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A NEW PRODUCTION METHOD OF HIGH SPECIFIC ACTIVITY RADIONUCLIDES TOWARDS INNOVATIVE RADIOPHARMACEUTICALS: THE ISOLPHARM PROJECT

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Abstract. *Radionuclides of interest in nuclear medicine are generally produced in cyclotrons or nuclear reactors, with associated issues such as highly enriched target costs and undesired contaminants. The ISOLPHARM project (ISOL technique for radioPHARMaceuticals) explores the feasibility of producing extremely high specific activity β-emitting radionuclides as radiopharmaceutical precursors. This technique is expected to produce radiopharmaceuticals very hardly obtained in standard production facilities. Radioactive isotopes will be obtained from nuclear reactions induced by accelerating 40 MeV protons in a cyclotron to collide on a UC_x target. By means of: high working temperatures and high vacuum conditions, the migration of the radioactive elements towards an ion source, a potential difference up to 40 kV, and a mass separation device, an isobaric beam of desired radionuclides will be produced and implanted on a deposition target. The availability of innovative isotopes can potentially open a new generation of radiopharmaceuticals, based on nuclides never studied so far. Among these, a very promising isotope could be Ag-111, a β- emitter with a half-life (7.45 d), an average β- energy of 360 keV, a tissue penetration of around 1 mm, and a low percentage of γ-emission. The proof of principle studies on Ag-111 production and radiolabeling are currently under investigation in the ISOLPHARM_EIRA project, where both its production and possible application as a radiopharmaceutical precursor will be evaluated in its computational/physics, radiochemistry, and radiobiology tasks. Currently, innovative macromolecules meeting the specific requirements for the chelation and targeted delivery of Ag-111 are being developed, which will be further tested in vitro on 2D and 3D models, as well as in vivo for their pharmacokinetics and therapeutic potential onto xenograft models.*

Keywords: *Ag-111, chelators, cyclotron, deposition targets, radionuclides production, gamma detection, ISOL, radiopharmaceuticals, radiotherapy*

1. INTRODUCTION

One of the biggest challenges in medicine is providing efficient tools for diagnosing and treating a wide range of diseases and tumors. Among the most widely studied and developed tools in nuclear medicine, radiopharmaceuticals, *i.e.*, drugs containing radionuclides delivering a predefined dose of radiation to target tissues for diagnostic or therapeutic purposes, have been extensively and efficiently exploited [1]. High penetrating radiation, such as γ emission, is mainly used for early diagnosis, while particle emission such as α, β^- and Auger electrons, induces cell death. For this reason, particle emission is widely considered a very efficient tool for anticancer therapy. The final goal of radionuclide therapy is to deliver a cytotoxic level of radiation onto a disease site without compromising the healthy tissues [2]. The rapid advance of nuclear medicine has recently led to the marketing authorization of the theranostic pair [^{68}Ga]Ga-DOTATOC (as SomaKit TOC®) and [^{177}Lu]Lu-DOTATATE (as Lutathera®) in 2017 both in Europe and the US [3].

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The physical production of the selected radioactive atoms for nuclear medicine is regarded as one of the main limitations in radiopharmaceutical production. High costs of production, low reaction cross sections, and especially the limited product purity of the current techniques are the main issues to be addressed. Radionuclides can be defined by their specific activity, *i.e.*, the ratio between the radioisotope radioactivity and the total mass of the considered element. If the only present isotope of the selected element is the one of interest, it is defined as carrier-free, whereas if diluted by other isotopes, it is defined as carrier-added. Carrier-free isotopes are then characterized by a very high specific activity, which is desirable for radiopharmaceuticals, especially in the case of radioimmunotherapy (RIT) [4] and peptide receptor radionuclide therapy (PRRT), since cancer cells express only a few surface-specific sites for the drug binding. High specific activity is then required to bind these sites with tumor-seeking agents carrying the radioactive isotope and not the cold isotope, which exerts no therapeutic effect. Most of the radioisotopes currently used in therapeutic radiopharmaceuticals are prepared in nuclear reactors by neutron capture reaction. In order to obtain high specific activity values, high particle fluxes and cross-sections are essential. The need for novel routes for the production of radionuclides for therapy is given importance because of the aging of nuclear reactors in Europe.

In this framework, an innovative and visionary production method is currently under development at the INFN–LNL (Istituto Nazionale di Fisica Nucleare – Laboratori Nazionali di Legnaro) within the multidisciplinary ISOLPHARM project. ISOLPHARM will exploit the Radioactive Ion Beams (RIBs) produced in the future ISOL (Isotope Separation On Line) SPES (Selective Production of Exotic Species) facility [5].

2. The ISOLPHARM method

In the ISOLPHARM method, a nuclear reaction is induced by a 40 MeV energy proton beam accelerated by a cyclotron recently installed and tested at LNL [6]. The beam will collide with a primary target, *e.g.* made of uranium carbide (UC_x), thus inducing nuclear reactions generating neutron-rich radionuclides within the range of 80-160 a.m.u [7]. Proton-rich isotopes may be obtained by simply changing the material of the primary production targets.

The nuclear reactions will reheat the primary target above 2000°C, thus inducing diffusion and effusion of the radionuclides. Under high vacuum conditions (10^{-6} mbar), the radioactive nuclei will evaporate from the target towards an ionizing source, where they will be ionized to the 1+ state passing through a transfer line [8]. The Front-End SPES facility will afterward accelerate the radioactive ions into a RIB [9]. An electromagnetic mass separator will allow the selection of the desired radioisotopic mass, creating the isobaric beam and eliminating the isotopic contaminants. The ultrapure beam will then be collected onto an implantation substrate, which will be further processed to recover the radionuclide for the subsequent radiolabeling [7, 10]. The few remaining isobaric contaminants could be eliminated by chemical separation. The whole production process is summarized in Fig. 1. Proof of concept tests on ionization and deposition of cold isotopes (*i.e.*, stable isotopes of the selected elements) as surrogates of Sr-89, Y-90, I-125/131, Cu-64/67, and Ag-111 were successfully performed at LNL using the SPES Front End (FE) in off-line modality [9-11].

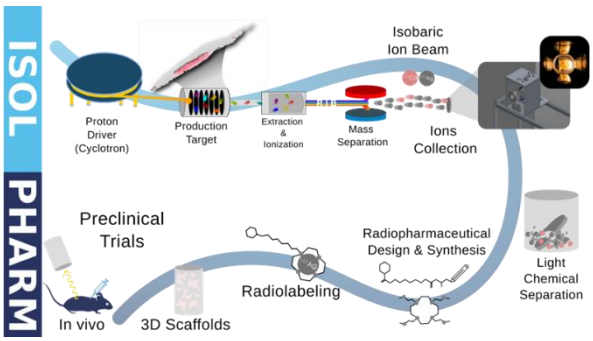

Figure 1. Representation of the ISOLPHARM method: the proton beam starts a nuclear reaction in the primary target. The radionuclides thus obtained are accelerated, selected in mass, collected on a deposition target, then recovered for radiopharmaceutical labeling.

The crucial point in this process is the mass separation step, which allows the selection of the desired isotopes, leading to the generation of isobaric beams. Such beams can be collected to obtain medical radionuclides, as the specific elements of interest are provided with an extremely high specific activity. Moreover, the same production target can be employed to harvest a set of isotopes by simply changing the mass separator settings and switching to a new deposition target, leading to high flexibility. In addition, the proposed method will bring a low environmental and social impact since nuclear waste will be highly reduced compared to the production in nuclear reactors. As proof of the proposed innovation, this method was recognized with an international INFN patent [12].

ISOLPHARM will mainly deal with both fundamental aspects of the research in the field of radiopharmaceuticals: the isotope production with the ISOL technique, and the development of novel radioPHARMaceuticals and their labeling with the produced nuclei, after the radionuclide purification.

3. The ISOLPHARM project: silver-111 and EIRA

The ISOLPHARM method will not only be an ideal alternative production method for highly pure radionuclides but also will provide radionuclides hardly producible with traditional methods. Once a proper production target is defined, the ISOL technique can make carrier-free isotopes available from many regions of the nuclide chart. Among these nuclides, Ag-111 could be a promising radionuclide for internal radiotherapy. It is a β^- emitter with a medium half-life (7.45 d), convenient emission energy (average β^- energy 360 keV), medium tissue penetration (~1 mm), and a low percentage (~6%) of associated γ-emission [2]. These features make this radionuclide a promising novel candidate for radiotherapy; moreover, since its use has been very little investigated, the low associated

γ radiation enables its tracing and investigation in real-time throughout the preclinical and clinical studies, as in the case of Lu-177. Ag-111 can be produced in carrier-free form only when a costly Pd-110 enriched target is irradiated in a nuclear reactor [13]. Its proof-of-concept production in a highly pure form with the ISOL technique and its targeted delivery for medicine are currently investigated within the ISOLPHARM project. In the SPES UC_x target, after 5 days of irradiation with a 40 MeV 200 μA beam, more than 80 GBq could be produced [11]. Among the isobaric contaminants, only the stable Cd-111 isotope should be chemically separated from Ag-111 [14]. From the first promising results obtained in the ISOLPHARM_Ag experiment [11], another experiment was funded to further explore the feasibility of Ag-111 production and efficient administration to patients. To this extent, ISOLPHARM_EIRA (Experiment on Interdisciplinary research on Radioactive Ag) was developed by branching the research into three main areas: physics, radiochemistry, and biology.

The physics task (Task 1) aims to improve the production of Ag-111 with the ISOL method at LNL-SPES. While the facility is under development and optimization, the radionuclide is temporarily produced in the TRIGA reactor in Pavia, by activation of a Pd-110 enriched target, enabling the preliminary studies with Ag-111 which will be performed in the next years. The radiochemistry task (Task 2) aims to synthesize and characterize chelators, linkers, targeting agents, and radioisotope purification for innovative radiopharmaceuticals. Different *in vitro* models were selected in the biology task (Task 3) to evaluate the best radiopharmaceutical precursor for preliminary *in vivo* studies (Fig. 2).

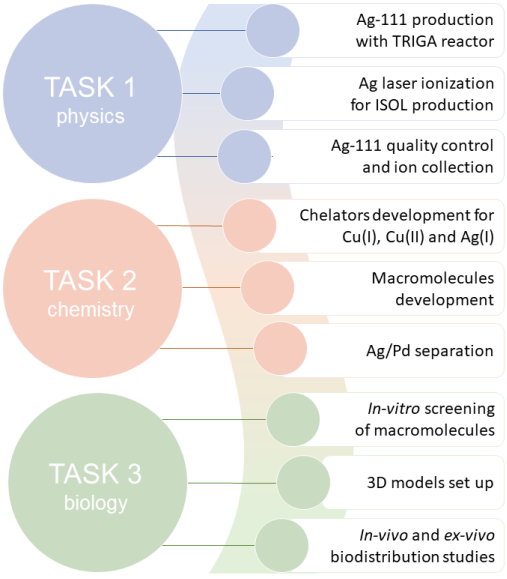

Figure 2. Description of the ISOLPHARM EIRA main objectives, divided into Tasks 1, 2, and 3.

In this project, a wide range of multidisciplinary knowledge must be combined, thus leading to a joint effort of INFN sections of Legnaro (LNL), Padova (PD), Pavia (PV), Trento (TIFPA) and Southern Italy (LNS), Universities from Padova, Pavia, Brescia, Siena, and Trento (UNIPD, UNIPV, UNIBS, UNISI, UNITN), and research divisions in hospitals (USL-IRCCS of Reggio Emilia).

4. ISOL PRODUCTION: SILVER IONIZATION, DETECTION AND DEPOSITION

The pathway to achieve this innovative production of Ag-111, as well as several other radionuclides for medical use, requires many steps to assess its feasibility. Suitable amounts of carrier-free Ag-111 for the subsequent radiolabeling of biomolecules with high efficiency can be produced with the ISOL method using the SPES UC_x target. Radioactive silver nuclides were already successfully produced using a SPES UC_x target prototype and delivered to experimental areas in dedicated experiments [15].

The produced silver isotopes will then be ionized and accelerated. Ionization and extraction processes have been tested and successfully performed by using the SPES Front-End facility in off-line mode and replacing the radioactive ions with stable forms, thus enabling the possibility to conduct proof-of-concept experiments with higher safety for the operators since the chemical properties of cold and hot nuclides are deemed equivalent. The tests were performed by loading defined amounts of silver as nitrate salts ($AgNO_3$) into the ion source, exploiting the mass marker (MM) technique. Both laser ionization and plasma ionization processes could potentially be employed to ionize silver atoms since the first ionization potential is 7.58 eV. Laser resonant ionization (RLI) technique is currently being developed and tested at LNL to improve the ionization and extraction of Ag-111 from the SPES primary target [16]. For this reason, the first studies on silver ionization were performed by using the SPES Plasma Ion Source, achieving an ionization efficiency of up to 16%. Once switched to RLI, the process will be more selective because only the isotopes of the same element will be ionized; thus, eventual isobaric contaminants will be excluded from the following beam of the selected isotope, achieving extremely high purity in the final product [17].

The silver ions thus obtained were then efficiently accelerated towards an implantation substrate (also called deposition target), which will then be removed and processed to recover the silver atoms for the radiolabeling process. The targets are generally produced with a 13 mm or 40 mm dye in a manual press by application of 10 t of pressure. Several materials were considered to achieve an efficient recovery, starting from inorganic materials, such as the water-soluble sodium nitrate ($NaNO_3$), to obtain an aqueous solution of $AgNO_3$ when dissolved in pure water. This strategy allowed the recovery of Ag^+ ions in the range of 72-84% compared to the number of deposited atoms, most likely reduced by a slight overlapping with the target holder during the test, as shown in Fig. 3 [11]. However, large amounts of salts could interfere with subsequent processes such as the chemical purification or the radiolabeling step.

Based on these premises, systematic studies on different deposition targets were performed. Self-sustaining targets were prepared by using

pharmaceutical excipients. In particular, water-soluble (dextrates) and insoluble cellulose-based powder mixtures were investigated at different compression conditions, as well as at different weights. The tensile strength of the system highlighted the higher fragility of the salt-based discs, thus making these preparations difficult to handle in the semi-automated system for their insertion and removal in the Front-End SPES. Moreover, both soluble and insoluble discs allowed good recovery of the deposited Ag. In fact, it was demonstrated that the deposition of silver, as well as different metals, occurs within less than 0.5 mm from the target surface. Thus, this study confirmed the possibility of using low-porosity materials for metal depositions without completely dissolving the implantation substrate to recover the deposited atoms [18]. An automated system for the deposition targets handling is currently under development and validation at LNL to insert and extract the substrates without the operators' radiation exposure.

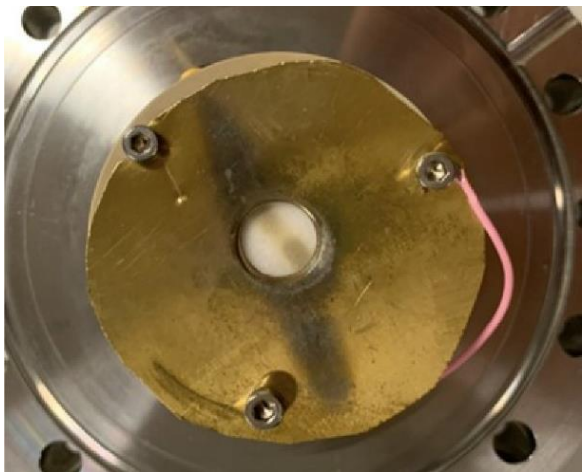

Figure 3. Implantation substrate in soluble dextrates material with cold Ag deposited on its surface.

As previously mentioned, the preliminary ionization and deposition tests were performed with stable ions, and the recovery of the metals was quantified by atomic absorption spectroscopy (GF-AAS). However, the deposition of the radioactive ions will require different quantification systems, such as γ counters. In particular, small, cost-effective, and portable systems for the detection of γ emissions were developed in this project to assess the radiations from Cu-64. A simple set-up was proposed, bearing a 1" x 1" inch cylindrical detector with Lanthanum Bromo-Chloride (LBC), $La_{2.85}Cl_{0.15}$:Ce, scintillator crystal manufactured by SCIONIX, coupled to a HAMAMATSU R11102 PhotoMultiplier Tube (PMT). This system showed optimal Minimum Detectable Activity (MDA) within our region of interest (511 keV ± 3σ) at acquisition times ≤ 15 min, and it was successfully used in a preliminary biodistribution study of Cu-64 administered with DO2A2S chelator [19].

While the development and optimization of the production process is currently being performed at the LNL unity, innovative radiopharmaceuticals are being developed and evaluated within the wide collaboration of ISOLPHARM_EIRA.

5. Chelating agents

In order to efficiently develop a targeted radiopharmaceutical, the radionuclide has to be efficiently attached to a carrier system. The carriers are generally made of four moieties: 1) a vector molecule, 2) a linker, 3) a bifunctional chelator (BFC) and 4) a metallic radionuclide. The chelating moiety must trap the radionuclide in a range of pH between 5 and 7 to prevent loss of radiometal *in vivo*, and connect it to the linker and the vector molecule to be effectively delivered to the target tissue. The development of novel BFC for Ag(I) is challenging because this metal ion is known to be very labile, and in the chelator moiety it can be rapidly replaced by oligoelements of the body [20]. The chelator choice is based on the ionic radius of the radiometal and the presence of the best donor groups for the radiometal [2].

The evaluated chelators were investigated for binding the soft metal ions Ag(I), Cu(I) and Cd(II), as well as the borderline cation Cu(II). All the compounds bear the sulfide functional group, which led to solid binding of the metals [21, 22]. The first library of chelators (first generation) based on the cyclen scaffold (DO4S, DO3S, DO3SAm, DO2A2S, Fig. 4A) differed from the second generation compounds (TACD3S, TRI4S, TE4S, Fig. 4B) in their ring sizes or the number of functional groups. The chelators synthesis was achieved starting from the corresponding non-alkylated ring, using similar procedures as those adopted to synthesize DO4S [23].

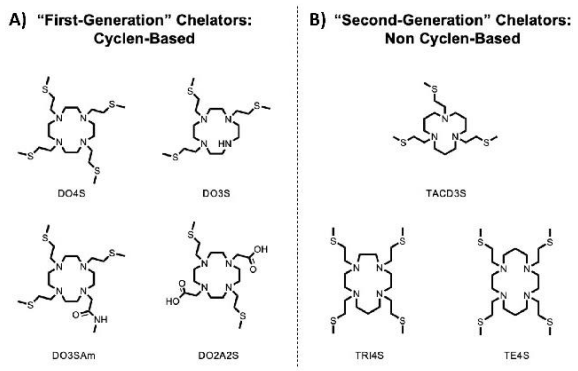

Figure 4. Structure of the "first generation" (cyclen-based) and "second generation" (with a different ring) chelators for soft or borderline metal ions.

Complexes stabilities with cold metal ions Ag(I), Cu(I), and Cu(II) were assessed through thermodynamic studies, NMR, EPR, cyclic voltammetry, and X-ray crystal analyses (if crystals are obtained). Not all thermodynamic data have been obtained so far, but DO4S appears to form the most stable complexes with Ag(I) and Cu(I), whereas DO2A2S forms the most stable complexes with Cu(II). The chelators will then be conjugated to targeted radiopharmaceuticals, which are currently under evaluation in preclinical studies.

6. Preclinical evaluation of innovative targeted radiopharmaceuticals

In targeted radiation therapy, the targeting moiety of the radiopharmaceutical is fundamental for the molecular recognition between the drug and a biological entity, like a receptor, usually overexpressed on cancer cells. The biological target considered in the ISOLPHARM_EIRA experiment is the cholecystokinin receptor 2 (CCK2R), which is extensively studied in (nuclear) medicine since it is overexpressed in different tumor types [24, 25]. Either mAbs and peptides have been studied to target CCK2R, and recently even a small molecule (Z-360, [26, 27]) has been developed. In this project, small molecules bearing Z-360 as a targeting agent were developed. The first compound, IP-001, was successfully synthesized and radiolabelled with In-111. The biodistribution of [^{111}In]In-IP-001 was assessed on BALB/c nude mice bearing A549 xenograft tumors, showing retention in the tumor tissue up to 24 hours, although with a certain degree of nonspecific binding to healthy tissues, as shown in Fig. 5 [28].

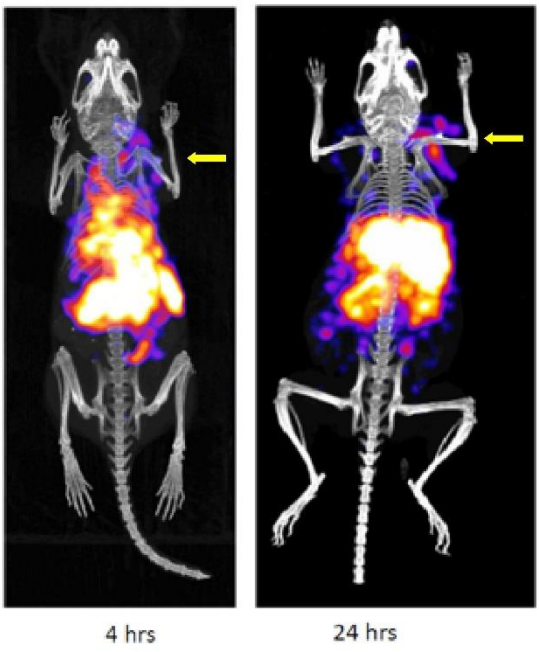

Figure 5. Single photon emission tomography (SPECT)/CT scans of an A549 tumor-bearing mouse at 4 and 24 h post-injection of about 7.4 MBq of [^{111}In]In-IP-001. The tumor position is shown by the arrow.

This phenomenon could be caused by the high lipophilicity of Z-360 [26]. For this reason, novel macromolecular compounds bearing mono-, di-, or tri-saccharides were developed and tested preliminarily *in vitro* and tracked by replacing the chelating agents with a fluorescent probe to identify the best performing candidate (Fig. 6A). Association and competition tests highlighted that by increasing the hydrophilicity of the compounds it was possible to improve the specificity and selectivity towards CCK2R overexpressing cells (Fig. 6B). The developed ligands will then be tested in preclinical models, both *in vitro* by using 3D cellular models, or *in vivo* on murine models.

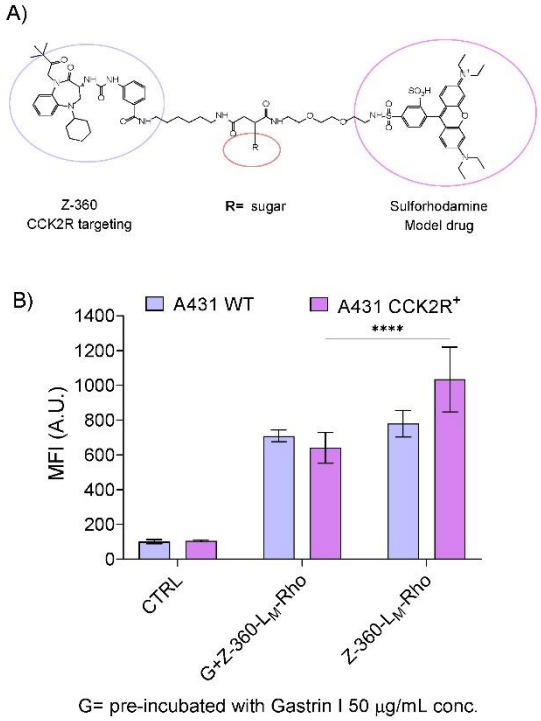

Figure 6. A) Structure of the proposed macromolecular systems. B) Mean fluorescence intensity (MFI) of native A431 (WT) or CCK2R-overexpressing cells incubated with the Z-360-L_M-Rho macromolecule. The signal reduction in the presence of large excess of gastrin (G) indicates a receptor-mediated association, thus confirming the compound's affinity towards CCK2R-overexpressing cells.

7. Conclusion

ISOLPHARM is a multidisciplinary project which aims to develop an innovative production method for radionuclides with superior purity to be used for targeted radiopharmaceuticals. This ambitious pathway will require the joint effort of several institutions to develop new infrastructures, facilities, and radiopharmaceuticals, primarily based on the innovative radionuclide Ag-111. Promising results were achieved so far in the ionization and deposition of cold silver ions, together with the development of innovative implantation substrates. The metal ions will be subsequently employed for the labeling of the newly developed chelating agents, which proved stable chelation of Ag(I), Cu(I), and Cu(II). The complex will be linked to the radiopharmaceuticals, which proved their selectivity towards CCK2R overexpressing cells. These studies will allow to obtain extremely pure radionuclides and open the way to proof-of-concept applications of Ag-111 as a theranostic agent.

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