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New paradigms in nuclear human decorporation using macromolecular systems

Laurane Léost, Florian Lahrouch, Christophe Den Auwer, Christophe Di Giorgio and coworkers.

Abstract Actinides elements (that are all radioactive) are the subject of special attention considering the important amount that has been produced for military and civil applications. They often present a dual toxicity: chemical and radiotoxicological from α and β decay. In case of dissemination during an accidental nuclear event, the consequences of contamination can initiate the vital process. Ingestion, inhalation and then retention in the target organs will occur. Currently, the golden standard of decorporation is DTPA (diethylenetriaminepentaacetic acid) injected intravenously. It presents a strong complexing constant for some actinides but poor chemical specificity and it is only valid for removing actinides from blood, immediately after contamination. Objectives are to explore the design of biocompatible nanoparticles or macromolecules able to release the decorporation agent directly into the target organ. This should constitute a new class of decorporation agents.

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1 Context

Since the discovery of nuclear fission in the middle of the 20th century, actinide elements have been studied continuously. This family of unstable elements, of which uranium and plutonium are the two most famous representatives, has marked the history of science and humanity. Currently uranium and plutonium are strategic resources exploited at an industrial level. Schematically, these two radioactive elements are used for the production of electrical energy and for the manufacture of atomic weapons. The past use of nuclear weapons (atmospheric and submarine tests, Hiroshima and Nagasaki bombs) and industrial nuclear accidents (Chernobyl, and Fukushima mainly) have resulted in significant environmental pollution and human contamination. In the current context, the risk of actinide dispersion is still present, and possible cases of internal contamination may mainly affect nuclear workers or soldiers.

In case of internal contamination, plutonium and uranium can be distributed to organs via the bloodstream. Plutonium (Pu) in its oxidation state +IV under atmospheric conditions is retained mainly by the bones and liver. The soluble forms of Pu(IV) may be taken up by iron proteins while the insoluble forms are supported by the reticuloendothelial system. Uranium (U), on the other hand, is mostly found in its dioxo-cationic form, uranyl $\{UO_2^{2+}\}$ at oxidation state +VI and preferably targets the mineral part of the bone matrix (hydroxyapatite). In summary, skeleton, liver and kidney that are the primary target organs for actinide retention can be damaged by radiotoxicity or chemical toxicity of these elements. The consequences of prolonged contamination are an increased risk of developing leukemia or (bone) cancer. In case of contamination with depleted uranium (^{238}U) kidney dysfunctions may occur.

To promote actinide excretion and limit organ damage, chelating agents have been developed. They are called decorporation agents. At the present time, the calcium salt of diethylenetriamine pentaacetate (CaDTPA) is the standard chelating agent in France for Pu(IV) to promote blood elimination [1, 2]. Sodium bicarbonate, on the other hand, is the only countermeasure employed to favor U(VI) blood excretion and to limit kidney damage in case of acute uranium poisoning [3]. More recently, promising ligands for actinide(IV) and (III) decorporation have been developed based on catecholate (CAM) and hydroxypyridonate (HOPO) attached to spatially suitable molecular backbones [4]. The development strategy for such chelating molecules has long been based on optimizing affinity for actinides, which has allowed the development of chelating agents forming very stable complexes. But this strategy often lacks chemical selectivity with regards to biological cations that show similar chemical properties as actinides. This is the

case of Fe(III) for instance. Also, these molecular strategies for decorporation are of limited efficiency in removing actinides once incorporated in the target organs.

2 A new strategy

An alternative to the molecular strategy would be to enhance organ tropism and prevent accumulation. In that sense, polymeric chelates or nano-chelates may represent a real breakthrough in the actinides decorporation or protecting strategy because of their higher loading capacity (larger abundance of chelating sites per mg of polymer that could enhance uptake rates), but also their indirect vectorization properties correlated to a specific biodistribution into bone, kidney or liver [5]. We are currently exploring the use of phosphonate macromolecules in two systems: polyethyleneimine (PEI) as a polymeric chelator and chitosan (trimethyl chitosan, TMC) as a promising candidate for nanoparticle platforms. This strategy has already been applied to medical applications but never for actinide decorporation. For instance, the use, *in vivo*, of methylphosphonate functionalized polyethyleneimine (PEI-MP) for bone cancer imagery and scintigraphy has been reported [6]. We have proposed the use of PEI-MP for the chelation of Th(IV) and U(VI) in the specific case of bone contamination [7]. TMC on the other hand is biodegradable and therefore presents low toxicity for the human body [8]. We have proposed to develop a polyanionic chelating agent as a cross-linker for structuring the TMC into nanoparticles: the phosphonic analogue of DTPA, diethylenetriamine-pentamethylenephosphonic acid (DTPMP). The polycationic character of this polymer under physiological conditions improves tissue/cell adhesion and permeation, which leads to an increased residence time in biological systems. As a consequence, we have proposed TMC-DTPMP as a good candidate to be used as a drug delivery system for the specific case of lung epithelium [9]. Both systems are schematized in Figure 1.

Uranium in its natural isotopy (called ^{Nat}U) is a weakly radioactive nuclide that is easy to handle in our laboratory. Plutonium, however, is a strong chemical and radiological toxic whatever its isotopy. In this case thorium (Th) may be considered as a plutonium chemical analogue because it is stable at the unique oxidation state +IV and also because the specific activity of ^{232}Th is comparable to that of natural uranium, which makes both of them easy to manipulate in the laboratory. Thorium has frequently been reported to mimic plutonium chemistry [10], although this must always be taken with caution. Thorium is also of interest by itself as the most concentrated natural

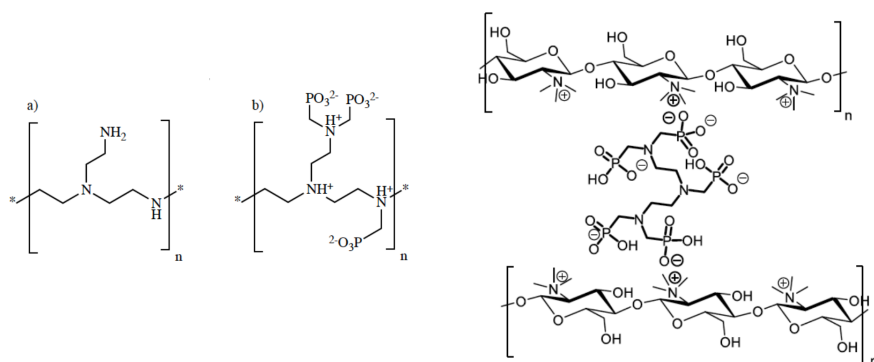


Fig. 1 Left, representation of the monomeric unit of starting PEI (a) and PEI-MP (b) as if functionalization were equal to 100% and with an arbitrary protonation state; right, ionic cross-linking between TMC and DTPMP (with arbitrary protonated states).

actinide in the earth's crust and also because of its use a promising alternative fuel for the next reactor generation. In any case thorium is considered here as a preliminary step before investigating plutonium.

Uptake curves have been obtained with U, Th and each macromolecular system using a microfiltration technique followed by actinide quantification in the filtrate. The curve exhibits a linear increase up to a plateau, meaning that full complexation has occurred. For the U/PEI-MP system for instance, the plateau occurs for a monomer molar ratio of U: PEI-MP around 1.3 - 1.5 [7]. This corresponds to a maximum load comprised between 0.56 and 0.80 mg of uranium (elemental) per milligram of PEI-MP. For Th, the saturation regime that is not as clearly defined but would correspond to a maximum load comprised between 0.15 and 0.20 mg of thorium (elemental) per milligram of PEI-MP. For the Th/TMC-DTPMP system the resulting uptake curves for 10% DTPMP load corresponds to a maximum load of about 0.54 mg of Th(IV) (elemental) per mg of DTPMP [9]. Although different, these values are of the same order and exhibit the chelating capacity of the two platforms to chelate U(VI) and Th(IV) and more generally actinides at both oxidation states +IV and +VI.

In parallel, structural investigations have also been performed on both systems in order to decipher the coordination pattern of the actinide cation. X-ray Absorption Spectroscopy is a chemically selective spectroscopic technique that can probe local atomic arrangement, whatever the physical state of the sample. In order to better describe the actinide complexation site in both PEI-MC and TMC-DTPMP, Extended X-ray Absorption Fine Structure (EXAFS) spectra at the U, Th and Pu L_{III} edge were recorded (this corresponds formally to an electronic transition from 2p to nd states of the ac-

tinide). Measurements were conducted at the European Synchrotron Radiation Facility (ESRF) in Grenoble, at the ROBL beam line. As an example, one may describe the data obtained for uranyl complexed to PEI-MP. The first coordination sphere is composed of the short axial contribution of the two oxo bonds and of the longer equatorial contributions. The best fit metrical parameters for the equatorial uranyl plane are 4.7(2) equatorial oxygen atoms positioned at 2.35 Å (U-O_{eq}). The second coordination sphere is composed by 3.3(5) phosphorous atoms at U...P = 3.77 Å. Both U-O_{eq} and the U...P distances are typical distances for such phosphonate ligands as reported by Kubici *et al.* for a monodentate phosphate (U...O_P = 2.28 Å and U...P = 3.64Å) [11].

Data obtained to date suggest that a macromolecular chelating approach to acting against actinide incorporation in target organs could be a valuable strategy. Studies aiming at determining the optimal molecular weight or size that directly impacts biodistribution and hence the toxicity and long-term kinetics experiments are also required to determine whether or not the actinide complexes could be naturally excreted with time. In a near future, the physical chemical approach presented above in model conditions will have to be complemented with biological assessments.

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