such as ^{44}Sc/^{47}Sc, ^{64}Cu/^{67}Cu, ^{86}Y/^{90}Y…[40] Today, the definition of theranostics moved to define a single molecule, which enables both diagnosis and therapy. More and more chemists also used this term for a molecule, which displayed both imaging and therapy modalities, even if such a molecule needed a vector moiety to help establish a diagnosis. Compounds corresponding to this last definition can also be called trackable therapeutic agents. This article will be limited to trackable therapeutic agents, with a focus on metal-based drugs.

Trackable therapeutic agents display numerous interests, which is reflected by the increasing number of recent publications on this topic. The main strength of this new class of drugs is the ability to track the compounds in real time without altering the treated cell/animal, which results in reduced costs (fewer animals, less time). Application of trackable therapeutic agents allows rapidcomparison of the targets, pharmacokinetics of analogues and the efficiency of different biovectors. This strategy can be generalized to any drug, which can be organic, biologic, or nano but this article will focus only on small single molecule metal-based therapeutic agents. Metal-based drugs, refers to organometallic or coordination complexes displaying therapeutic properties with the exception of radiometals, whose biological effect come from their emitted radiation.

Concerning the development of metal-based theranostic agents, the main strategy consists of attaching an imaging probe, which can be an organic fluorophore, a luminescent complex, or a radioisotope to the therapeutic metal-based centre. As for the development of bimodal imaging agents, an important consideration when conceiving a theranostic compound is the compatibility in term of concentration of the two modalities. For example, it is complicated to develop a drug displaying submicromolar IC_{50} values and a MRI probe with a millimolar sensitivity (this combination – molecular theranostic/MRI – is possible if the probe and the therapeutic agent are efficient at a similar concentration as reported by Guo and coworkers[11]).

These systems can be optimized by tethering a vector to improve the targeting and to approach the more classical definition of theranostics. Another evolution is the recent development of smart trackable compounds: these molecules bring additional information(s) on the mechanism of action of the drug, and enable deeper understanding of the biological behaviour and stability of the new developed therapeutics.

This article will report the advances made in the field, the latest trends and the evolutions of these trackable metal-based therapeutic agents.

"Metal-based drugs tracked by optical imaging: optical theranostics"

This class of trackable metal-based drugs is the most developed due to the ease of handling luminophores when compared to radionuclides. Moreover, optical imaging plays a crucial role, because it enables *in vitro* visualization of the behaviour and the cellular targets of the compounds, therefore facilitating the understanding of the *in cellulo* modifications and localization of the drugs. However, even if fluorescence is well adapted for in vitro optical imaging, clinical applications are unfortunately more limited due to their poor penetrability in the tissues.

Organic fluorophores. From organic fluorophores to inorganic luminescent complexes, the panel of probes, which can be attached to the therapeutic metal complexes is very large. Nevertheless, introducing an organic fluorophore is the most common method in the design of trackable metal-based therapeutic agents. The main reason for this, is the commercial availability of most of these fluorophores and their ease to be modified. For example, polyaryle derivatives such as anthracene or pyrene were investigated (Figure 1, compounds 1 and 2),[15, 16] most frequently, they are introduced by alkylation of one ligand of the complex. Their photophysical properties are not optimal, *i.e.* fluorescence in the UV region, low quantum yields, and a high lipophilicity. Nevertheless, some interesting studies have been performed with these fluorophores; for example, Reedijk and coworkers used an anthracenyle group to investigate the influence of glutathione on the sequestration of a platinum derivative in lysosomes.[17] Other fluorophores such as coumarin,[18] BODIPY[19] or porphyrin[15c, 21] were also investigated (Figure 1, compounds 3-5). They display numerous advantages, such as high quantum yields,[18] good photochemical and chemical stabilities, and tuneable optical properties (especially for BODIPY derivatives). However, they often require several synthetic steps and are quite lipophilic, resulting in a poor water solubility of the resulting compounds. The phenomenon is particularly noticeable for porphyrin derivatives, and requires relevant modifications to tackle this issue (Figure 1).[15c, 21a]

In addition to the previous examples, several other fluorophores have been reported, such as anthraquinone (Figure 1 compound 6), benzodiazole, curcumin, naphtalimide (Figure 1, compound 7) andphenanthroline derivatives.[23b, 24]

The panel of fluorophores is therefore very large, but one important point to be considered when choosing the fluorophore is that some quenching of the probe can occur, depending on the metal centre, *via* photoinduced electron transfer mechanisms or desexcitation *via* triplet excited states.[25] For example, gold(III), Ru(II), Os(II), or Cu(II) often induce a significant quench of the fluorescence.[19, 21b, 25] The opposite can be observed for other metals such as Au(I), which did not interfere with the probes (such as coumarin, BODIPY...), therefore preserving their fluorescence properties.

Luminescent metal complexes. In addition to organic fluorophores, some luminescent metal complexes, such as trisbipyridine ruthenium complexes (Figure 2, compound 8)[26] or metalated porphyrins (Figure 2, compound 9)[21] were also coupled to the therapeutic metal moiety, resulting in bimetallic compounds.

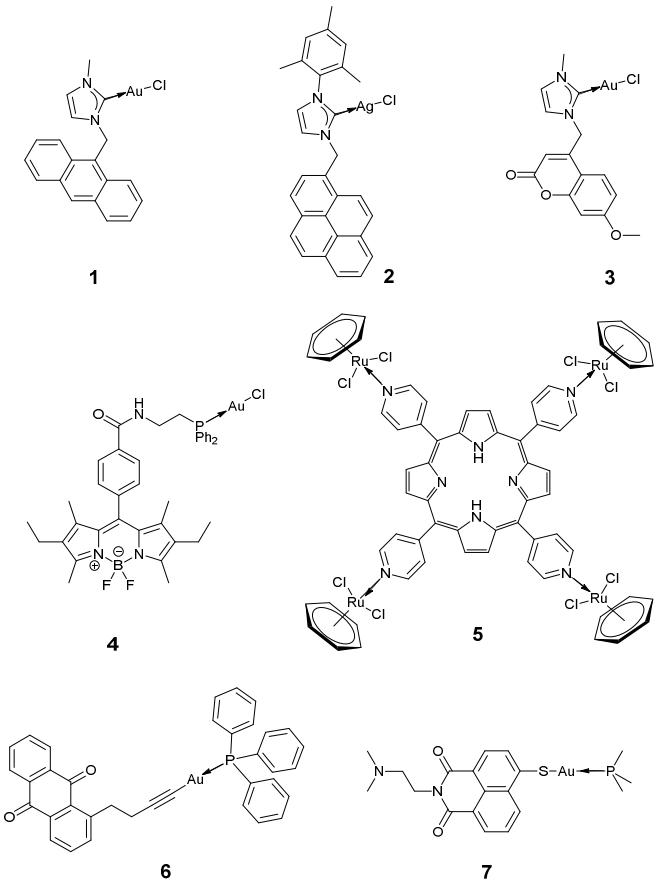

Figure 1: Examples of optical theranostics.[15a, 16, 18a, 19, 15c, 23]

The synthesis of these bimetallic complexes is more difficult than for theranostics displaying an organic fluorophore. It is due to the possible incompatibility between the two complexes, as illustrated by one of our previous studies.[27] Three main strategies can therefore be envisioned in order to synthesize such compounds. Firstly each complex can be synthesized separately and then coupled in a final step. It requires a sufficient stability of the two complexes, to prevent any degradation or ligand exchange and an excellent yield of the coupling reaction to avoid any complicated purification step. Secondly another strategy consists in designing a bifunctional

chelating agent, which can selectively bind one metal on a specific chelating site and the other one on the second ligand moiety. It works well with very different metal centres (*e.g.* early-late)[29] but it can become tricky when the metal atoms are similar (e.g. late-late).[30] The last main strategy consists in a stepwise synthesis: synthesis of one metal complex, construction of the second chelating moiety, and then complexation of the second metal. In this case the first complex needs to be very stable.[31]

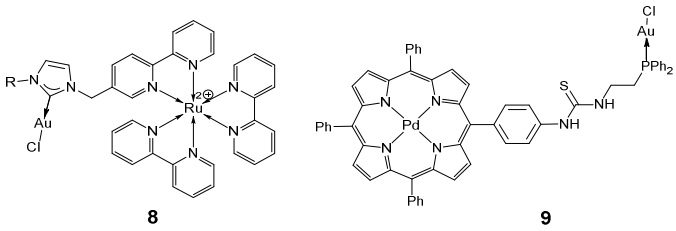

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Figure 2: Examples of theranostics displaying a metal-based luminescent probe.[26, 21a]

It is worth noting that some biologically relevant metal complexes are luminescent by themselves. Among these complexes, are Pt(II) and Au(III) NHC,[40] or Au(III), Pt(II) and Pd(II) iminophosphorane complexes (Figure 3).[32]

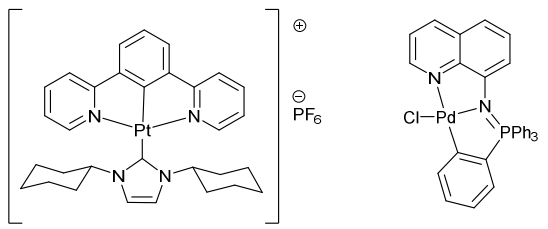

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Figure 3: Examples of luminescent theranostics where the metal plays both the role of the probe and of the therapeutic moiety.[31b, 32]

Finally, a "biologically active" fluorophore can be added to the metal centre, which further increases the therapeutic potential of the resulting systems. Pope[33] and Ott[23a,34] obtained very promising results with systems based on a naphtalimide fluorophore, which presents angiogenic properties, and was linked to a gold(I) centre (Figure 1, compound 7). Porphyrin derivatives can also be considered as biologically active, since they can be used for PhotoDynamicTherapy (PDT).[35] Another advantage of porphyrins is their ability to strongly chelate copper, which enables the design of probes which can be tracked by either optical or PET imaging (when chelating ^{64}Cu).[36] In addition to porphyrins, other luminescent complexes, which present PDT properties were also studied, such as Re(I) or Ir(III) polypyridine derivatives.[37]

The main use of the probe is to check if the drug entered the cell, and to observe its localization. However it is sometimes also applied to define targets of the drug, to evaluate its uptake and to provide insight in the comprehension of its mechanism of action. Moreover, in contrast to ICP-MS measurements, which is a destructive technic, trackable therapeutic agents can be imaged in real time.

Most of the developed systems are perfectly adapted for *in vitro* investigations, but some further efforts are needed in order to translate the studies to *in vivo* preclinical models (even if nice high-resolution images have been obtained by Weissleder and coworkers)[19b] because of the limitation of optical imaging, due to its low tissue penetration. More specificaly fluorophores that emit in the therapeutic region (between 650 and 900 nm), where light has its maximum depth of penetration in tissues, will have to be used. One emerging and important application of optical imaging in clinics concerns optical guided surgery, and one can imagine the high potential of the theranostics in this field, *i.e.* administrating the chemotherapeutic to patients, followed by precise resection of the remaining diseased tissues using the fluorescence guided surgery.[20]

Metal-based drugs tracked by radionuclear imaging: "radiotheranostics"

Optical imaging is the gold standard technique for *in vitro* investigation, and is well adapted for preclinal imaging and clinical optical-guided surgery. Nevertheless, it is clinically limited due to poor tissue penetration. Changing the fluorophore to a radioelement enables tracking of the resulting compounds *in vivo*, without tissue penetration limitations.

This strategy can be used for radionuclides emitting radiation relevant for both imaging and therapy.[38] For example, ^{177}Lu and ^{153}Sm emit γ photons for SPECT imaging as well as β^- particles for therapy and ^{64}Cu emits β^+ particles for PET imaging and β^- particles for therapy. Radionuclides have also been used in the tracking of organic drugs such as cytotoxic antibodies,[39] glycoconjugates,[40] and toxoids.[41] However, examples of metal-based drugs labelled by a radionuclear probe are extremely rare. A patent published in 2014 described how to label titanocene derivatives with [^{18}F]-fluorine, even though the proof of concept was only performed with [^{19}F]-fluorine.[42]

As noted previously, synthesizing a bifunctionnal chelating agent to complex two metals is particularly challenging. It is even more complicated when one of the metals is radioactive because this complexation should take place as the last step. We succeeded in designing a DOTA-phosphine ligand in which the ruthenium moiety was selectively complexed by the phosphine and the resulting monometallic complex was labelled by [^{153}Sm]-samarium (Figure 4).[27] The radiometal enabled imaging of the biodistribution of such a radiotheranostic on healthy mice.

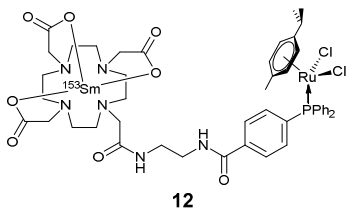

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Figure 4: Example of theranostics displaying a radioisotopic metal-based probe.[27]

How to optimize such systems?

In order to specifically target the diseased tissues, therefore increasing the efficiency of the drugs, while limiting the side effects a biovector can be introduced (which can be for example a small organic molecule, a peptide or an antibody).[43b] Additionally, this strategy can be used for screening a range of vectors in order to evaluate their impact on the uptake and the efficiency of the resulting theranostics.[44, 18] Indeed, the presence of the imaging moiety is ideal in the theranostics: it enables the assessment of the specific and efficient recognition of the target by the vector. Despite the huge interest in this approach, it is surprising that only few studies investigated the introduction of biovectors on metal-based theranostics.[44] This approach will have to be considered for future research, in order to develop more specific and efficient potential future treatments.

Currently, the trend is to develop smart technologies, and therefore to head towards the development of "smart theranostics". What can be considered as "smart theranostics"? We decided to include in this class all theranostics that can bring additional information on the mechanism of action of the drug. For example, the group of Che and coworkers developed a theranostic agent, which additionally enables the detection of the change of oxidation state of the gold centre.[45b] The principle is that when Au(III) is reduced, the bisimidazolylpyridine ligand is released and becomes fluorescent. This property was also used to detect the presence of thiols.[45]. Liu and coworkers also designed some elegant examples of such smart theranostics; one system enabled the detection of the activation of a prodrug using FRET phenomenon[43b] and another allowed the detection of cells entering into apoptosis.[43a] In this last case, the Pt(IV) complex is reduced to a Pt(II) complex (in this case to cisplatin) once in the cytoplasm. It resulted in the release of its apical carboxylate ligands, one of these ligands is a profluorescent molecule. This can be metabolized by an enzyme produced only during apoptosis, yielding to fluorescence of the resulting metabolites.

Liu's studies are particularly interesting for *in vivo* because the probe switches "ON" when the theranostic reaches its target (Figure 5). For our part, we designed a coumarin-phosphine-gold, which enabled us to monitor, by fluorescence, the decomposition of the metal complex and therefore to investigate the stability of such theranostics *in vitro* and in zebrafish larvae .[21b, 25] Such systems are extremely promising for the development of future theranostics, because they give crucial informations on the biological behaviour and evolution of the molecules.

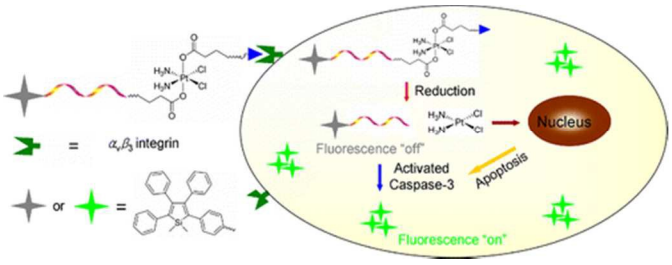

Figure 5: Example of a concept of smart theranostic (figure from Liu and coworkers's study[25a]).

Conclusion

Designing trackable therapeutic metal-based drugs is a very recent field, which is attracting a growing interest. Currently, the research on the subject is still at the early stage, and although systems are still far from clinical applications, the potential of this strategy is clear and the results are very promising. Indeed, this class of theranostics brings crucial information from the cellular level and up to the preclinical *in vivo* level, depending of the type of probes, which is attached to the metal complex.

However, one has to consider that this strategy has to be integrated at the beginning of the study. If a probe is tethered to an optimized drug, it is likely to strongly modify its behaviour. We have demonstrated it by tethering different probe on the same therapeutic moiety: porphyrins led to formation of aggregates which stack on the external cell membranes, coumarin led to accumulation in raft and BODIPY in cytoplasm (Figure 6). Therefore the probe should be a moiety of the original compound and then the optimization process can begin.

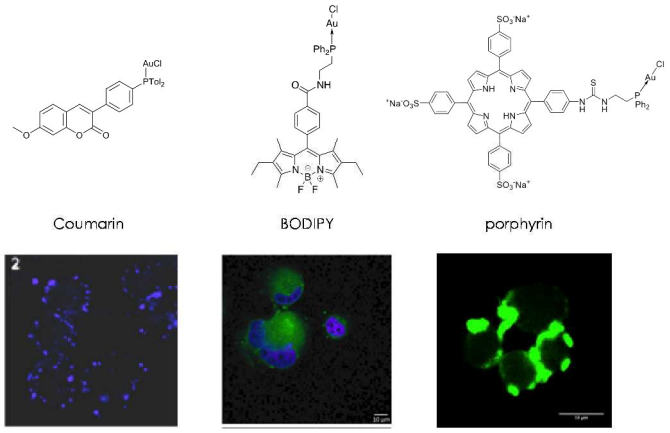

Figure 6: Impact of the probe on the localization of the theranostics in cells (complexes appeared in blue on the picture on the left and in green on the pictures in the middle and on the right).[15b, 26, 17a]

Finally, it is very likely that in the near future, that from just a therapeutic agent bearing simply a probe; trackable therapeutic agents will become increasingly smart, giving valuable information on their metabolism, their oxidation state, the induced overexpression of proteins. Other directions can also be explored, such as vectorization, or multimodal probes, which can be detected with different imaging techniques.

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Notes and references

[a] Institut de Chimie Moléculaire, UMR 6302 CNRS Université de Bourgogne Franche-Comté, 9 avenue A. Savary, 21078 Dijon, France. Christine Goze: Tel: +33 (0)3 80 39 90 43; Email: christine.goze@u-bourgogne.fr.
Ewen Bodio: Tel: +33 (0)3 80 39 60 76; Email: ewen.bodio@u-bourgogne.fr.
[b] School of Chemistry, University of East Anglia, Norwich, NR4 7TJ, UK
[§] the two authors contributed equally to this work

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