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Review

New Use of Metals as Nanosized Radioenhancers

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Abstract. *Since the discovery of cisplatin about 40 years ago, the design of innovative metal-based anticancer drugs is a growing area of research. Transition metal coordination complexes offer potential advantages over the more common organic-based drugs, including a wide range of coordination number and geometries, accessible redox states, tunability of the thermodynamics and kinetics of ligand substitution, as well as a wide structural diversity. Metal-based substances interact with cell molecular targets, affecting biochemical functions resulting in cancer cell destruction. Radionuclides are another way to use metals as anticancer therapy. The metal nucleus of the unstable radionuclide becomes stable by emitting energy. The biological effect in different tissues is obtained by the absorption of this energy from the radiation emitted by the radionuclide, the principal target generally agreed for ionizing radiations being DNA. A new area of clinical research is now emerging using the same experimental metal elements, but in a radically different manner: metals and metal oxides used as crystalline nanosized particles. In this field, man-made functionalized nanoparticles of high electron density and well-defined size and shape offer the possibility of entering cancer cells and depositing high amounts of energy in the tumor only when exposed to ionizing radiations (on/off activity). These nanoparticles, such as hafnium oxide engineered as 50 nm-sized spheres, functionalized with a negative surface (NBTXR3 nanoparticles), have been developed as selective radioenhancers, which represents a breakthrough approach for the local treatment of solid tumors. The properties of NBTXR3 nanoparticles, their chemistry, size, shape and surface charge, have been designed for efficient tumor cell uptake. NBTXR3 brings a physical mode of action, that of radiotherapy, within the cancer cells themselves. Physicochemical characteristics of NBTXR3 have demonstrated a very promising benefit-risk ratio for human healthcare across a broad non-clinical program. NBTXR3 has entered clinical development in therapy of advanced soft tissue sarcomas and head and neck cancer.*

The local treatment of solid tumors is the oldest therapy modality for cancer. Whether the objectives of treatment are cure or palliation depends on the stage of the specific cancer. Surgery was the first and remains the gold-standard for eradicating these diseases. Innovations for advancing effective surgery of the primary tumor have improved not only tumorectomy but, importantly, the oncological outcomes and quality of life of patients. Awareness of the patterns of tumor growth and invasion has made possible specific local approaches, where surgery and radiation are the most successful means of treating localized tumors. For each tumor anatomic site, there are specific local criteria that place the patient unequivocally in a determined group, which defines the treatment needed, and the width of the therapeutic window, in particular for radiotherapy.

Radiosensitivity of healthy tissues close to the tumor means that a narrow range of energy dose must be delivered to the malignant cells, whereas other anatomic constraints could have a fundamental role in determining the global prognosis. Radiotherapy has a universal and predictable mode of action, *i.e.* a physical mode of action consisting in the deposit of a dose of energy in tissues. Cancer cell damage is proportional to the energy dose. However, the main limitation of radiotherapy is the lack of spatial control of the deposition of energy, *i.e.* it penetrates the healthy tissues, damages them and renders unfeasible the delivery of an efficient energy dose to the malignant tumor. Given the potential clinical benefit of increasing cancer cell destruction, radiotherapy has been combined with chemical agents, radiosensitizers and radioprotectors in order to improve tumor response and achieve a global cooperation to control the disease (1-8). However, additive effects of efficacy and the 'toxicity independence' principle do not work in many cases (9-13).

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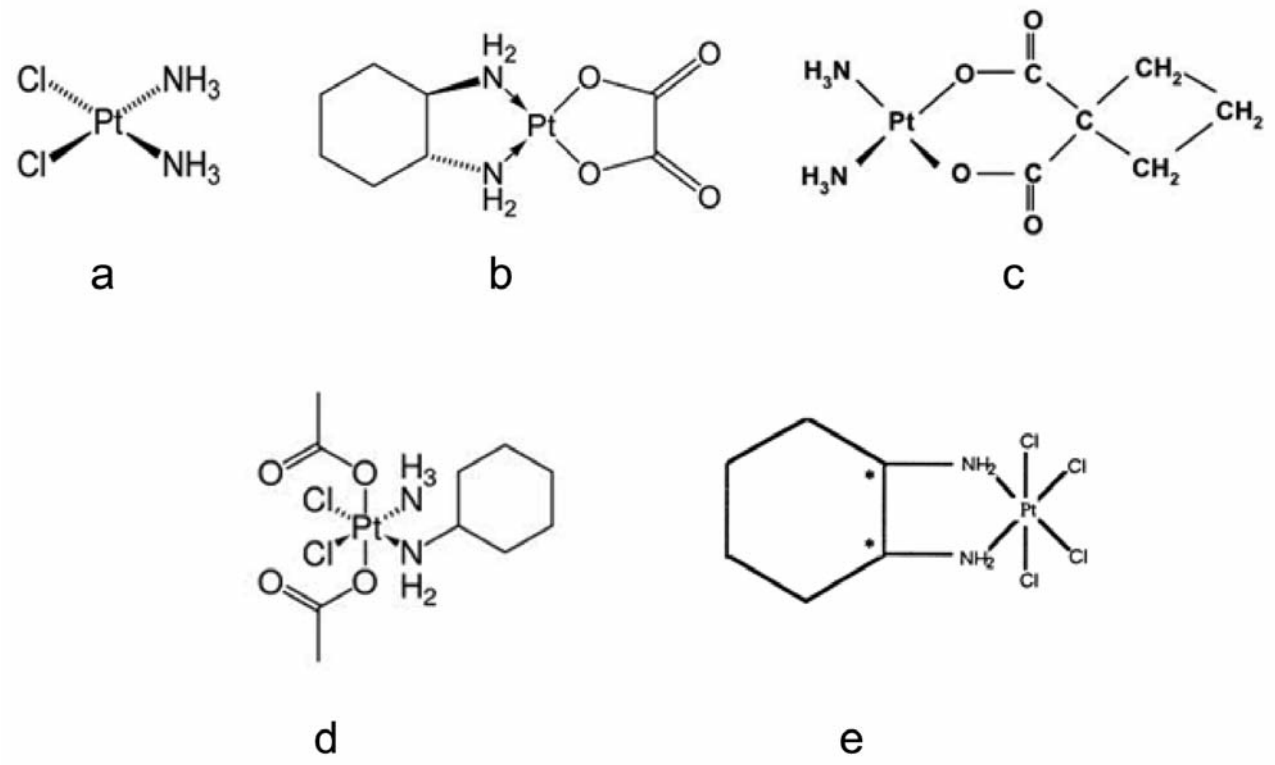

Figure 1. *Structures of platinum complexes. Cisplatin (a), oxaliplatin (b), carboplatin (c), iproplatin (d), and tetraplatin (e).*

For example, products targeting cell molecules are effective when the target is present, accessible, and with some degree of stability, and all these parameters are closely-related to the pharmacokinetics and pharmacogenetics of the treated patient (14). In other words, the complexity of genomics and proteomics, as well as pharmacology, lead to a high degree of unpredictability, which limits the efficiency of clinical radiosensitization.

Above all, the absence of selectivity of the localization of these products, in the tumor *versus* the healthy surrounding tissues and distant organs, is the most important drawback. In fact, all efforts so far have focused on circumventing this limitation using different substances or biologics, as well as technological tools, because the introduction of a greater energy dose, exactly within the tumor structure without passing through surrounding tissues, is not yet feasible (15, 16).

A comprehensive breakthrough for local treatment and radiotherapy is the possibility to depositing a high quantity of energy within the tumor mass, without penetrating healthy tissues or impacting them. Indeed, systemically-administered products have pharmacological actions on different organs and systems, and the use of radionuclides determines continuous action until decay not adaptive to individual cases, in addition to the fact that most modern approaches are administered by systemic routes (radioimmunotherapy) (17).

Nanotechnology has created a new profile of interactions of materials with cell biology. Nanosized agents are taken-up by cells depending on factors such as the size, surface, density, and shape (18-21). They accumulate in the lysosomes and cell division can 'dilute' the concentration of the nanoparticles in the cell (22). The use of metals as a high electron density material tailored at the nanoscale when exposed to radiotherapy is a unique approach that can allow entry to the cell and make feasible the absorption/deposition of a high-energy dose (23-29) within the tumor cell alone. A new area of clinical research is emerging using some metals in a radically different manner: metals and metal oxides used as crystalline nano-products. A well-controlled size makes export of the nanoparticles from the cell negligible, which may allow a single administration of the product because of the reliable intra-tumor availability over the complete radiotherapy program. The optimal design of these anticancer agents should include nano-products that do not change during use (degradation) or generate new components, not only to achieve sustained tumor availability, but also to ensure the concept of local intervention in oncology practice.

This short review focuses on metal elements used as oncology therapies. It highlights a breakthrough in anticancer product design for the local treatment of tumors: metal-based

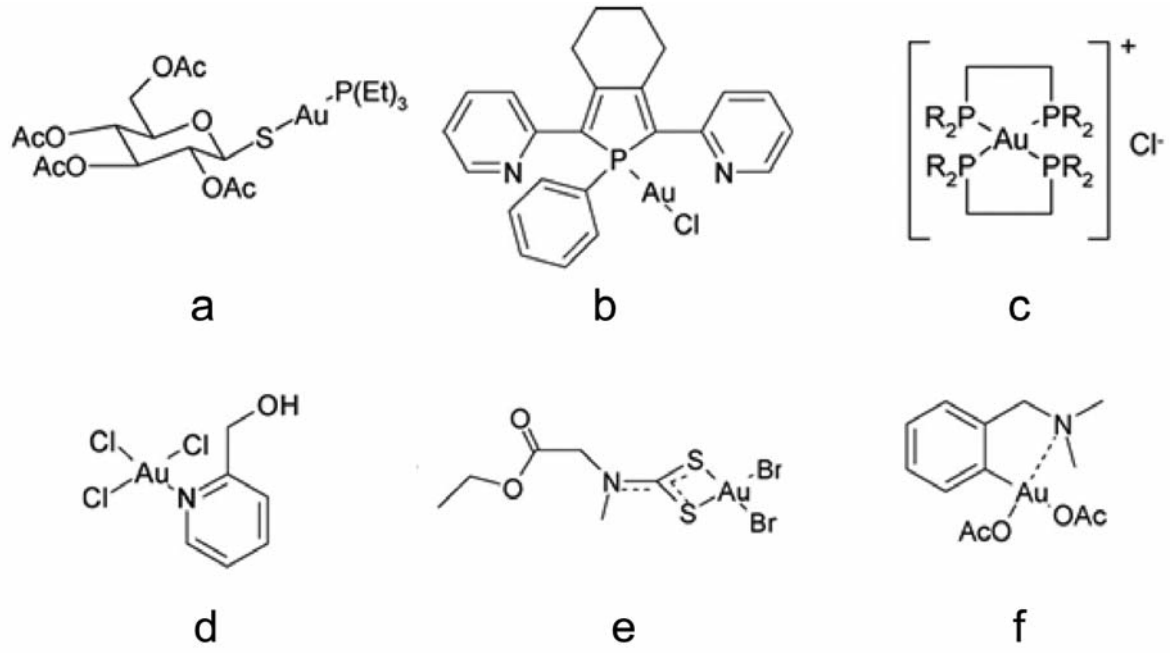

Figure 2. *Structures of gold complexes. Auranofin (a), gold phosphole complexes (GoPI) (b), [Au(dppe)$_2$]C l (c), AuCl$_3$(Hpm) (d) [(ESDT)AuBr$_2$] (e) and [Au(acetate)$_2$(damp)] (f).*

nanosized agents, spatial and time-controlled deposition of energy, and precise deposition at the tumor site when exposed to ionizing radiation.

These nanosized agents could bring a significant increase of the therapeutic index of radiotherapy to patients, acting as more potent cancer cell killers and ultimately allowing lower radiation doses to healthy tissues.

Metals as Anticancer Agents

Organic compounds constitute the majority of anticancer drugs currently used in the clinic. Meanwhile, the inorganic world has contributed with powerful products to treat different types of cancer. Platinum, gold and ruthenium are among the most commonly used metal elements, forming transition metal complexes addressing different subcellular targets within the cell. These complexes have accessible redox states and 'tunability' of the thermodynamics and kinetics of ligand substitution, aiming to modulate the therapeutic activity of metal-based anticancer drugs (30-33). A number of platinum-based agents have demonstrated meaningful clinical benefit, including the prolongation of survival for some groups of patients with cancer. They have been used for the inhibition of malignant cell proliferation; in systemic use, platinum compounds have been leaders of the local treatment of cancer due to their sensitization of solid tumor when further exposed to radiation therapy (34).

Platinum. Platinum has 2+ and 4+ oxidation states. According to the hard and soft acids and bases (HSAB) concept, Pt(II) is a soft acid and interacts with soft bases such as thiolate, whereas Pt(IV) is a hard acid and interacts with hard bases such as hydroxide. The most well-known complex of Pt(II) is cisplatin (*cis*-[$PtCl_2(NH3)_2$] used against a wide variety of solid tumors (Figure 1a). Inside the cell, where a low chloride environment exists, the chloride ions from cisplatin are substituted by water molecules. The aquated agent is highly reactive toward nucleophilic sites in macromolecules (35). Since thiolate anion has a high affinity for Pt(II) ion, this process is modulated by the level of available molecules with free thiol groups, which capture cisplatin species and prevent them from binding other targets. In some observed mechanisms of resistance to cisplatin, one of the contributing factors is an adaptive increase in the rate of intracellular detoxification mediated by the thiol group of glutathione or metallothioneins (36-39).

Subsequent testing of Pt(II) compounds has led to the design of complexes with the general formula: *cis*-[PtL_2X_2] (where L is ammine or amine and X is a leaving group such as halide or carboxylate). Modifications of the ligand are seen as a way of modulating the kinetic profile of biomolecule interactions. Hence, the reactivity of the compound towards thiol-containing molecules may reduce resistance to cisplatin as well as improve its toxicity profile.

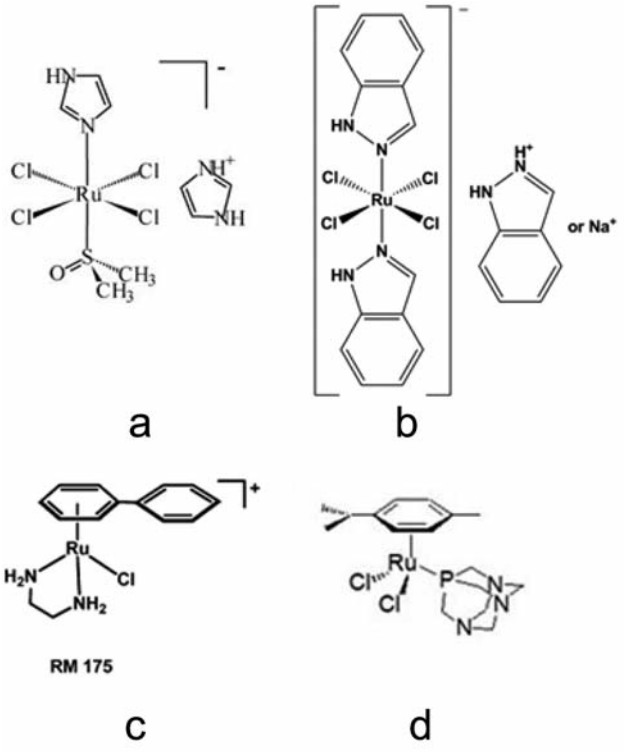

Figure 3. *Structures of ruthenium complexes. Nami-A (a), KP1019 (b), Rm175 (c) and RAPTA-C (d).*

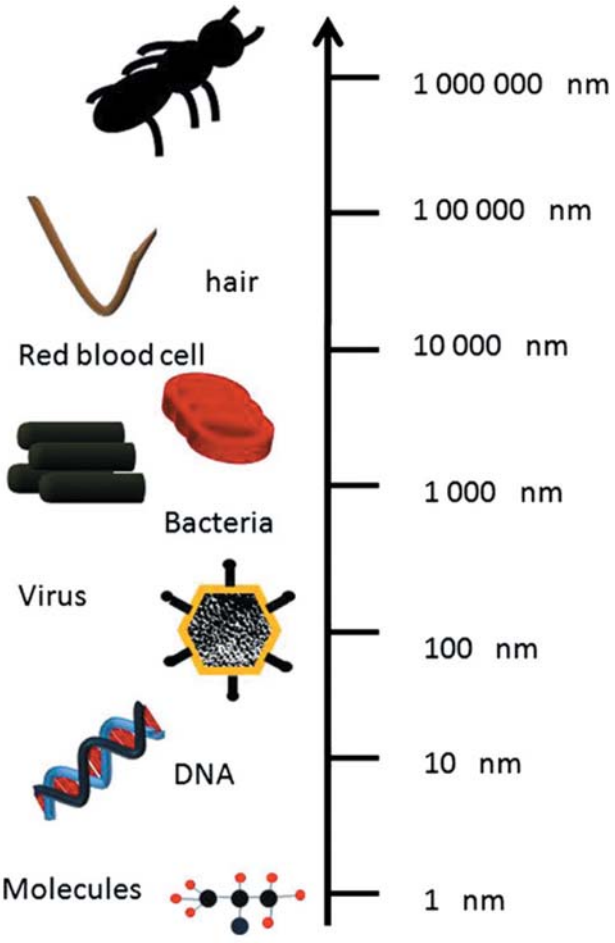

Figure 4. *Scale of size (cited in 69).*

Two additional FDA-approved Pt(II) complexes are carboplatin and oxaliplatin (Figures 1b and c). In general, carboplatin has been found to be less toxic than cisplatin. This may be explained by the increased stability of carboplatin due to its dianionic *bis*carboxylato leaving group, which leads to a slower rate of aquation (40). Oxaliplatin has been shown to be active against some cisplatin-resistant cancer cell lines. Differences in the activities of oxaliplatin and cisplatin may be explained by lower DNA adduct formation by oxaliplatin and the more hydrophobic and bulkier cyclohexanediamine ligand. It induces DNA bending different from that of cisplatin action. In addition, the DNA adducts induced by oxaliplatin are differentially recognized by a number of cellular proteins (41, 42).

Complexes with Pt(IV), 4+ oxidation state, have a higher coordination number than those with Pt(II) and offer the possibility of introducing ligands which may modulate the lipophilicity, stability and reduction potential state of the compound. The Pt(IV) complexes are kinetically more inert than their Pt(II) counterparts and have a lower reactivity with biomolecules. They undergo reduction in the intracellular milieu. During this process, the axial ligands are released and the corresponding anticancer active square planar Pt(II) analogs are formed. The clinical outcomes of therapy with iproplatin and tetraplatin (Figure 1d and e) have been shown to be quite correlated to their reduction properties. It has been found that *in vivo*, a large amount of iproplatin was not reduced, resulting in low toxicity and equally low signs of activity (43). In contrast, tetraplatin was very rapidly reduced, which probably explains the very high toxicity observed with its use (43, 44).

Gold. Only complex species of Au(I) and Au(III) occur in aqueous solution, and they are generally strong oxidizing agents. Au(I) is considered a soft acid and prefers soft bases such as thiolates and soft halides. Au(III) is a borderline cation, which has preference for soft ligands, as well as nitrogen donors. Biological activity of gold compounds, subsequent to ligand exchange reactions, arises from the coordination of gold to specific sites of the target biomolecules. Au(I) and Au(III) compounds are known to target thiol and imidazol groups of proteins in a potent and selective manner. In addition, gold-centered redox reactions are associated with oxidative cell

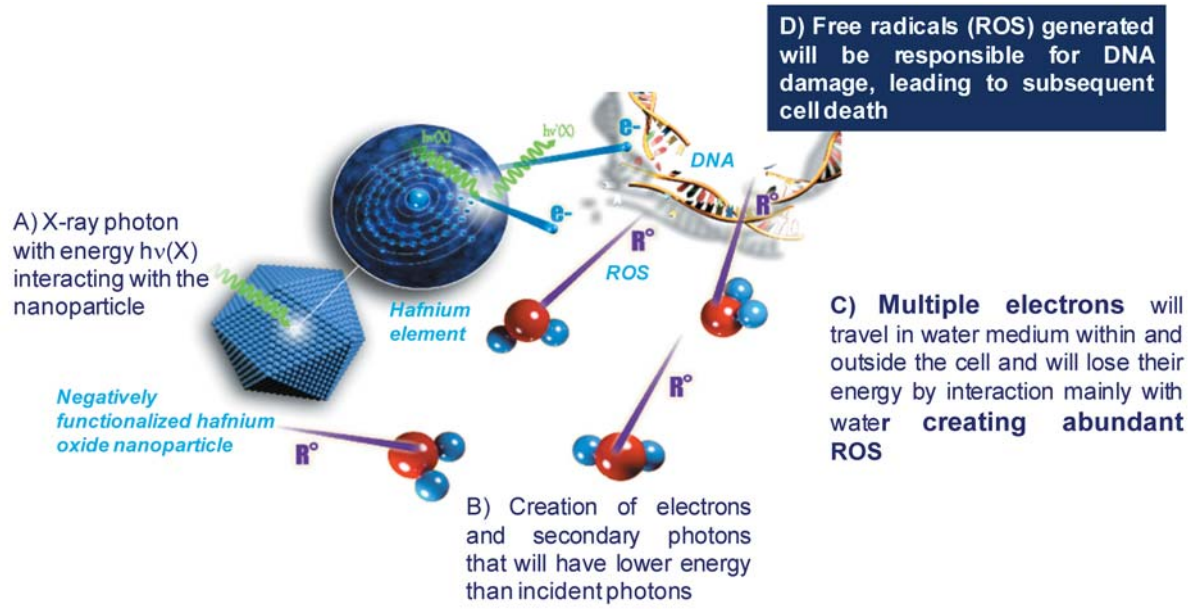

Figure 5. *Mechanism of action of NBTXR3.*

damage (Figure 2) (45-47). Auranofin (2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranosato-*S*-[triethyl-phosphine] gold) is the only gold-based anticancer agent currently tested in human research for two different indications (Figure 2a). A pilot clinical trial for patients with ovarian, peritoneal, or fallopian tube cancer and a phase II study for patients with chronic lymphocytic leukemia, or small lymphocytic or prolymphocytic lymphoma are evaluating the product.

Ruthenium. The most relevant oxidation states of ruthenium compounds in the biological environment are 2+ and 3+. Nami-A and KP1019 (Figure 3a and b) are the two Ru(III) anticancer agents currently in clinical development (48, 49). Comparable to Pt(IV), the principle of 'activation by reduction' is a central hypothesis in the mode of action of many Ru(III) compounds under research. However, the coordination geometry remains widely unchanged upon reduction, but causes labilization and subsequent ligand exchange reactions, such as chloride ion exchange with water molecules in the case of KP1019 (50). Consequently, reduction facilitates and often increases the reactivity with biomolecules and, in some cases, even determines the structure of the formed adducts.

Following the assumption that Ru(II) may be an important component of the final active drug, Ru(II) complexes have also been synthesized. Mono-functional Ru(II)-arene complexes [η^6-arene Ru(en)X]$^+$ (en, ethylenediamine or derivative, X, halide) have been designed and showed a unique binding mode to DNA, inducing different structural distortions in DNA compared to cisplatin effects (Figure 3c). The initial step has been shown to involve the hydrolysis of the Ru-Cl bond, once the complexes are inside the cell, to generate the active compounds (51, 52). This may explain why those complexes were not cross-resistant with cisplatin. Bi-functional Ru(II)-arene complexes [η^6-arene Ru(PTA)X_2] (PTA, 1,3,5-triaza-7-phospha-adamantane) contain two chloride ligands susceptible to hydrolysis (Figure 3d). Interestingly, such complexes also appear to act on molecular targets other than DNA (53).

New pharmaceutical agents containing metal elements represent an attractive approach, offering the possibility of addressing different subcellular targets within the cell. Yet the control of their intracellular activation is still needed; they should reach their target sites and be pharmacologically-active in a more selective manner to avoid unwanted effects. Currently, as for many anticancer compounds, transition metal complexes most often lack spatial and time-controlled therapeutic activity. Consequently, significant toxicity is often associated with the administration of these chemotherapy agents and the dose necessary to shrink the tumor cannot be delivered due to this toxicity profile.

Metals as Radioactive Anticancer Agents

Radionuclides are often metal elements that are radioactive. The nucleus of the unstable radionuclide becomes stable by emitting energy. The biological effect in different tissues is obtained by the absorption of energy from the radiation emitted by the radionuclide. There is a general agreement that cell death is secondary to DNA damage created by

Table I. *Examples of α-particle emitters.*

Radionuclide	Physical half-life	Mean energy emitted per disintegration (MeV)	Range in tissue (μm)
Bi-213	46 min	8.32	75
At-211	7.2 h	6.79	60
Ra-223	11.4 d	5.78	<100
Ac-225	10 d	6.83	61

Table II. *Examples of β-particle emitters.*

Radionuclide	Physical half-life	Mean β energy (KeV)	Maximum range in tissue (mm)
Y-90	64.2 h	937	11
I-131	8 d	190	2
Re-186	3.8 d	349	4.7
Sr-89	50.5 d	583	6.7
Sm-153	1.95 d	224	3.4

Table III. *Examples of auger electron emitters.*

Radionuclide	Average number of electron emitted per decay	Physical half-life
In-111	15	3 d
I-123	11	13.3 h
I-125	20	60.5 d

ionizing radiation (17, 54, 55). Three main types of radioactive elements constitute the anticancer arsenal of the currently used therapeutic radionuclides.

The α-particle emitters have energies ranging from 5 MeV to 9 MeV, with typically a mean range of energy deposition from 40 μm to 100 μm, covering short distances in the biological milieu. These emitters deposit an energy dose (linear energy transfer, LET) between 80 keV/μm and 100 keV/μm. Classical α-particle emitters include bismuth-213, astatin-211 and radium-223 radioactive elements (Table I) (56-59).

The β-particle emitters have energies ranging between 50 keV and 2300 keV. The mean range of energy deposition varies from 0.5 mm to 12 mm. Their LET is about 0.2 keV/μm. Well-known β-particle emitters use yttrium-90, iodine-131, samarium-153 or strontium-89 radioactive elements (Table II) (60-64).

Finally, radionuclides that emit auger electrons have energies ranging between eV and keV. The mean range of energy deposition covers a very short distance, between 2 nm and 500 nm with a corresponding LET between 4 keV/μm and 26 keV/μm (65). Examples of radionuclides that release energy as auger electrons are indium-111 and iodine-125 (Table III) (66, 67).

In each category, there are multiple radionuclides with different ranges of emitted particle radiation in tissues, half-lives and chemistries. This panel of radioactive elements offers attractive possibilities to tailor-make the compound with properties adapted to the characteristics of the tumor. Molecular targeted radionuclides, for example coupled to monoclonal antibodies, should ideally damage only malignant cells. However, part of the limitation for using these anticancer agents arises from inadequate matching of the physical half-life of the radionuclide with their *in vivo* targeting profile. Today, BEXXAR, I-131 tositumomab, and ZEVALIN, Y-90 ibritumomab tiuxetan, are two commercially approved radioimmunotherapy agents which treat indolent B-cell lymphoma and related cancer. Several other products based on the same concept are currently the object of intensive research.

Metals as Nanosized Anticancer Agents

Reviewing Mendeleev's periodic classification of the elements allows one to realize that nanoparticles from metal cations in periods 4, 5, 6 and 7 including the lanthanides and actinides, are potential dose enhancers of radiation delivered to tissues. Those elements possess a high electron density. They are also referred as high Z elements, where Z is the atomic (proton) number of the element. In an atom of neutral charge, the atomic number is also equal to the number of electrons.

A new area of clinical research is emerging using metal elements but in a radically different manner: metals and metal oxides used as crystalline nanosized materials (68, 69).

Nanotechnology has allowed for an unprecedented control of the material world, at the nanoscale, providing the means by which systems and materials can be built with exact specifications and characteristics (70). At this scale, man-made structures typically match the size of natural functional units in living organisms (Figure 4). Nanoparticles are able to gain access to and even to operate within cells (71-73). This allows particles at the nanoscale size to interact with subcellular structures.

Radiation dose deposition within tissues is linked to their ability to absorb/interact with incoming X-rays. This absorption depends on electron density (mainly water molecules in the case of tissues), and the energy used. Introduction of a material with high electron density in the X-ray pathway can increase absorption as compared to water alone (23-29). High electron density nanomaterials can thus bring greater efficacy, based on a well-known mechanism of

action, that of radiotherapy. The presence of these nanoparticles within the cell may create an unprecedented situation considering their localization and impact on the subcellular organelles. Chemical composition and structure of nanoparticles are essential attributes controlling the interactions between nanoparticles and ionizing radiation (74). Their characteristics, size and shape, as well as surface properties, will affect the interactions of nanoparticles with biological systems (18-21, 75). Thus, the design of nanoparticles as true radioenhancers requires the control of their main properties, including the surface functionalization, which ultimately constitutes the interface for interactions with biological surfaces. Furthermore, determining the spatial (within the tumor structure) and time selectivity for radioenhancement (when the ionizing radiation beam is on) have become feasible using these nanotechnology metals. Specifically, only high electron density elements assembled in a well-defined manner at the nanometer scale can absorb/interact with ionizing radiation at the subcellular level, and in this way, open the therapeutic window for radiotherapy in an unprecedented manner. Contrary to radionuclides and chemotherapy agents, which lack the spatial and time control of therapeutic activity, the use of nanosized products administered directly in the tumor may achieve the paradigm of local treatment of solid tumors.

Metal Nanoparticles. Synthesized high electron density metallic nanoparticles include noble or precious metals, such as Au and Pt, and less extensively Ru. The reduction of metallic salts in solution is an interesting route for the synthesis of metallic nanoparticles, involving a large variety of salts and reducing agents. Highly electropositive metals, such as Au, Pt and Ru, react readily with mild reducing agents, while more electronegative metals (typically Fe, Co and Ni) need strong reducing agents and have to be manipulated with care because the metallic nanoparticles are very sensitive to oxidation (70).

Among metal nanoparticles, gold nanoparticles are widely used for diagnosis as a contrast agent, and in therapy (76-80). They have already demonstrated efficient radioenhancement in non-clinical models when activated by radiotherapy (23, 80-82). Concerning their biodistribution and interactions with the different organs and tissues in animals, some articles have questioned the inert (*i.e.* absence of significant toxicity) behavior of the synthesized gold nanoparticles (83-86). Indeed, gold nanoparticles have a chemically active surface, and strong interactions between their surfaces and protein-thiol domains may occur, leading to protein conformation changes.

Metal Oxide Nanoparticles. The metal oxide nanoparticles represent an interesting alternative to metal nanoparticles for healthcare applications. Well-defined metal oxide nanoparticles using metal cations in an aqueous solution (bottom-up approach) may be obtained by carefully adjusting the parameters of the synthesis such as the acidity, temperature, redox conditions, concentration and ionic strength (70, 87).

Few metal oxide nanoparticles are already on the market (iron oxide) or currently evaluated in oncology clinical trials as a diagnostic compound (silicon oxide), or a therapeutic agent (hafnium oxide) (88, 89).

Our group has developed hafnium oxide nanoparticles (NBTXR3). This chemistry was selected considering the unique balance of the high absorption of energy and the friendly behavior of the surface when interacting with different biological interfaces. Hafnium has a high atomic number, which is crucial for efficient interaction between nanoparticles and ionizing radiation. High electron density nanoparticles of hafnium oxide are expected to have a quite inert behavior in biological media: a low solubility, absence of redox phenomena or electron transfer, and no marked surface acidity (25). These properties have suggested the absence of significant toxicity of NBTXR3 and constitute part of the foundation for its clinical development.

NBTXR3 Nanoparticles Reconciliate Spatial and Time-Controlled Actions. NBTXR3 nanoparticles are hafnium oxide engineered as 50 nm-sized spheres with a homogeneous negative surface. NBTXR3 is a potent radioenhancer with the same mechanism of action of radiotherapy (Figure 5). It has been designed for a single intratumoral injection and to be activated by radiotherapy.

In radiosensitive and radioresistant human tumor xenograft models, from mesenchymal and epithelial cell lines, NBTXR3 nanoparticles exhibited an optimal intratumor bioavailability, with a long permanence within the tumor mass. The nanoparticles were found both in the center and at the periphery of the tumor, within the cancer cells, forming clusters in the cytoplasm. Importantly, the absence of marked leakage from the tumor structure to the surrounding normal tissues has also been demonstrated in all these cancer models (25).

Regarding the safety and tolerance in animals, NBTXR3 not activated and activated by ionizing radiation has a very good profile either for loco-regional or systemic evaluation (25).

In the meantime, marked antitumor efficacy of NBTXR3 activated by ionizing radiation, including significantly prolonged survival, has been demonstrated in a large panel of human cancer xenograft models.

NBTXR3 nanoparticles entered clinical development in 2011, starting its evaluation in patients with advanced soft tissue sarcoma of the extremities. A single intratumoral injection provides the tumor with an adequate dispersion and bioavailability of the nanoparticles over the whole delivery of the radiotherapy program. The absence of NBTXR3 significant leakage to the adjoining healthy tissues and

passage to the systemic circulation was consistent with the findings observed across a non-clinical program and in a phase 0 of comparative oncology for domestic cats (unpublished data). All these results have generally proven NBTXR3 to be efficient and safe. They have opened-up the way for expansion of its clinical development in patients with locally advanced head and neck carcinomas.

Metal Complex, Radionuclide or Nanoparticle Anticancer Agent? Metal elements specifically engineered as nanoparticles constitute an exciting area of clinical research. Indeed, metal or metal oxide nanoparticles may bring well-known physical modes of action within malignant cells and therefore achieve the paradigm of local cancer treatment.

Looking back to Mendeleev's table, a large number of metal elements are already used as anticancer therapeutics. However, the selection of the most appropriate element for the design of a specific type of anticancer agent has to be carefully evaluated, according to the intended use and the ultimate possible benefit.

Typically, gold, platinum and ruthenium elements are well-suited for designing metal complexes with accessible redox state and tunability of the thermodynamic and kinetics of ligand substitution. As such, they represent a family of systemic anticancer compounds which may target various subcellular structures, aiming at damaging malignant cells.

Meanwhile, radioactive metal elements constitute another family of potent anticancer treatments. The selection of radionuclide with specific physical properties needs to be adapted to the characteristics of the tumor. Nevertheless, despite their advances, their use involves global body exposure to ionizing radiation.

As metals are engineered as nanoparticles for a given purpose, the physicochemical properties of the resulting products are of the utmost importance. Beyond the intended function, the chemical composition and structure determine its chemical stability in a given environment. For instance, gold, platinum or ruthenium are stable as metallic nanoparticles. However, their reactive surface may develop unwanted interactions with healthy tissues. These elements as nanoparticle products may not always represent the most appropriate selection when considering the inert behavior and the principle of on/off activity.

In fact, the Mendeleev's table of chemical elements can be seen as a toolbox which has to be carefully visited before designing new metal-based anticancer therapies.

Conclusion

Inorganic chemistry has highly contributed to the treatment of cancer. Metals have been used as compounds based on classical chemistry, such as the platinum family, whose use in oncology has brought significant benefit to patients, including improvement of the survival time. Platinums have been used as systemic therapy and as radiosensitizers. New-generation platinum agents include the combination of numerous chemical modifications. They have been noted to alter the interactions of platinum with subcellular targets, yielding new efficacy findings and safety profiles. More recently, other metals have been identified and are under development, such as Au and Ru. It is now clear that some of these new metal agents target cell molecular structures other than DNA.

In another category, there are multiple metal radioactive elements with different ranges of emitted particle radiation in tissues, half-lives and chemistries. This panel of radionuclides offers attractive possibilities to tailor the properties of the compound to the characteristics of the tumor. However, one limitation for using these anticancer agents arises from inadequate matching of the physical half-life of the radionuclide with their *in vivo*-targeting profile.

Above all, the absence of selectivity of the localization of these products, in the tumor versus the healthy surrounding tissues and distant organs, remains the main drawback. Importantly, this is also the main limitation of radiotherapy, which partially lacks spatial control of energy deposition, damaging healthy tissues and rendering unfeasible the delivery of an efficient dose to the tumor. The circumvention of this limitation has used different substances or biologics because the introduction of a greater energy dose, exactly within the tumor structure without passing through surrounding tissues, is still not feasible.

Nanotechnology now allows for an unprecedented control of the material world, at the nanoscale. At this scale, man-made objects are able to gain access within cells. Moreover, high electron density nanoparticles can efficiently interact with ionizing radiation and increase the absorption of energy as compared to water alone. Introduction in the tumor of these nanoparticles has created an unprecedented situation. Indeed, they absorb/deposit the energy dose exactly in the tumor mass.

In summary, new metal elements are being developed and used for the treatment of cancer. Each of the metallic elements offers specific characteristics due to their intrinsic properties and could be used in relation to their final state: a metal complex versus a radionuclide versus a metal-based nanoparticle product.

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