# Optimization of Dosimetry in Alpha Therapy : Microlocalisation of 223Ra in Mouse Models of Metastasis from Prostate Cancer and Renal Cell Carcinoma

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computing architecture achieves optimal computing efficiency by integrating memory and processing units on a single chip and has been extensively applied in artificial intelligence (AI) application acceleration. In this work, our developed neuromorphic engine with employing novel nano-device (e.g. memristor) for highly enhanced computing parallelism is applied in the MC simulation. Basic computation models in the MC simulation such as Bayesian network is computed by the proposed neuromorphic engine. Improved neuromorphic design is further developed in algorithm and hardware to fit the computations in the MC simulation of the TAT. The simulation results of alpha particles penetration into tumor cells of TAT with highly improved computing speed and energy are presented.

### Isolation of At-211 by Dry-distillation under Oxidative Conditions for Targeted Alpha Therapy in Osaka University

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Astatine (At)-211 is one of the most promising radionuclides for the targeted alpha therapy (TAT). In Osaka University, we have recently started the collaborative project for the TAT using $^{211}$At which can be produced in nuclear reactions using an accelerator. At present, cyclotron production, chemical separation, radiopharmaceuticals preparation, and pre-clinical trials of $^{211}$At are under study. In this contribution, our cyclotron production and chemical purification of $^{211}$At are presented.

Astatine-211 was produced in the $^{209}$Bi($\alpha$, 2n)$^{211}$At reaction at Research Center of Nuclear Physics (RCNP), Osaka University. A thin metallic Bi target was bombarded by 28.2-MeV 4He2+ beam with 0.5-1 particle $\mu$A for a few hours. The Bi target was set at 45o to the beam axis in an irradiation chamber. Beam energy was adjusted to avoid simultaneous synthesis of 210At decaying into highly toxic 210Po. After the irradiation, dry distillation was carried out with a simplified distillation apparatus to isolate $^{211}$At from the target materials . We used mixed helium and oxygen gas and also added a moisture content in the distillation system to yield oxidized At species which are easily transported, trapped, and dissolved in a small volume of distilled water. The irradiated Bi target was heated at 840oC. Vapored At species were transported to a Teflon tube cooled with ice water. During accumulation of $^{211}$At in the trap, a trapped amount of $^{211}$At was monitored with a CdTeZn detector. After a few tens of minutes, trapped $^{211}$At was stripped with 100 $\mu$L of distilled water at a flow rate of 250 $\mu$L/min. The radioactivity of $^{211}$At was determined by $\gamma$-ray spectrometry using a Ge detector. The $^{211}$At solution was supplied to pharmaceutical preparations, pre-clinical tests, and/or our chemical analysis. Recovery yield of $^{211}$At was 70-80% under optimum conditions. The separation time was typically within 30 min. In the symposium, results on our chemical analysis will be also presented.

### Nanoparticles for the Treatment of Metastatic Non Small Cell Lung Cancer with $^{225}$Ac

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Non small cell lung cancer (NSCLC) is the most common form of primary lung neoplasia with nearly 40% of patients having metastasis at the time of diagnosis, resulting in a 5year survival rate ranging from 13-36% in patients with nodal metastasis, and decreasing to as little as 2% for those with distant metastasis. Furthermore, pulmonary metastatic disease is the most common form of secondary lung tumors, being identified in 30-55% of all cancer patients. Targeted $\alpha$-radiotherapy (TAT) agents have great potential for treating micro-metastatic disease, given their short, densely ionizing track length and high relative biologic effect (RBE). The use of in vivo alpha generators allows for multiple alpha decays from a single radioactive nucleus, but retaining the radioactive daughters at the target site throughout the decay process is a challenge. We present preclinical data describing a multilayered nanoparticle-antibody conjugate that can deliver multiple $\alpha$ radiations from the in vivo $\alpha$-generator $^{225}$Ac at biologically relevant receptor sites while also containing the radioactive daughters at those sites. The layered nanoparticles (NP) consist of an $^{225}$Ac-doped (La0.5Gd0.5)PO4 core coated with four layers of GdPO4 and an outer layer of Au. These multi-shell particles combine the radiation resistance of crystalline lanthanide (Ln) phosphate to contain atoms of the therapeutic radionuclide and its radioactive daughters, the magnetic properties of gadolinium for facile separation during synthesis, and the chemistry of gold for attachment of targeting agents to the nanoparticle surface. In a proximity delivery model of cancer, $^{225}$Ac-NPs conjugated to mAb 201b resulted in a 73% decrease in the number of EMT6 colonies in the lung five days after treatment [1]. On biodistribution studies and SPECT/CT imaging, over 85% of the injected dose was delivered to the target tissue, and approximately 90% of the fourth daughter, $^{213}$Bi, was retained in the target 24 hours after injection. Competition assays demonstrated specific binding of the conjugated radiopharmaceutical to the target. Current studies are evaluating the application of these $^{225}$Ac nanoparticles to A549 NSCLC grown in a mouse orthotopic lung cancer model, while a spontaneous cancer model in canine patients is also being explored.

**References:**

[1] M.F. McLaughlin, J.D. Robertson, P.H. Pevsner, J.S. Wall, S. Mirzadeh, and J. Kennel, "LnPO4 Nanoparticles Doped with Ac-225 and Sequestered Daughters for Targeted Alpha Therapy," Cancer Biotherapy and Radiopharmaceuticals 29(1), 34-41 (2014).

### Optimization of Dosimetry in Alpha Therapy: Microlocalisation of $^{223}$Ra in Mouse Models of Metastasis from Prostate Cancer and Renal Cell Carcinoma

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**Background:** In nuclear medicine, beyond providing a starting administered activity for clinical studies, dosimetry has an important role in determining optimal treatment regimens and to identify patients in whom treatment is likely to have little benefit. For alpha-emitter radiopharmaceuticals, a personalized dosimetry is challenging because of the short range of alpha-particles. So, in order to better assess the relationship between dose and biological effects, it is crucial to characterize the distribution of alpha-emitter radiopharmaceuticals at the microscopic level, as recommended by the MIRD pamphlet 22. This is then the aim of this work which focused on $^{223}$Ra, the first alpha-emitter to be use in clinical routine.

**Methods:** Three animal models were developed: a control model with healthy mice, a diseased model with osteoblastic/osteolytic metastasis and a diseased model with osteolytic metastasis. The metastasis cells were selected to modelize the osteoblastic lesions generated by the prostate cancer which are treated in clinical routine and the osteolytic lesions generated by the renal cell carcinoma which are the subject of a new clinical trial. Mice were dosed with $^{223}$Ra (30 kBq, n=5-6 per experimentation group) and killed at 15 min, 4, 24, 48 and 96 hours for prompt dissection. Tissue activity was assayed by gamma counting for several organs in order to determine the macroscopic biodistribution of $^{223}$Ra. Both tibias of diseased mice were then used to achieve fresh frozen, undecalcified tissue sections. Microdistribution analysis was performed using a

digital autoradiographic system. Autoradiographies of both tibias for each euthanasia time were acquired.
**Results:** Differences of uptake between both types of metastases were studied. Results showed a rapid renal clearance and an important uptake in the bones from 15 min for each model. No significant difference was observed at a macroscopic scale between the healthy tibia and the diseased tibia in each mouse of the metastasis models. The autoradiographies showed differences of localizations of $^{223}$Ra uptakes between the healthy tibia and the diseased one. In both tibias, $^{223}$Ra is homogeneously distributed in the cortical and trabecular bone. Moreover, there is an important uptake of $^{223}$Ra in the growth plate, in both tibias. This uptake is higher in the healthy tibias than in the diseased ones. $^{223}$Ra does not localize directly to the tumor, regardless of type. Instead, activity accumulates at the apposite bone surface surrounding the lesion. The differences of $^{223}$Ra repartition between the healthy tibia and the diseased tibia and between metastasis due to prostate cancer and metastasis due to renal cell carcinoma have been quantified. Finally, a biokinetic model was deduced for each metastasis model thanks to the images at different times.
**Conclusion:** These data will have important implications for the design and interpretation of clinical studies evaluating treatment with $^{223}$Ra, to guide clinical application with adapted dosing, and ultimately for more effective application in human. This work conducted prior to clinical trial is crucial and will allow us to develop a methodology for clinical routine and for other alpha-emitter radiopharmaceuticals.
**Funding Agency:** Institute for Radiological Protection and Nuclear Safety.

### Evaluation of Novel Antibodies to Centrin-1 for Radioimmunotherapy of Pancreatic Cancer

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Pancreatic ductal adenocarcinoma (PDAC) is the third leading cause of cancer death in the US with a very low survival rate. Unlike other solid malignancies, a biopsy of the pancreas is very invasive and recommend only with a mass suspected to be PDAC. Centrin1 (CETN1), a cancer/testis antigens (CATs), has been showed a 25-fold upregulation in 50% of the tumors from pancreatic cancer patients. Since testes are an immunoprivileged site, CETN1 could be a perfect target of radioimmunotherapy as the side effects of the treatment would be minimal. In this study, we developed novel antibodies (69-11 and 76-6) that are highly specific to CETN1, compared to its compensatory protein CENT2, which is widely expressed in all eukaryotic cells. 69-11 and 76-6 are either labeled with $^{213}$Bi, an alpha emitter, or with $^{177}$Lu, a beta emitter, for the treatment study. The radiolabeled antibodies were administered to PDAC xenografts-bearing nude mice. The localization of the radiolabeled antibodies in the tumors and normal organs was determined with micro SPECT/CT imaging. The tumors were monitored for 50 days. The toxicity assessment included weekly blood chemistry and kidney and liver functions assessment when PDAC-bearing mice were sacrificed at the end of the study. Labeling with $^{213}$Bi converted CETN1-specific antibodies into a very effective radioimmunotherapy reagent with tumor growth significantly ($P=0.01$) slowed down by either 100 or 200 μCi single injection. Importantly, the effect of the antibodies on the tumors was CETN1-specific, as 200 μCi control IgG had no effect on the tumor growth. In spite of impressive localization in the tumor demonstrated during the imaging experiments, $^{177}$Lu-labeled antibody was not very effective in slowing down tumor growth with no difference from $^{177}$Lu-IgG control ($P=0.06$) and was several folds less effective than $^{213}$Bi-labeled antibody. Both $^{213}$Bi and $^{177}$Lu groups showed only transient hematologic toxicity and absence of liver and kidney toxicity attesting to the very high safety margin of targeting CETN1 with radioimmunotherapy. In conclusion, the novel antibodies have the ability to detect CETN1 in vivo and in vitro, are highly efficacious and safe for treatment of PDAC, and warrant further work on developing them into clinical agents for diagnosis and therapy of PDAC.

### Evaluation of Inorganic Ion Exchange Materials for Purification of $^{225}$Ac from Thorium and Radium Radioisotopes

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Targeted alpha therapy with Actinium-225 ($^{225}$Ac) or its daughter Bismuth-213 ($^{213}$Bi) is an emerging and promising treatment for various types of cancers. $^{225}$Ac can be produced from a $^{229}$Th/225Ra generator system or from proton irradiated $^{232}$Th at high or $^{226}$Ra at low proton energies. Several types of inorganic ion exchange materials were synthesized to aid in chemical separations. Distribution coefficients (Kd) were determined for $^{225}$Ac, Thorium, and other co-produced isotopes metals as a function of the pH of initial solution. Based on the results the column separation was designed. Whenever possible, Ac-225, Th-227 and Ra-223 tracers were used. Otherwise La and Ba were used as surrogate for Ac-225, and Ra-223. The inorganic ion exchanger retained $^{227}$Th and $^{223}$Ra while $^{225}$Ac passed through. Further $^{227}$Th and $^{223}$Ra were recovered by eluting with different pH solution. In the optimized purification method >90% of $^{225}$Ac was recovered with radiopurity >99% (calculated from $^{225}$Ac, $^{227}$Th and $^{223}$Ra). The studies further showed the material could be used for a single column separation of $^{225}$Ac from the $^{229}$Th/225Ra generator. The capacity of the inorganic ion exchange materials for Barium and $^{232}$Th was determined to be 24.19 mg/mL for Barium and 5.05 mg/mL for Thorium. The studies indicate the material could be used to purify $^{225}$Ac from a ~300 mg production scale $^{226}$Ra target. However, the material would not have the capacity needed for a 50-100 g production scale $^{232}$Th target. To supplement these studies the integrity of the ion exchanger in: 1) ammonium acetate at various pH values, and 2) varying HCl and nitric acid conditions was determined.
**Funding Agency:** US Department of Energy, Office of Nuclear Physics.

### Coordination Chemistry of +3 Actinium

Dr. Stosh Kozimor, Dr. Enrique Batista, Dr. Kevin John, Dr. Eva Birnbaum, Dr. Veronika Mocko, Dr. Laura Lilley, Dr. Amanda Morgenstern and Dr. Benjamin Stein
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Targeted alpha therapy (TAT) represents an emerging technology that has potential in treatment of disease. Amongst many isotopes showing promise in TAT, 225-actinium ($^{225}$Ac) stands out. Its half-life is compatible with many medical applications and its decay is accompanied by emission of four alpha-particles, which augments 225-Ac's therapeutic benefit in comparison to isotopes that produce only one alpha-particles. A challenge facing 225-Ac's use in medicine is identification an appropriate chelator, one that (1st) achieves fast room temperature Ac-binding kinetics and (2nd) irreversible binds AcIII during transport through the patient to the target. Unfortunately, it is difficult to predict what chemical factors lead to successful chelation, in large part, because Ac-coordination chemistry is poorly characterized. This presentation will document our recent efforts toward advancing predictive capabilities in Ac-chelation. The talk will center on comparative EXAFS, NMR, and DFT studies focused on advancing understanding of Ac(III)–binding with numerous macrocyclic chelates.
**Funding Agency:** LDRD.

### Thorium-229 Generator Production of Actinium-225 at Oak Ridge National Laboratory

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**Background and Objective:** Oak Ridge National Laboratory (ORNL) is a major producer of $^{225}$Ac and supplies research and clinical trials for the treatment of various forms of cancer with this promising radioisotope. Actinium-