Targeted Alpha Therapy Symposium

Report of Contributions

Contribution ID: **0** Type: **not specified**

This is a placeholder abstract

Placeholder text.

Funding Agency

TRIUMF

Email Address

conferences@triumf.ca

Presentation Type

Poster

Primary author: Ms THOMSON, Jana (TRIUMF)

Co-author: Dr RADCHENKO, Valery (TRIUMF)

Presenter: Dr RADCHENKO, Valery (TRIUMF)

Contribution ID: **1** Type: **not specified**

Generic MUC1 Epitope for Targeted Alpha Therapy of Metastatic Cancer

The limitations of many systemic cancer therapies are that they are not potentially curable and recurrence is common. In particular, radio-immunotherapy with beta emitting radioisotopes is not curative and most vectors are cancer type specific. To overcome these limitations, new therapies are needed that are potentially curative, have minimal adverse events in humans and preferably have generic application to many cancers. These objectives could be met by targeted alpha therapy (TAT) using the C595 MAb against the cancer expression epitope (CE) of the MUC1 receptor, labelled with an alpha emitting radioisotope to form the alpha immunoconjugate (AIC).
In this paper, preclinical testing of the 213Bi-C595 AIC is reviewed for prostate, ovarian and pancreatic cancers, all of which are found to express the targeted MUC1-CE epitope. We have investigated the role of this unique AIC for control of these cancers by preclinical in vitro and in vivo studies of labelling yields, stability, in vitro cytotoxicity, efficacy and toxicity response in preclinical TAT. Results show conclusively that normal tissues have minimal expression of the MUC1-CE epitope and that the alpha-immunoconjugate can selectively kill cancer cells in vitro and inhibit the development and growth of tumours in vivo in a dose dependant way. As such, generic targeted alpha therapy against the MUC1-CE epitope has potential for the clinical management of epithelial cancers that express this epitope.

Funding Agency

nil

Email Address

bja940@outlook.com

Presentation Type

Contributed Oral

Primary author: Prof. ALLEN, Barry (Western Sydney University)

Presenter: Prof. ALLEN, Barry (Western Sydney University)

Contribution ID: **2** Type: **not specified**

Theoretical study of the Thorium structural in solution by EXAFS techniques

Ir Nzambimana Edouard, Msc, radiochemist, Burundi Bureau of Standards and Quality Control, Radiochemistry laboratory,alinzamed@yahoo.fr, nzambimana.1978@gmail.com

Abstract

Thorium with symbol Th is radioactive metal which emits the alpha rays. This metal can be founded in different forms and can cause the negatives impacts on human health and environment. This is the reason which explains the importance to know the structure of this metal in different forms including the structure of hydrated Thorium. Structural information helps to understand and assess peculiarities this ion in different natural and technological processes taking place in aqueous solutions. The most and efficacy technique to know about distances between atoms and coordination numbers is EXAFS (extended X Ray Absorption Fine Structure) technique because it permits to know these above informations. My project research is was to determine the structure of hydrated, solvated Thorium ion in metal ions. For my research, I preferred to use the EXAFS method to study the structure of the hydrated Th ion and to determine the Th-O bond distance, and from that estimate the coordination number. Th-O distance in the case of hydrated Thorium appeared to be 2.44 Å which corresponds to 9-coordination, as also found in the solids.
The Th-O bond distance in solvated plutonium is ca. 2.41 Å, which corresponds to eightcoordination. These informations have shown me that for Thorium ligand size and coordination number are correlated. In case of Thorium hydrated studies, I saw that shown don't precipitate at the law concentration.
As conclusion, when pH is in range, centrifugation is possible and thorium is in monomeric form, but for pH above 4 Thorium is restrained and centrifuging shown that Thorium is in non-ionic form.

Key notes: EXAFS (extended X-ray Absorption Fine Structure), hydrated thorium, Solvated thorium, monomeric form, non-ionic form

Email Address

alinzamed@yahoo.fr

Presentation Type

Poster

Primary author: Mr NZAMBIMANA, Edouard (Burundi Bureau of Standards)

Presenter: Mr NZAMBIMANA, Edouard (Burundi Bureau of Standards)

Contribution ID: **3** Type: **not specified**

US DOE Tri-Lab Research and Production Effort to Provide Accelerator-Produced 225Ac for Radiotherapy: 2019 Update

The current availability of accelerator produced 225Ac from the US Department of Energy Isotope Program's Tri-Lab (ORNL, BNL, LANL) Research and Production Effort to Provide Accelerator-Produced 225Ac for Radiotherapy will be presented. Additional details will be presented on recent production improvements and ongoing plans for further scaling up our operations. In addition, impacts associated with the radionuclidic quality of the accelerator-produced 225Ac product, concentrating on the 227Ac byproduct, will be provided. Specifics regarding preparations for Current Good Manufacturing Practices (CGMP) level of processing, development of a supporting Drug Master File (DMF) and details of routine material availability will also be discussed.

Funding Agency

US DOE Isotope Program

Email Address

kjohn@lanl.gov

Presentation Type

Contributed Oral

Primary author: JOHN, Kevin (Los Alamos National Laboratory)

Presenter: JOHN, Kevin (Los Alamos National Laboratory)

Track Classification: Nuclide Production Supply

Contribution ID: **4** Type: **not specified**

RNA-seq reveals tumor radiation response and novel molecular targets on α-emitting meta-211At-astato-benzylguanidine therapy for malignant pheochromocytoma

Purpose: Targeted α-particle therapy is a promising option for patients with malignant pheochromocytoma. Recent observations of *meta*-211At-astato-benzylguanidine (211At-MABG) in a pheochromocytoma mouse model showed a strong anti-tumor effect, but its molecular mechanism remains elusive (Y. Ohshima et al., 2018). Here, we showed the first comprehensive RNA-sequencing (RNA-seq) data of pheochromocytoma cells from *in vitro* 211At-MABG administration experiments, and screened key genes and pathways in the tumor α-particle radiation response, in order to obtain novel molecular imaging and therapeutic targets.

Methods: We evaluated genome-wide transcriptional alterations of rat pheochromocytoma cell line (PC12) at 3, 6, 12 h after 211At-MABG treatment. In order to highlight 211At-MABG specific gene expression, we carried out the control experiment of 60Co γ -rays irradiation. Ten-percent and eighty-percent iso-survival dose (0.8 and 0.1 kBq/ml for 211At-MABG, 10 and 1 Gy for 60Co γ-rays) were used for the comparison of both treatments.

Results: Enrichment analysis of the differentially expressed genes (DEGs) and analysis of the gene expression profiles of the cell cycle checkpoints showed similar modes of cell death via p53-p21 signaling pathway following 211At-MABG treatment and γ-ray irradiation. Ten percent iso-survival dose of γ-ray irradiation and 211At-MABG showed cell cycle arrest at G2/M phase. Representative DEGs of 211At-MABG-treated cells between 80\% and 10\% survival showed the expression of key genes not only on the decrease in the survival, but also on the anti-therapeutic effects such as DNA repair, invasion, and metastasis. Furthermore, representative DEGs between ɣ-ray irradiation and 211At-MABG demonstrated that the expression of four potential genes including Otub1 related to ubiquitin mediated proteolysis was remarkably elevated only after treatment with 211At-MABG. Western blot analysis indicated the increase of translocator protein 18 kDa (TSPO) expression in 211At-MABG treated cells, suggesting the potential PET imaging probe.

Conclusion: Comprehensive RNA-seq revealed contrasting cellular responses to γɣ-ray irradiation and targeted α-particle therapy leading to the identification of four novel potential genes (Mien1, Otub1, Vdac1 and Vegfa) for molecular imaging and therapeutic targets of 211At-MABG therapy. Moreover, our results suggest possible mechanism of the anti-tumor effect of 211At-MABG in pheochromocytoma.

Reference: Y. Ohshima, H. Sudo, S. Watanabe, K. Nagatsu, A.B. Tsuji, T. Sakashita, Y.M. Ito, K. Yoshinaga, T. Higashi, N.S. Ishioka, Antitumor effects of radionuclide treatment using α-emitting *meta*-211At-astato-benzylguanidine in a PC12 pheochromocytoma model, *Eur. J. Nucl. Med. Mol. Imaging*, **45**, 999-1010. (2018)

Acknowledgement: The authors thank Yuki Takai for technical assistance in sequencing, and the staff of Takasaki ion accelerators for advanced radiation application and food irradiation facilities of QST for their operation.

Funding Agency

The Yamagata Prefectural Government and Tsuruoka City, Japan.

Email Address

ohshima.yasuhiro@qst.go.jp

Presentation Type

Poster

Primary author: Dr OHSHIMA, Yasuhiro (National Institutes for Quantum and Radiological Science and Technology)

Co-authors: Mr SASAKI, Ichiro (National Institutes for Quantum and Radiological Science and Technology); Dr ARAKAWA, Kazuharu (Keio University); Dr KONO, Nobuaki (Keio University); Dr ISHIOKA, Noriko (National Institutes for Quantum and Radiological Science and Technology); Dr WATANABE, Shigeki (National Institutes for Quantum and Radiological Science and Technology); Dr SAKASHITA, Tetsuya (National Institutes for Quantum and Radiological Science and Technology); Dr YOKOTA, Yuichiro (National Institutes for Quantum and Radiological Science and Technology)

Presenter: Dr OHSHIMA, Yasuhiro (National Institutes for Quantum and Radiological Science and Technology)

Contribution ID: **5** Type: **not specified**

Microdosimetric and Biokinetic Modelling of Alpha-Immuno-Conjugate Transport in Endothelial Cells

Background and Objective:
The characterization of the Alpha-Immuno-Conjugate (AIC) targeted delivery process under vascular environment is very challenging due to the small scale of AIC particles, decay chain of the labeled radionuclide and the complex in vivo vascular system. To understand such a complex system, computational biokinetic model and microdosimetric model have been developed at Canadian Nuclear Laboratories (CNL) to help understand the AIC targeted delivery process and efficacy. The overall aim is to assist in the optimization and personalization of the treatment of patients.
Methods:1) Biokinetic model based on computational fluid dynamics (CFD) method is developed to study the blood flow through a two-dimensional Endothelial Cell (EC) embedded in a solid tumour or a normal cell. This model includes the collision model to handle the interactions of multiple particles in an administered conjugate. Immersed boundary method was used to handle the multiple moving particles in the capillary after the intravenous injection of AIC. A mesoscale modeling is applied in order to gain an understanding of AIC transport in capillary so that the time-dependent location of the AICs can be predicted. The resulting locations of radiation sources can be used as an input by the dosimetric model to predict the absorbed dose. 2) Microdosimetic modeling based on alpha Monte Carlo simulation toolkit was developed in FORTRAN programming language to calculate the amounts of the energy deposited in a simplified nucleus model from internal moving emitters and evaluate the single-event spectra for alpha particle emitters. The model can handle various alpha kinetic energies based on emitters with long decay chains. 3)The coupled biokinetic and Monte Carlo models would be integrated into a generic coupling framework such as SALOME as reusable modules in order to capture the rapid changes involving the phenomenological interdependencies in biological effects to evaluate the efficacy and toxicity of the AIC. The resulting large amount of data calculated by the coupled high fidelity CFD simulation and microdosimetric analysis can be processed in real time by a visualization tool.

Results and Discussions: A coupled model based on a simplified and the Geant4 Monte Carlo microdosimetry technique and Computational Fluid Dynamics analysis for multiple particle movement was established. The transient AIC delivery process and the absorbed dose to the EC cells in the capillary are investigated to determine the transient toxicity of the AIC. The model to implement the decay scheme for radionuclide such as 225Ac is under development. The Multiphysics model presented in this abstract demonstrates the feasibility of combined biokinetic and microdosimetric modeling to evaluate the efficacy of the TAT.

Funding Agency

CNL

Email Address

tao.xu@cnl.ca

Presentation Type

Poster

Primary author: Dr XU, Tao (CNL)

Co-authors: Dr DUGAL, Clifford (CNL); Dr LI, Gang (CNL); Ms LIU, Tong (CNL); Dr LIU, Yu (Clarkson University)

Presenter: Dr XU, Tao (CNL)

Contribution ID: **6** Type: **not specified**

Assessing Melanin Capabilities in Radiation Shielding and Radioadaptation

There is a need in creating efficient and light weight radioprotectors which would protect against both sparsely and densely ionizing radiation for use in radiation therapy, nuclear industry, protection of military personnel and in space exploration. The presence of melanin pigment imparts a selective advantage to fungi promoting survival and cellular fitness. Selective growth of melanized fungi in extreme locations with high levels of ionizing radiation such as the damaged nuclear reactor at Chernobyl and the Antarctic deserts, demonstrates their survival advantage. Following exposure to ionizing radiation melanized fungi demonstrate various biological responses including improved survival, radiostimulation, radiotropism, and radioadaptation. Melanin's unique structure enables it to interact with ionizing radiation providing several levels of protection and advantage. First, melanin provides physical shielding, which we have demonstrated in Cryptococcus neoformans where melanized fungal cells showed improved structural cellular integrity against alpha particle and deuteron particle bombardment than that of a non-melanized control. This physical shielding reduces the relative biological effectiveness of the ionizing radiation. Second, melanin acts as chemical shield through its radical scavenging activities. Third, melanin's electrochemical properties change in response to irradiation. The ability of melanin to interact and respond to ionizing radiation results in improved survival and health of organisms, suggesting a melanin-dependant mechanism whereby radiation is transduced into other usable and advantageous forms of energy for the organism, or is involved in cellular communication. We have shown in a recent publication that melanized C. neoformans is more resistant to alpha particles than gamma rays at the same radiation dose which suggests that melanized fungi have the potential capability to differentiate between different types of radiation sources. By subjecting the melanized fungi C. neoformans and Wangiella dermatitidis to long term exposure to various radionuclides we have developed radiation adapted strains in the lab that demonstrate radiostimulatory and radiotropic responses. We will use these radiation adapted strains to determine if they are capable of differentiating between the types of radiation. In developing these strains we hypothesize that they could be utilized to identify sources of ionizing radiation based on the biological response of the laboratory adapted strains. The data generated here will provide insights for future research to design effective biological system for detection of even minute levels of nuclear fallout. Additionally we hope to advance our understanding of the relationship between melanin, fungi and resistance to ionizing radiation providing us new knowledge of radiation shielding, quenching, energy generation, and cellular communication.

Funding Agency

Defence Threat Reduction Agency

Email Address

mem510@mail.usask.ca

Presentation Type

Poster

Primary authors: Mr FRANK, Connor (University of Saskatchewan); Mrs MALO, Mackenzie E. (University of Saskatchewan)

Co-author: Mrs DADACHOVA, Ekaterina (University of Saskatchewan)

Presenters: Mr FRANK, Connor (University of Saskatchewan); Mrs MALO, Mackenzie E. (University of Saskatchewan)

Track Classification: Miscellaneous

Contribution ID: **7** Type: **not specified**

The Use of Radioimmunotherapy for the Treatment of Metastatic Melanoma

In 2017, an estimated 7 200 Canadians (91 000 Americans) were diagnosed with melanoma skin cancer. While surgical resection of the primary tumour can be effectively accomplished, there is no satisfactory treatment for patients with metastatic melanoma who do not respond or become resistant to immunotherapy. This reality projected that approximately 1 250 diagnosed Canadians (9 300 Americans) will have succumbed to the disease by the end 2017. Thus, there is a need for alternative effective approaches to treatment of metastatic melanoma. The approval of 223-Radium chloride (Xofigo) for treatment of metastatic prostate cancer and of 177-Lutetium-labeled somatostatin receptor binding peptides for neuroendocrine tumors, as well as recent successes of 177-Lu-A617 compound in patients with metastatic prostate cancer demonstrate the potential of targeted alpha or beta emitting radionuclides in treatment of cancers resistant to all other therapies. Through the use of targeted antibodies containing therapeutic radionuclides it becomes possible to deliver a site-specific lethal dose of radiation to cancer cells providing a direct and effective method for the treatment of metastatic melanoma. Biodistribution and microSPECT/CT imaging results show that a humanized antibody that targets “free”melanin in the tumour microenvironment, has high tumour uptake in B16F10 murine melanoma tumours in C57Bl/6 mice, while little to no uptake in naturally melanized tissues. Initial results indicate that 213Bi (alpha emitter) is more effective than 177Lu (beta emitter) for treatment of metastatic melanoma while both radiolabels did not produce significant side effects. Currently MTD and fractionation studies are underway to determine the best course of treatment.

Funding Agency

Radimmune Therapeutics, National Institutes of Health

Email Address

kja782@mail.usask.ca

Presentation Type

Poster

Primary author: Dr ALLEN, Kevin (University of Saskatchewan)

Co-authors: Dr DADACHOVA, Ekaterina (Univeristy of Saskatchewan); Mrs MALO, Mackenzie (University of Saskatchewan); Dr JIAO, Rubin (University of Saskatchewan)

Presenter: Dr ALLEN, Kevin (University of Saskatchewan)

Contribution ID: **8** Type: **not specified**

Highly Effective Treatment of CD38 Positive Experimental Lymphoma with 225Actinium-Daratumumab.

Daratumumab is a human cytolytic antibody specific for CD38 that is used clinically for treatment of patients with multiple myeloma (MM). Current therapeutic regimens require multiple injections over months of treatment, therefor increasing the potency of daratumumab to shorten the length of treatment would be very advantageous. 225Ac is an α-particle emitting radionuclide that has potent cytotoxic activities over relatively short distances, allowing for precise targeting of a lethal dose of radiation. Previously we have established that labeling daratumumab with 225Ac increased more than 10-fold its ability to kill MM cell lines in vitro. In this study we evaluated the therapeutic potential of 225Ac-daratumumab by treating mice with established CD38-positive tumors. Mice deficient in T- and B-cells were injected subcutaneously with human tumor (Daudi) cells and once tumors reached an average volume of ~200 mm3, mice were treated with 225Ac-daratumumab. To determine the localization of daratumumab within the tumor-bearing mice it was labeled with 111In, which can be easily imaged and is used as a surrogate to estimate the localization of 225Ac-daratumumab. The distribution of the 111In-daratumumab was then followed for 10 days using a microSPECT/CT scanner. To evaluate the antitumor ability of the 225Ac-daratumumab, tumor-bearing mice were injected with 225Ac- daratumumab at a dose of 400 nCi/0.3 μg of antibody, and 200 nCi/0.3 μg of antibody. As a control, mice were injected with either saline or an equivalent amount of unlabeled daratumumab. In addition, a group of mice was also treated with 30 times greater dose of unlabeled daratumumab (10 μg) - a dose which was previously shown to be effective against established tumors. 111In-daratumumab begun to accumulate in the tumor 24 hours after intraperitoneal injection and by 7 days was exclusively present in the tumor. The growth of the tumors in mice treated with 400 nCi/0.3 μg was significantly retarded compared to mice treated with equal concentration of unlabeled daratumumab or saline. Tumor growth was similar between mice treated with 400 nCi/0.3 μg of 225Ac-daratumumab and mice treated with 10 μg of unlabeled daratumumab. In conclusion, this study shows that labeling daratumumab with 225Ac increases its antitumor activity at least 30-fold. This study suggests that 225Ac labeling daratumumab increases its potency and could greatly reduce the amount of daratumumab needed for treatment in the clinic. This study also highlights the potential of targeting α-emitters to tumors as a viable therapeutic approach.

Email Address

w.dawicki@usask.ca

Presentation Type

Contributed Oral

Primary authors: Dr DADACHOVA, Ekaterina (University of Saskatchewan); Dr DAWICKI, Wojciech (University of Saskatchewan)

Co-authors: Dr LUDWIG, Dale (Actinium Pharmaceuticals Inc.); Dr THOMAS, Keisha (Actinium Pharmaceuticals Inc.); Dr ALLEN, Kevin (University Of Saskatchewan); Mrs MALO, Mackenzie (University of Saskatchewan); Dr BURGER, Mark (Actinium Pharmaceuticals Inc.); Dr JIAO, Rubin (University of Saskatchewan)

Presenter: Dr DAWICKI, Wojciech (University of Saskatchewan)

Contribution ID: **9** Type: **not specified**

A dual generator concept to yield 226Th: an isotope of interest for targeted alpha therapy

Introduction-Thorium-226 (t1/2=30.6m) is an isotope of interest for targeted alpha therapy (TAT). It decays via a four alpha decay chain to long-lived (t1/2=22.3 y) Pb-210 with a 111 keV gamma-line (3.29%) that can be used for SPECT imaging; thus providing theranostic capabilities. A generator concept is necessary to provide a consistent supply of Th-226 from its parent U-230 (20.23 d) [1]. Furthermore, Th-226 needs to be supplied in a form that is amenable to direct labeling with the chelate; minimizing the amount of time required for its preparation for use. Uranium-230 is best obtained by the proton irradiation of thorium targets via formation of Pa-230 (17.4 d), which partially decays to U-230. To yield a consistent supply of Th-226, a dual generator concept was developed: first to yield U-230 from the decay of Pa-230, and second, to separate Th-226 from the parent U-230.

Methods-Protactinium-230 used in this work was obtained from Oak Ridge National Laboratory as a side product from the production of Ac-225 [2]. An extraction chromatography resin approach was used for both the design of a Pa-230/U-230 generator, and a U-230/Th-226 generator. Uranium-230 and its decay product Th-226 were first sorbed on a solid phase in acid media. Uranium-230 was then eluted in acid as Th-226 remained on the stationary phase. In a third step, Th-226 was eluted from the resin in acidic media.

Results-The Pa-230/U-230 generator provided U-230 in high radiochemical yield and purity (>99.9%). The U-230/Th-226 generator yielded approximately 90% of the Th-226 with a >99.5% recovery of parent U-230 for each elution cycle. Thorium-226 was obtained with high radiochemical purity (>99.9%). Multiple elutions have been performed successfully with consistent radiochemical yields and purities.

Conclusions-A dual generator system was successfully designed and tested to provide a relibale supply of Th-226. Uranium-230 can be conveniently supplied from a Pa-230/U-230 generator. The U-230/Th-226 generator, in turn, provides Th-226 in high radiochemical yield and purity and in a form that is amenable to direct labeling with chelates for use in targeted alpha therapy.

Acknowledgments-This research was funded by the United States Department of Energy, Office of Science via a grant (FOA LAB 14-1099) from the Isotope Development and Production for Research and Applications subprogram in the Office of Nuclear Physics.

Funding Agency

United States Department of Energy, Office of Science, Nuclear Physics

Email Address

mifa@lanl.gov

Presentation Type

Contributed Oral

Primary author: Dr FASSBENDER, Michael (Los Alamos National Laboratory)

Co-author: Dr MASTREN, Tara (Los Alamos National Laboratory)

Presenter: Dr FASSBENDER, Michael (Los Alamos National Laboratory)

Contribution ID: **10** Type: **not specified**

Alpha-radioimmunotherapy against liver metastasis of HER2-positive gastric cancer in a mouse model

Gastric cancer (GC) is one of the leading causes of cancer-related death worldwide. Almost 1/3 of GC patients have distant metastasis at the time of diagnosis and 4-14% are liver metastasis (LM). The therapeutic efficacy of current standard treatments for LMGC is still limited and the five years survival is less than 10%. HER2 became a target for GC because 20% of GC is HER2-positive (HER2+) and trastuzumab, anti-HER2 antibody, is clinically used for the treatment of HER2-positive GC.
Alpha-emitter is getting higher attention, because of the high linear energy transfer and short range, and astatine-211 (211At) can be point out as one of the promising one. Adopting alpha emitter into radioimmunotherapy (RIT), ideal targeted radionuclide therapy can be provided with target specific antitumor effect and minimum toxicity to untargeted normal tissues.
The aim of this study is to evaluate the therapeutic efficacy of alpha-RIT against HER2+ LM of GC (LMGC) using 211At-labeled trastuzumab (211At-trastuzumab).
Luciferase-labeled NCl-N87, a HER2+ human GC cell line, was transplanted through the splenic vein to establish LMGC mouse model. 211At was labeled to trastuzumab by tin-halogen exchange. Biodistribution of 211At-trastuzumab in LMGC mice was evaluated up to 24h post intravenous (i.v.) injection. Tumor accumulation of 211At-trastuzumab were increased along with the time and reached about 12% at 24 h post injection and mainly excreted from urine. Experimental therapy was performed by injecting 211At-trastuzumab to LMGC mice from tail vein. Mice in three control groups received injection of PBS, intact trastuzumab or 211At labeled non-specific IgG (211At-HuIgG). Tumor was monitored by luminescence imaging to evaluate the antitumor effect. Monitoring body weight and the number of white blood cells and biochemistry examination of liver and kidney function were performed in order to check the toxicity. 211At-trastuzumab effectively eradicated the LMGC in our mouse model while the tumors in control groups were aggressively grown. No severer toxicity was observed.
This study provided the proof of concept that alpha-RIT using 211At-trastuzumab has high potential as a novel therapeutic option for HER2+ LMGC.

Email Address

hasegawa.sumitaka@qst.go.jp

Presentation Type

Poster

Primary author: Dr HASEGAWA, SUMITAKA (Radiation and Cancer Biology Team, National Institutes for Quantum and Radiological Science and Technology)

Co-author: Dr LI, Huizi Keiko (Radiation and Cancer Biology Team, National Institutes for Quantum and Radiological Science and Technology, Research Fellow of Japan Society for the Promotion of Science)

Presenter: Dr HASEGAWA, SUMITAKA (Radiation and Cancer Biology Team, National Institutes for Quantum and Radiological Science and Technology)

Contribution ID: **11** Type: **not specified**

Barium ferrite magnetic nanoparticles labeled with 223Ra: a new potential radiobioconjugate for targeted alpha therapy and magnetic hyperthermia

Among all alpha particle emitters, only a few nuclides are in considerable interest for targeted radionuclide therapy because of their properties, such as half-live, high cytotoxicity and short path length. One of the most important issues, which affects wider use of targeted α therapy in nuclear medicine, is the availability and the price of the radionuclides.

223Ra, as radium chloride, is the first commercially and widely used α-radiopharmaceutic. It is easily obtained from the 227Ac/223Ra generator. However, 223Ra is used mostly for treatment of bone metastases derived from primary prostate cancer, because 223Ra, as a member of Alkaline Earth
metals, forms very weak complexes. There is a lack of chelators which can effectively bind 223Ra for the purposes of receptor targeted therapy. In our studies we propose to use barium ferrite (BaFe12O19) nanoparticles as multifunctional carriers for 223Ra radionuclide for targeted α therapy and magnetic hyperthermia.

Barium hexaferrite nanoparticles labeled with 223Ra were synthesized by a modified autoclave method described by Drofenik et al [1]. The reaction mixture of FeCl3, BaCl2 and 223RaCl2 was alkalized with NaOH solution. Next, the reaction mixture was stirred in autoclave at 210 Celsius degrees for 5 h. Obtained radioactive, magnetic [223Ra]BaFe12O19 nanoparticles were washed with distilled water and hydrochloric acid (0.001 mol/L HCl). Yield of labeling was about 70% (for 100kBq 223Ra). Stability of the obtained radioactive nanoparticles was tested in various biological solutions: 0.01M PBS,0.9% NaCl and in human blood serum. It is confirmed that 223Ra was highly retained inside nanoparticles in every tested solution. Only about 20% of 211Pb (decay product of 223Ra) was released to the solution.

Obtained magnetic BaFe12O19 nanoparticles were characterized by transmission emission microscopy and dynamic light scattering. The diameter of synthesized nanoparticles was ~20 nm and the determined magnetization of nanoparticles in room temperature was about 42 emu/g.

In order to synthesize a radiobioconjugate having affinity to HER2 receptors, the monoclonal antibody trastuzumab was conjugated to the obtained barium ferrite nanoparticles. Firstly, the surface of barium ferrite nanoparticles was modified with 3-phosphonopropionic acid (CEPA) linker using a method described by Mohapatra et al [2], and then, the monoclonal antibodies were coupled to the barium ferrite nanoparticles using the carbodiimide chemistry. Synthesized bioconjugate was characterized by thermogravimetric analysis, dynamic light scattering and were tested for stability in biological fluids. The obtained [223Ra]BaFe12O19-CEPA-trastuzumab radiobioconjugate almost quantitatively retains 223Ra and majority of the daughter products. Radiobioconjugate has high receptor affinity towards HER2 receptors expressing on ovarian cancer cells and exhibits high cytotoxic effect in vitro.

Acknowledgement

This work was supported by National Science Centre of Poland (Grant NCN Preludium 2015/17/N/ST4/03943).

REFERENCES:

[1] M.Drofenik et al Mat.Chem.Phys. 2011; 127: 415–419

[2] S.Mohapatra et al Nanotechnology 2007; 18: 385102–11

Funding Agency

Institute of Nuclear Chemistry and Technology

Email Address

wu.maliszewska@gmail.com

Presentation Type

Poster

Primary author: Mrs GAWĘDA, Weronika (Institute of Nuclear Chemistry and Technology)

Presenter: Mrs GAWĘDA, Weronika (Institute of Nuclear Chemistry and Technology)

Contribution ID: **12** Type: **not specified**

Investigation of Monocarbon Carboranes as Pendant Groups for Labeling Small Molecules with Astatine-211

The dianionic boron cage molecule *closo*-decaborate(2-) is being used as a pendant group to label monoclonal antibodies with the alpha-emitting radionuclide, astatine-211 (211At). While this works very well for antibody labeling, it appears that application of the same moiety for labeling small molecules can significantly alter blood clearance of biomolecule conjugates. As an example, in a murine model an 211At-labeled biotin derivative used in a cancer pretargeting approach clears the blood so rapidly that it fails to reach the antibody-streptavidin conjugate bound with tumor cells. Our hypothesis is that the dianionic nature of the astatinated pendant group facilitates rapid excretion of the biotin conjugate. Therefore we are investigating the use of another boron cage moiety, a monocarbon carborane, *closo*-1-carba-nonadecaborate(1-) {referred to as *closo*-1-CB9H10} as an alternative 211At-labeling moiety.

Two *closo*-CB9H10(1-) derivatives, 1-carboxyl-1-CB9H9, **1**, and 1-*p*-benzoate-1-CB9H9, **2**, were prepared following literature reports (Chem. Commun. 328-329,2004 & Dalton Trans. 3552-3561, 2004). Tetrafluorophenyl esters of the carboxylates in **1** & **2** were prepared and were reacted with an amine in a biotin-sarcosine derivative to provide biotin derivatives that contain the two anionic *closo*-CB9H9(1-) moieties. Electrophilic astatination reactions of the derivatives containing *closo*-CB9H9(1-) were found to be low yielding, even at elevated temperatures. To facilitate the astatination reactions, 10-substituted phenyl iodonium salts of **1** & **2**, compounds **3** & **4**, were prepared and astatination of those derivatives were evaluated using [211At]sodium astatide. While astatination occurred (up to 50%), it was noted that a new less lipophilic product was formed in the reaction, particularly at elevated temperatures. The labeling reactions of 1-*p*-benzoate-10-phenyliodonium-*closo*-CB9H8, **4**, had fewer side products than **3**, so that reagent was selected for our subsequent studies. Reactions conducted under the same conditions, but without 211At present, provided an opportunity to isolate and characterize the reaction side product. NMR and mass spectral data supported characterization of the compound as the 10-hydroxyl-1-*p*-benzoate-*closo*-CB9H8, **5**. Compound **5** is readily prepared from **4**. Electrophilic astatination of **5** provided a single compound in ~80% radiochemical yield, making it an attractive pendant group for small molecule labeling of 211At.

Astatination studies are continuing with compounds **2**, **4** and **5** to optimize the radiochemical yields, as are astatinations of biotin derivatives containing these moieties. Tissue biodistribution studies are planned to determine the in vivo stability of the 211At-labeled compounds. It should be noted that the use of the phenyliodonium intermediate allows introduction of 211At under nucleophilic non-oxidizing conditions, so this labeling method can be used for 211At-labeling of compounds that are sensitive to oxidizing (electrophilic) conditions.

Funding Agency

We thank the U.S. DOE (DE-SC0018013) & U.S. NIH (NCI CA076287) for financial support of the studies.

Email Address

dswilbur@uw.edu

Presentation Type

Contributed Oral

Primary author: Dr LI, Yawen (University of Washington)

Co-authors: Prof. WILBUR, D. Scott (University of Washington); Dr GREEN, Damian J. (Fred Huchinson Cancer Research Center); Mr HAMLIN, Donald K. (University of Washington); Dr CHYAN, Ming-Kuan (University of Washington); Dr PRESS, Oliver W. (Fred Hutchinson Cancer Research Center)

Presenter: Dr LI, Yawen (University of Washington)

Contribution ID: **13** Type: **not specified**

Astatine and iodine chemical species in solutions prepared by dry distillation

Objectives: ^{211}At, an astatine radionuclide, with half-life of 7.2 h is one of the prospective candidates for targeted alpha radiotherapy of cancers. Astatine shows some different chemical behaviors in comparison with its homologue iodine. The understanding of basic properties of astatine has been required to develop targeted alpha therapy agents for cancers [1]. In this work, astatine and iodine chemical species in solutions prepared by a method of dry distillation have been determined by control experiments of thin layer chromatography (TLC) [2].

Methods: The astatine radionuclides ^{208,209,210,211}At and iodine ones ^{120,121,123}I were simultaneously produced through the ^{nat}Pb(^{7}Li,xn)^{208,209,210,211}At and ^{nat}Sn(^{7}Li,xn)^{120,121,123}I reactions, respectively, by ^{7}Li beam irradiation of a stack of lead and tin targets at the JAEA tandem accelerator facility [2]. After measuring activities produced in the targets, the astatine and iodine radionuclides were each separated from the targets and purified in a test tube by dry distillation [2]. No-carrier-added astatine or iodine was recovered by rinsing the test tube with 1.8 mL of ethanol or distilled water. In order to study oxidation-reduction degrees of astatine ions, astatine in the aqueous solution was reacted with an oxidizing of KIO_4, a reducing agent Na_2SO_3 or hydrazine hydrate. Separation of the astatine and the iodine ions in the solutions was conducted by TLC on a silica gel plate with an ethanol/water solution (v/v, 1:1). The astatine and iodine radioactivity separated on the silica gel plates was measured by using imaging plates. The distribution of radioactivity on the plates was visualized by Bioimaging Analyzer System to determine Rf values and amounts of the ions separated by TLC. In addition, the Rf values of the non-radioactive standard iodine ions, iodide I^-, iodate IO_3^-, and periodate IO_4^-, were determined under the same condition of the TLC for radioactive astatine and iodine.

Results and Conclusion: The R_f values of the non-radioactive standard iodine anions were determined to be R_f = 0.87 for I^-, 0.78 for IO_3^- and 0.00 for IO_4^-. TLC for radioactive iodine shows one spot with R_f = 0.84-0.86 while that for astatine shows three (or two) spots with R_f = 0.74-0.82, 0.66-0.69 and 0.00. Iodine was identified as a single chemical form of I^- in the solutions prepared by dry distillation, while astatine was three anions of At^-, AtO_3^- and AtO_4^-, compared with the standard iodine anions. The relative amounts of the astatine anions were dependent on the presence of oxidizing and reducing agents. This reveals that astatine species are certainly identified as At^-, AtO_3^- and AtO_4^-.

References

1. D. S. Wilber, Nat. Chem., 5, 246 (2013).
2. I. Nishinaka et al., J. Radioanal. Nucl. Chem., 1-9 (2018) First online.

Funding Agency

JSPS KAKENHI Grant Numbers JP23600013, JP15K04741 and JP18K11939.

Email Address

nishinaka.ichiro@qst.go.jp

Presentation Type

Poster

Primary author: Dr NISHINAKA, Ichiro (Tokai Quantum Beam Science Center, National Institutes for Quantum and Radiological Science and Technology (Ibaraki, Japan))

Co-authors: Dr SUZUKI, Hiroyuki (Graduate School of Pharmaceutical Sciences, Chiba University (Chiba, Japan)); Dr HASHIMOTO, Kazuyuki (Tokai Quantum Beam Science Center, National Institutes for Quantum and Radiological Science and Technology (Ibaraki, Japan))

Presenter: Dr NISHINAKA, Ichiro (Tokai Quantum Beam Science Center, National Institutes for Quantum and Radiological Science and Technology (Ibaraki, Japan))

Contribution ID: **14** Type: **not specified**

Targeted alpha therapy with PSMA-TTC: Preclinical activity at different dosing schedules and total antibody doses in prostate cancer xenograft models

Targeted alpha therapy (TAT) agents deliver high linear energy transfer (LET) alpha-radiation selectively to tumors. The first TAT approved is radium-223 which prolongs overall survival in metastatic castration resistant prostate cancer (mCRPC) patients with symptomatic bone metastasis. The PSMA targeted thorium-227 conjugate PSMA-TTC represents another TAT approach in mCRPC. It consists of a fully human PSMA IgG antibody covalently linked to the chelator moiety (3,2 HOPO). This antibody-chelator conjugate is radiolabeled with thorium-227, which decays with a half-life of 18.7 days to radium-223 via alpha-particle emission. Anti-tumor activity of PSMA-TTC in cell line and patient derived prostate cancer xenograft models has been shown previously.

Here we describe the impact of different total antibody doses applied on tumor targeting and anti-tumor activity of PSMA-TTC in the prostate cancer xenograft models 22Rv1 and LNCap, which harbor moderate or high PSMA target levels, respectively. Additionally, anti-tumor activity was assessed at different dosing schedules, applying the same radioactivity dose as single bolus or multiple dosing at weekly or biweekly schedules.

At the thorium-227 dose of 500 kBq/kg, the anti-tumor activity of PSMA-TTC was comparable at total antibody doses ranging from 0.14 to 1.5 mg/kg; while a substantial decrease in anti-tumor activity was observed at 5 mg/kg. Additionally the efficacy of PSMA-TTC at total antibody doses of 0.43 and 1.5 mg/kg was not affected by pretreatement of the unlabeled antibody-conjugate 5 days before treatment with PSMA-TTC at equivalent total antibody doses. In the preclinical models, comparable anti-tumor efficacy was observed at a cumulative radioactivity dose of 500 kB/kg, irrespective of whether the drug was administered as single or multiple doses at weekly or biweekly schedules.

In summary, PSMA-TTC shows strong anti-tumor activity within a range of different total antibody doses and dosing schedules in preclinical prostate cancer models. These data warrant further clinical investigation of this targeted alpha agent.

Funding Agency

Bayer AG

Email Address

stefanie.hammer@bayer.com

Presentation Type

Poster

Primary authors: Dr ZITZMANN-KOLBE, Sabine (Bayer AG, Pharmaceuticals Division); Dr HAMMER, Stefanie (Bayer AG, Pharmaceuticals Division)

Co-authors: Dr LARSEN, Aasmund (BAYER AS); Dr CUTHBERTSON, Alan (Bayer AS); Mrs ELLINGSEN, Christine (Bayer AS); Dr GRANT, Derek (Bayer AS); Dr MUMBERG, Dominik (Bayer AG, Pharmaceuticals Division); Dr HENNEKES, Hartwig (Bayer AG, Pharmaceuticals Division); Dr KARLSSON, Jenny (Bayer AS); Dr RYAN, Olav B (Bayer AS); Dr VON AHSEN, Oliver (Bayer AG, Pharmaceuticals Division); Mr BJERKE, Roger M (Bayer AS); Dr HAGEMANN, Urs B (Bayer AG, Pharmaceuticals Division)

Presenter: Dr ZITZMANN-KOLBE, Sabine (Bayer AG, Pharmaceuticals Division)

Contribution ID: **15** Type: **not specified**

Alpha-particle nanotherapeutics against recurrent, chemoresistant Triple Negative Breast Cancer

Metastatic and/or recurrent chemoresistant Triple Negative Breast Cancer (TNBC) is currently incurable. TNBC accounts for 12-17% of breast carcinomas with the lowest 5-year survival rates among all breast cancer patients due to high proliferation and reoccurrence outside the breast combined with lack of effective targeted therapeutic modalities. For such cases, key to the progression of the disease is the choice of therapeutics which need to be both tumor selective and potent against cancer cells. Given the vast heterogeneity of the disease identified as TNBC, this choice could be a major challenge.

Alpha-particle radiopharmaceutical therapy has already been shown to be impervious to most resistance mechanisms. However, historically, the short range of α-particles in tissue has hampered the use of α-particle emitters for the treatment of solid tumors; the diffusion-limited penetration depths of radionuclide carriers combined with the short range of α-particles result in only partial tumor irradiation. This is quite unfortunate given the killing power of α-particles.

In the past we have had remarkably promising initial results in effectively controlling the growth of TNBC tumors in vivo and in prolonging survival using α-particle nanoradiotherapy (lipid nanoparticles loaded with α-particle emitters)[1]. The key design element of these nanoradiotherapeutics to enable uniform tumor irradiation, was to engineer nanoparticles ('releasing' NPs) that upon their uptake by tumors they release highly-diffusive forms of the α-particle emitters within the tumor interstitium, resulting in uniform distribution of emitters within tumors, and uniform irradiation of tumors without - as we demonstrated - additional toxicities.

In this work, to maximize the fraction of emitted energy retained by tumors we designed NPs ('adhering' NPs) that, in addition to interstitial release, they adhere on the extracellular matrix and on cancer cells but DO NOT become internalized; this has the potential to enable slower clearance of NPs from tumors increasing the time-integrated delivered doses.

We systematically varied the release and adhesion properties on NPs loaded with the alpha-particle emitter Actinium-225 and present the effect of these properties on the dose response of large TNBC MDA-MB-231 spheroids used as surrogates of solid tumors' avascular regions. Preliminary data on SCID mice demonstrate the translational potential of this approach on controlling the growth rate of orthotopic TNBC xenografts and on delaying the spreading of spontaneous metastases.

Our findings demonstrate the potential of this 'diffusion-based' approach to lead to a new class of α-particle nanoradiotherapy as a platform technology to control tumor growth and/or spreading for a variety of difficult-to-treat tumors.

References

[1]. Zhu, C.; Sempkowski, M.; Holleran, T.; Linz, T.; Bertalan, T.; Josefsson, A.; Bruchertseifer, F.; Morgenstern, A.; Sofou, S. Alpha-particle radiotherapy: For large solid tumors diffusion trumps targeting. Biomaterials 2017, 130, 67-75.

Funding Agency

American Cancer Society, National Science Foundation, Elsa Pardee Foundation

Email Address

ssofou1@jhu.edu

Presentation Type

Contributed Oral

Primary author: Prof. SOFOU, Stavroula (Johns Hopkins University)

Co-authors: Dr MORGENSTERN, Alfred (European Commission, Joint Research Centre, Directorate for Nuclear Safety and Security); Mr PRASAD, Aprameya (Johns Hopkins University); Dr BRUCHERT-SEIFER, Frank (European Commission, Joint Research Centre, Directorate for Nuclear Safety and Security)

Presenter: Prof. SOFOU, Stavroula (Johns Hopkins University)

Contribution ID: **16** Type: **not specified**

PET imaging of DNA damage response following 225Ac-radioimmunotherapy in a pancreatic ductal adenocarcinoma mouse model.

Objective: When the integrity of the DNA is impaired, a series of DNA damage responses lead to the recruitment, upregulation or activation of specific protein within the nucleus. When present in sufficient copies, these proteins can represent attractive targets for molecular imaging. This presentation will present our recent efforts to image DNA damage repair proteins via PET imaging following α-radioimmunotherapy(αRIT). Such non-invasive approach will be a precious tool for the monitoring of treatment response as well as the determination of optimal therapeutic dose. Two DNA damage repair proteins will be evaluated as potential target for the evaluation of DNA damage following αRIT. First, the poly(ADP-ribose) polymerase 1 (PARP-1) enzyme, involved in the DNA repair of single strand breaks, will be targeted using a PARP inhibitor radiolabeled with fluorine-18 ([18F]F-PARPi). Then, the γH2AX protein, most commonly probed biomarker for DNA double strand breaks, will be targeted using an anti-γH2AX antibody radiolabeled with zirconium-89 ([89Zr]Zr-DFO-anti-γH2AX-TAT).

Methods: Pancreatic ductal adenocarcinoma αRIT was previously developed in our laboratory using a fully-human antibody targeting the carbohydrate antigen CA19.9 (5B1) radiolabelled with actinium-225. Mice bearing CA19.9 positive PDAC tumors (n=5/cohort) were administered a single injection of [225Ac]Ac-DOTA-5B1 with an injected activity of 37 kBq, known to result in significant prolonged survival as compared to control mice. DNA damage imaging was performed using [18F]F-PARPi (11-15 MBq, 1 nmol) and [89Zr]Zr-anti-γH2AX-TAT (500 kBq, 5μg) following the αRIT. As positive and negative controls, mice were either irradiated with 10 Gy or mock-treated (0 Gy). Mice were sacrificed following the PET imaging. Volume of interest analysis of the PET images were performed and correlated to the biodistribution data.

Results: PET imaging with [18F]F-PARPi shows accumulation of the radiotracer at the tumor site. Transverse representative images are shown in Figure 1. Tumor uptake at 4h, 24h and 72h (0.98±0.20, 1.08±0.39 and 1.01±0.24 %ID/g) post-αRIT was greater as compared to the negative control mice (0.62±0.23 %ID/g) even though no significant difference was observed. Imaging with [89Zr]Zr-anti-γH2AX-TAT results in tumor uptake of 7.6±2.2 %ID/g 72h post-αRIT with [225Ac]Ac-DOTA-5B1 This uptake was significantly higher than mock-treated control group (5.1±0.9 %ID/g, $P<0.05$). Mice irradiated with 10 Gy demonstrated tumor uptake of 6.8±1.2 %ID/g. Transverse representative images are shown in Figure 1.

Conclusion: DNA damage response proteins PARP1 and γH2AX were targeted and imaged via PET using 18F- and 89Zr-radiolabeled conjugates after PDAC targeted αRIT. Both proteins seems like promising targets for the monitoring of α-radiotherapy response.

Email Address

potys@mskcc.org

Presentation Type

Contributed Oral

Primary author: Dr POTY, Sophie (Memorial Sloan Kettering Cancer Center)

Co-authors: Prof. CORNELISSEN, Bart (CRUK/MRC Oxford Institute for Radiation Oncology); Dr KNIGHT, James C (2CRUK/MRC Oxford Institute for Radiation Oncology); Prof. LEWIS, Jason S (Memorial Sloan Kettering Cancer Center); Mrs MANDLEYWALA, Komal (Memorial Sloan Kettering Cancer Center); Mr DONABEDIAN, Patrick (Memorial Sloan Kettering Cancer Center); Dr REINER, Thomas (Memorial Sloan Kettering Cancer Center)

Presenter: Dr POTY, Sophie (Memorial Sloan Kettering Cancer Center)

Contribution ID: **17** Type: **not specified**

Radiation imagers for quantitative, single-particle digital autoradiography of alpha-and beta-particle emitters for targeted radionuclide therapy

Over the last several years new quantitative digital autoradiography imaging tools have been developed that are sensitive to both alpha- and beta-particle emitters. These include scintillation-, gaseous-, and semiconductor-based radiation-detection technologies that localize the emission location of charged particles on an event-by-event basis at resolutions up to 20 μm FWHM. These imaging systems allow radionuclide activity concentrations to be quantified to unprecedented levels (mBq/μg) and provide simultaneous, real-time imaging capabilities of both high- and low-activity samples without dynamic range limitations that plague traditional autoradiography. Additionally, large-area imagers are available (>20 × 20 cm2) to accommodate high-throughput imaging studies. This presentation reviews the various detector technologies and their associated performance trade-offs to provide targeted alpha therapy researchers with an overview of the current technologies available for selecting an optimal detector configuration to meet imaging requirement needs.

Email Address

brian.w.miller@ucdenver.edu

Presentation Type

Contributed Oral

Primary author: Dr MILLER, Brian (University of Colorado School of Medicine)

Presenter: Dr MILLER, Brian (University of Colorado School of Medicine)

Contribution ID: **18** Type: **not specified**

Targeted therapy of osteosarcoma with radio-labelled monoclonal antibody to an insulin-like growth factor-2 receptor (IGF2R)

Introduction: Osteosarcoma is the most common non-hematologic primary bone malignancy. It has been reported that it is the most common primary malignant bone tumour and the fifth most common primary malignancy among adolescents and young adults. There is a need for alternative novel treatment approaches to osteosarcoma treatment, as conventional chemotherapy strategies are not effective in many patients. We are investigating a novel approach to therapy of Osteosarcoma utilizing Radioimmunotherapy (RIT) targeted to insulin growth factor receptor type 2 (IGF2R), which has shown a constant over-expression in Osteosarcoma.

Methods: The binding efficiency of the IGF2R specific monoclonal antibody 2G11 to the panel of osteosarcoma cells lines was assessed by flow cytometry with the purpose of selecting the cell lines with the lowest and highest IGF2R expression for the biodistribution and therapy experiments. Biodistribution studies were performed in osteosarcoma xenografts in SCID B17 mice using Indium-111-labeled 2G11 specific antibody and the isotype matching control MOPC21. For therapy

1)The mice injected with the two different cell lines were randomized into 4 groups per cell line. Group 1 received 80 µCi of 177Lu-2G11, group 2 received 80 µCi of 177Lu- MOPC-21, group 3 received unlabeled (cold) 2G11, and group 4 was left untreated. In addition, a group of mice injected with 143B cell line received 80 µCi of alpha-emitter 213Bi-labeled 2G11 mAb.

Results: Based on the flow cytometry results, OS-17 and 143B cell lines were selected for initiation of tumors in SCID mice for biodistribution and RIT experiments. The 111In -2G11 demonstrated IGF2R-specific uptake in both OS-17 and 143B tumors which was significantly higher than that of isotype matching control MOPC21. 177Lu-2G11 cleared fast from all organs except for the spleen which expresses high levels of IGF2R. The therapy studies with 177Lu –and 213Bi -2G11 in tumour bearing mice showed that administration of this radiolabelled antibody significantly slowed down the growth of both the 143B and OS-17 tumours in comparison with the untreated tumours, cold 2G11 and radiolabeled isotype control antibody MOPC-21. 213Bi- 2G11 mAb had a more significant effect on the tumours in comparison to 177Lu-2G11.

Conclusion: In conclusion, given the lack of new effective therapies for osteosarcoma, RIT targeting IRF2R warrants further investigation as alternative treatment for osteosarcoma.

Funding Agency

Wendy Walk Foundation

Email Address

sak412@mail.usask.ca

Presentation Type

Poster

Primary author: Ms KARKARE, Sharayu (University of Saskatchewan)

Co-authors: Mrs DADACHOVA, Ekaterina (University of Saskatchewan); Mr ALLEN, Kevin (University of Saskatchewan); Mrs MALO, Mackenzie (University of Saskatchewan); Mr HELAL, Muath (University of Saskatchewan); Mr JIAO, Rubin (University of Saskatchewan); Mr DAWICKI, Wojciech (University of Saskatchewan)

Presenter: Ms KARKARE, Sharayu (University of Saskatchewan)

Contribution ID: **19** Type: **not specified**

Synthesis and evaluation of 64Cu (225Ac)-labeled rituximab for CD20 expression

Objectives: Chimeric monoclonal antibody rituximab, which selectively binds to CD20 surface antigen on B lymphocytes, has become a standard treatment for non-Hodgkin's lymphoma. This study aims to synthesize 64Cu-DOTA-rituximab and evaluate its potential for targeted alpha therapy by in vitro, in vivo studies, and evaluation of the dosimetry of 225Ac-DOTA-rituximab.
Methods: DOTA-rituximab immunoconjugate was prepared by incubation of rituximab with DOTA-NHS-ester in 1:5, 1:10, and 1:20 ratios. DOTA-rituximab conjugate was incubated with dried 64CuCl2 in acetate buffer (pH 5-6), and radiolabeling yield was confirmed by ITLC. For stability test, 64Cu-DOTA-rituximab was incubated in serum or phosphate buffered saline for 48 hours, and %dissociation was analyzed by ITLC. Cell binding assay of 64Cu-DOTA-rituximab was performed using Daudi human lymphoma cell line, and specific binding was determined by comparing non-specific binding with total binding. Binding affinity was presented as %injected dose (%ID). Biodistribution was carried out using BALB/c mouse at 1, 2, 6, 24, and 48 h post-injection, and the data is expressed as %ID/g. Residence time were computed via time activity curves of the acquired biodistribution 5 time series data. In order to calculate 225Ac S-value was simulated by Monte Carlo simulations using mice CT images. The organ absorbed dose for 225Ac-labeled DOTA-rituximab was estimated by Monte Carlo simulated 225Ac S-value.
Results: MALDI-TOF indicated that 1.3, 2.6, and 5.5 molecules of DOTA were conjugated to rituximab from 1:5, 1:10, and 1:20 conjugation ratio, respectively. Radiolabeling efficiency was higher than 98%, and 64Cu-DOTA-rituximab was used directly without purification. In vitro analysis of the stability showed that no significant dissociation of radioactivity from the complex was observed until 48 h. 64Cu-DOTA-rituximab showed significant specific binding to Daudi cells upon 3-h incubation having 19.8-24.5 %ID. It was shown that the lower the number of DOTA conjugated to rituximab, the higher the binding affinity to CD20. Biodistribution in BALB/c mouse (n=4) indicated that 64Cu-DOTA-rituximab has prolonged blood circulation up to 48 h, and heart, liver, lungs, spleen, and kidneys had high uptake at early time point. The estimated 64Cu-DOTA-rituximab absorbed dose in liver, lung, spleen, and kidney were 0.099, 0.028, 0.079, and 0.14 mSv/MBq, respectively. The estimated 225Ac-DOTA-rituximab absorbed dose in liver, lungs, spleen, and kidneys were 18.1, 5.54, 1.57, and 29.5 mSv/MBq, respectively. The RBE5 of kidney was 0.33 SvRBE5/MBq.
Conclusions: DOTA-rituximab was successfully synthesized and in vitro and showed high binding affinity to CD20-expressing cells. DOTA-rituximab will be successfully applied to targeted alpha therapy by labeling with 225Ac.

Email Address

ck190@kirams.re.kr

Presentation Type

Poster

Primary author: Dr KANG, Choong Mo (Korea Institute of Radiological & Medical Sciences)

Co-authors: Dr LEE, Chul-Hee (Korea Institute of Radiological & Medical Sciences); Dr LIM, Ilhan (Korea Institute of Radiological & Medical Sciences); Dr PARK, Ji-Ae (Korea Institute of Radiological & Medical Sciences); Dr KIM, Kwang Il (Korea Institute of Radiological & Medical Sciences); Dr LEE, Kyo Chul (Korea Institute of Radiological & Medical Sciences); Dr LIM, Sang Moo (Korea Institute of Radiological & Medical Sciences); Dr WOO, Sang-Keun (Korea Institute of Radiological & Medical Sciences); Dr JANG, Su Jin (Korea Institute of Radiological & Medical Sciences); Dr LEE, Yong Jin (Korea Institute of Radiological & Medical Sciences)

Presenter: Dr KANG, Choong Mo (Korea Institute of Radiological & Medical Sciences)

Track Classification: Dosimetry & Instrumentation

Contribution ID: **20** Type: **not specified**

Development of novel radiopharmaceuticals to combat invasive fungal infections

In Canada, there were over half-a-million cases of serious fungal infections diagnosed in 2017. However, there is a low number of medications available for mycoses. Therefore, the need for a low toxicity, high efficient and low resistibility therapy is highly apparent. Radioimmunotherapy (RIT) utilizes antigen-antibody interaction to deliver lethal doses of ionizing radiation to cells. FDA, Health Canada and European regulatory authorities have approved this therapeutic modality for treatment of different cancer types. Our laboratory is interested in targeting invasive fungal infections, such as Blastomyces dermatitidis which affects both human and companion dogs using RIT. To achieve this, we initially compared the binding ability of radiolabeled antibodies to fungal beta-glucan and to fungal heat shock protein 60 (HSP60) antibody to the less invasive Cryptococcus neoformans. Our results show that antibodies that targeted beta-glucan had significantly higher binding capability. Therefore, the antibody to beta-glucan was chosen for further development into the RIT reagent against B. dermatitidis. For this purpose, we have set forward two objectives. Our first objective was the in vitro evaluation of the efficacy of the antibody to beta-glucans armed with alpha-particles emitting radionuclide 213Bismuth in killing B. dermatitidis cells. For this, B. dermatitidis cells were cultured, then exposed to alpha-RIT. The percentage of cell death was calculated by determining the colony forming units (CFU). Our second objective is the in vivo evaluation of the efficacy and long term toxicity of the RIT in mice infected with B. dermatitidis. Our in vivo experiments will be conducted by infecting the lungs of the mice with B. dermatitidis by intranasal intubation. The infected mice will be treated with 213Bi-labeled antibody to beta-glucans and the residual infections load in their lungs will be analyzed after 1 week. If the treatment is successful and safe, our next step in the project will be a clinical trial in companion dogs infected with B. dermatitidis.

Email Address

muath456@yahoo.com

Presentation Type

Poster

Primary author: Mr HELAL, Muath (College of Pharmacy and Nutrition, University of Saskatchewan)

Co-authors: Dr DADACHOVA, Ekaterina (University of Saskatchewan); Dr ALLEN, Kevin (University Of Saskatchewan)

Presenter: Mr HELAL, Muath (College of Pharmacy and Nutrition, University of Saskatchewan)

Contribution ID: **21** Type: **not specified**

Dosimetry Prediction of 225Ac-NOTA-Trastuzumab Based on 64Cu-NOTA-Trastuzumab in Breast Cancer: Preliminary Microdose Clinical Trial

Purpose: To predict the internal dosimetry of 225Ac-1,4,7-triazacyclononane-1,4,7-triacetic acid (NOTA)-trastuzumab and 225Ac-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA)-trastuzumab in breast cancer using 64Cu-NOTA-trastuzumab, a novel PET tracer for the HER2 and 64Cu-DOTA-trastuzumab.

Methods:
Prior to injecting the radiotracer, 45 mg of cold trastuzumab was administered for 15 mins. Five patients with breast cancer were injected with 296 MBq of 64Cu-NOTA-trastuzumab. Six patients with breast cancer were injected with 370 MBq of 64Cu-DOTA-trastuzumab. PET/CT was performed 24 and 48 hours after injection. The mean standardized uptake (SUVmean) was evaluated from the blood, liver, kidney, muscle, spleen, bladder, lung, and bone. Furthermore, the radiation activity of 64Cu-NOTA-trastuzumab and 64Cu-DOTA-trastuzumab for each organ was evaluated at imaging time points and the residence time of radiotracer was calculated from the activity of each organ. The internal dosimetry for 64Cu-NOTA-trastuzumab and 64Cu-DOTA-trastuzumab was evaluated using OLINDA/EXM software with an adult female model, which was used for evaluating the internal dosimetry for 225Ac-NOTA-trastuzumab and 225Ac-DOTA-trastuzumab.

Results:
The overall values of SUVmean in each organ decreased with time on both 64Cu-NOTA-trastuzumab and 64Cu-DOTA-trastuzumab PET images. However, the bladder showed an increasing pattern of SUVmean over time. In the liver, 64Cu-NOTA-trastuzumab showed relatively lower SUV mean (24 hours; 4.64 ± 0.28, 48 hours; 4.26 ± 0.50) compared to 64Cu-DOTA-trastuzumab (24 hours; 6.66 ± 1.57, 48 hours; 7.05 ± 1.72). 64Cu-DOTA-trastuzumab showed an increasing pattern of the SUVmean in the liver over time. In the blood pool, 64Cu-NOTA-trastuzumab showed relatively higher SUV mean (24 hours; 9.32 ± 1.23, 48 hours; 7.42 ± 1.85) compared to that of 64Cu-DOTA-trastuzumab (24 hours; 7.85 ± 1.76, 48 hours; 6.25 ± 1.64). Other tissues showed similar SUVmean values on both PET images. Any adverse was not reported. The calculated effective doses for 64Cu-NOTA-trastuzumab and 64Cu-DOTA-trastuzumab were 14.3 uSv/MBq and 53.1 uSv/MBq, respectively. 64Cu-NOTA-trastuzumab showed relatively lower radiation burden (46.4 uSv/MBq) compared to that of 64Cu-DOTA-trastuzumab (254 uSv/MBq). The predicted effective doses for 225Ac-NOTA-trastuzumab and 225Ac-DOTA-trastuzumab were 2.19 mSv/MBq and 7.83 mSv/MBq, respectively. In the case of the liver, 225Ac-NOTA-trastuzumab showed lower absorbed dose (8.44 mSv/MBq) compared to that of 225Ac-DOTA-trastuzumab (47.0 mSv/MBq).

Conclusions:
In the normal liver, lower uptake of 64Cu-NOTA-trastuzumab was observed compared to 64Cu-DOTA-trastuzumab. It may be more helpful to detect metastatic lesions in the liver. Furthermore, when the 64Cu is replaced with 225Ac for treatment purpose, liver damage may be reduced when using NOTA-trastuzumab compared to when using DOTA-trastuzumab.

Email Address

inkilee2080@gmail.com

Presentation Type

Contributed Oral

Primary author: Mr LEE, Inki (Korea Institute of Radiological and Medical Sciences)

Co-authors: Dr BYUN, Byung Hyun (Korea Institutes of Radiological and Medical Sciences); Dr KIM, Byung Il (Korea Institutes of Radiological and Medical Sciences); Dr CHOI, Chang Woon (Korea Institutes of Radiological and Medical Sciences); Dr KANG, Choong Mo (Korea Institute of Radiological and Medical Sciences); Dr KIM, Hyun-Ah (Korea Institutes of Radiological and Medical Sciences); Dr LIM, Ilhan (Korea Institutes of Radiological and Medical Sciences); Dr KANG, Joo Hyun (Korea Institutes of Radiological and Medical Sciences); Dr CHOI, Joon Ho (Korea Institutes of Radiological and Medical Sciences); Dr KIM, Kwang Il (Korea Institutes of Radiological and Medical Sciences); Dr LEE, Kyo Chul (Korea Institute of Radiological and Medical Sciences); Dr SEONG, Min-Ki (Korea Institutes of Radiological and Medical Sciences); Dr LIM, Sang Moo (Korea Institutes of Radiological and Medical Sciences); Dr WOO, Sang-Keun (Korea Institutes of Radiological and Medical Sciences); Dr NOH, Woo Chul (Korea Institutes of Radiological and Medical Sciences); Dr LEE, Yong Jin (Korea Institutes of Radiological and Medical Sciences)

Presenter: Mr LEE, Inki (Korea Institute of Radiological and Medical Sciences)

Contribution ID: **22** Type: **not specified**

Image-based approach for absorbed dose estimation of 64Cu/225Ac-DOTA-trastuzumab using Monte Carlo simulation

Purpose:
Image-based absorbed dose calculation studies have been performed to evaluate the characteristics of theranostic radiopharmaceuticals. The aim of this study was to evaluate the 64Cu and 225Ac-DOTA-trastuzumab absorbed dose in mice using image-based Monte Carlo simulation.

Materials and Methods:
64Cu-DOTA-trastuzumab PET image was acquired at 3 time point at 3, 24, and 48 hour after radiopharmaceuticals injection in mice. Time-integrated activity coefficient in source organs called residence time was calculate in region of interest (ROI) delineable organs. Image-based source organ 64Cu/225Ac S-value were calculate using Geant 4 Monte Carlo simulation. Absorbed dose for 225Ac-DOTA-trastuzumab was calculated by 64Cu-DOTA-trastuzumab residence time and Monte Carlo simulated 225Ac dose map. The relative biological efficiency (RBE) of the alpha particles emitted from 225Ac, was estimated to be 5 (RBE = 5). 225Ac-DOTA-trastuzumab absorbed dose was considered all decay step of 225Ac radioisotopes (221Fr, 217At, 213Bi, 213Po, 209Tl and 209Pb) and summed up after applying weighting factors in the two possible pathways, 2% for 209Tl and 98% for 213Po.

Results:
Residence time of 64Cu-DOTA-trastuzumav in liver was 1.80 MBq-h/MBq that is high uptake region in normal subject. Liver absorbed dose of 64Cu- and 225Ac DOTA-trastuzumab were 2.73E-02 mGy/MBq, 6.37E+00 SvRBE5/MBq. 64Cu-DOTA-trastuzumab absorbed does in lung, kidney, and spleen were 2.97E-03, 3.86E-04, 3.62E-05 mGy/MBq, respectively. 225Ac-DOTA-trastuzumab absorbed does in lung, kidney, and spleen were 3.10E-01, 9.18E-02, 9.12E-03 SvRBE5/MBq, respectively. 225Ac-DOTA-trastuzumab absorbed dose was 2.34E+02 fold higher than 64Cu-DOTA-trastuzumab.

Conclusion:
We performed the 64Cu-DOTA-trastuzumab PET imaging and estimated the image-based internal absorbed dose of 225Ac-DOTA-trastuzumab. This result may help to strategy of treatment for HER2-positive cancer patients using targeted alpha therapy of 225Ac radioisotope.

Email Address

skwoo@kirams.re.kr

Presentation Type

Poster

Primary author: Dr WOO, Sang-Keun (Korea Institute of Radiological and Medical Sciences)

Co-authors: Dr LEE, Chul-Hee (Department of Nuclear Medicine, Korea Institute of Radiological and Medical Sciences, Seoul, Korea); Dr LEE, Hwunjae (Department of Nuclear Medicine, Korea Institute

of Radiological and Medical Sciences, Seoul, Korea); Dr LIM, Ilhan (Department of Nuclear Medicine, Korea Institute of Radiological and Medical Sciences, Seoul, Korea); Dr LEE, Kyo Chul (Division of applied RI, Korea Institute of Radiological and Medical Sciences, Seoul, Korea); Dr LIM, Sang Moo (Department of Nuclear Medicine, Korea Institute of Radiological and Medical Sciences, Seoul, Korea); Mr KIM, Wook (Division of applied RI, Korea Institute of Radiological and Medical Sciences, Seoul, Korea); Dr LEE, Yong Jin (Division of applied RI, Korea Institute of Radiological and Medical Sciences, Seoul, Korea)

Presenter: Dr WOO, Sang-Keun (Korea Institute of Radiological and Medical Sciences)

Contribution ID: **23** Type: **not specified**

Estimation of internal dosimetry of 64Cu and 225Ac labeled PSMA-617

Purpose:
Evaluation of internal dosimetry should have performed before injection of theranostic radiopharmaceuticals. The aim of this study was to estimate the 64Cu-PSMA-617 biodistribution in mice and human absorbed dose of 64Cu and 225Ac-PSMA-617.

Materials and Methods:
The radiolabeling efficiency of 64Cu-PSMA-617 was showed over 95%, and stabilities of 64Cu-PSMA-617 has remained over 98% in both human and mouse serum for 48 h. 64Cu labeled PSMA-617 were used to calculate the biodistribution in mice (n = 4). Time-dependent biodistribution of 64Cu-PSMA-617 was measured at 2, 4, 6, 24, and 48 hours after injection. Biodistribution data from 64Cu-PSMA-617 in mice were used to calculate residence time and effective dose in human. Human absorbed dose of 64Cu and 225Ac-PSMA-617 was approximated by extrapolation data of 64Cu-PSMA-617 mice biodistribution. Absorbed dose and the effective dose were estimated by the OLINDA/EXM (Vanderbilt University, Nashville, TN) adult male model. Region residence time and absorbed dose have calculated the average with standard deviation (SD).

Results:
The highest uptake ratio was observed in the liver and kidney at 2 h. Rapid blood clearance was observed for 64Cu-PSMA-617. 64Cu-PSMA-617 residence time in liver and kidney were 3.23E+00 ± 3.69E-01 and 3.67E-01 ± 2.67E-02 MBq-h/MBq, respectively. Liver absorbed dose of 64Cu and 225Ac-PSMA-617 were 7.64E-03 ± 8.68E-04 and 2.82E+01 ± 3.24E+00 mGy/MBq, respectively. Kidney absorbed dose of 64Cu and 225Ac-PSMA-617 were 4.61E-04 ± 1.50E-04 and 2.04E+01 ± 1.50E+00 mGy/MBq, respectively. The effective dose of 64Cu and 225Ac-PSMA-617 were 1.77E-02 ± 5.07E-04 and 1.82E+00 ± 1.69E-01 mSv/MBq, respectively.

Conclusion:
We evaluated the human absorbed dose of 64Cu-PSMA-617 and 225Ac-PSMA-617. The 225Ac-PSMA-617 effective dose was 103 fold higher than 64Cu-PSMA-617. These result may help to a strategy of targeted alpha therapy calculate effective dose for metastatic castration-resistant prostate cancer (mCRPC) patients.

Email Address

skwoo@kirams.re.kr

Presentation Type

Poster

Primary author: Dr WOO, Sang-Keun (Korea Institute of Radiological and Medical Sciences)

Co-authors: Ms HEESU, Ahn (Division of applied RI, Korea Institute of Radiological and Medical Sciences, Seoul, Korea); Dr PARK, Hyeon (Division of applied RI, Korea Institute of Radiological and Medical Sciences, Seoul, Korea); Dr LIM, Ilhan (Department of Nuclear Medicine, Korea Institute of

Radiological and Medical Sciences, Seoul, Korea); Dr KIM, Jung Young (Division of applied RI, Korea Institute of Radiological and Medical Sciences, Seoul, Korea); Dr JUNG, Ki-Hye (Division of applied RI, Korea Institute of Radiological and Medical Sciences, Seoul, Korea); Dr LEE, Kyo Chul (Division of applied RI, Korea Institute of Radiological and Medical Sciences, Seoul, Korea); Mr HAN, Sang Jin (Division of applied RI, Korea Institute of Radiological and Medical Sciences, Seoul, Korea); Dr LIM, Sang Moo (Department of Nuclear Medicine, Korea Institute of Radiological and Medical Sciences, Seoul, Korea); Mr KIM, Wook (Division of applied RI, Korea Institute of Radiological and Medical Sciences, Seoul, Korea); Dr LEE, Yong Jin (Division of applied RI, Korea Institute of Radiological and Medical Sciences, Seoul, Korea)

Presenter: Dr WOO, Sang-Keun (Korea Institute of Radiological and Medical Sciences)

Track Classification: Preclinical

Contribution ID: **24** Type: **not specified**

Therapeutic efficacy of 225Ac-containing polymersomes

Cancer, still presenting one of the major challenges in modern healthcare, leads to more than 8.8 million deaths annually. While the main treatment options include surgery, chemotherapy, and radiotherapy, increasing attention is given to brachytherapy in e.g. the treatment of prostate cancer. Advantages of brachytherapy, as compared to radical prostatectomy and external beam radiation therapy, lie in the much higher radiation doses which can be given to the tumour tissue whilst spearing healthy tissue. Whereas in classic brachytherapy careful placement of the seeds is still essential for optimal irradiation of the tumour, recently a movement towards the use of micro and nano particles for intratumoural administration has begun. These particles are able to distribute themselves to and within the tumour tissue, and can be labelled with either beta or alpha emitters. We have shown in the past that polymersomes are ideal candidates to be used in alpha therapy, as they are able to retain the recoiling daughter nuclides of 225Ac to a large extent, thus limiting the renal toxicity caused by recoiling daughters1.

We have evaluated the suitability of 225Ac-containing polymersomes composed of polybutadiene-polyethylene oxide as intratumoural therapeutic agents. Polymersomes containing 10 kBq and 50 kBq 225Ac have been injected intratumourally in MDA-MB-231 tumour-bearing BALB/c nude mice. At 1 and 7 days p.i. the biodistribution and tumour retention has been assessed. Polymersomes were retained very well in the tumour tissue, whereas 225Ac-DOTA was rapidly cleared. This observed retention in the tumour tissue together with an increase in double-strand DNA breaks, determined by -H2AX staining, in the tumours treated with 225Ac-polymersomes indicates that vesicles containing alpha-emitters like 225Ac will be suitable agents for long-term irradiation of tumours. The overall survival of the treated and control animals as well as the tumour growth has been followed in time. We have found a definite tumour growth inhibition for the tumours injected with 225Ac-polymersomes, showing that these vesicles can be used for intratumoural cancer therapy.

Acknowledgements
The present study was funded by the ZonMw Early Career Scientist Hotel grant, project nr 43500401I

(1) de Kruijff, R. M.; Drost, K.; Thijssen, L.; Morgenstern, A.; Bruchertseifer, F.; Lathouwers, D.; Wolterbeek, H. T.; Denkova, A. G. Appl. Radiat. Isot. 2017, 128.

Email Address

r.m.dekruijff@tudelft.nl

Presentation Type

Contributed Oral

Primary author: Dr DE KRUIJFF, Robin (Delft University of Technology)

Co-authors: Dr MORGENSTERN, Alfred (European Commission, Joint Research Centre, Directorate for Nuclear Safety and Security, Karlsruhe, Germany); Ms KIP, Annemarie (Radiology and Nuclear Medicine, Radboud university medical centre; Nijmegen, the Netherlands); Dr DENKOVA, Antonia (Radiation Science and Technology, Delft University of Technology, Delft, the Netherlands); Dr

BRUCHERTSEIFER, Frank (European Commission, Joint Research Centre, Directorate for Nuclear Safety and Security, Karlsruhe, Germany); Ms MOLKENBOER-KUENEN, Janneke (Radiology and Nuclear Medicine, Radboud university medical centre; Nijmegen, the Netherlands); Dr RAAVÉ, Rene (Radiology and Nuclear Medicine, Radboud university medical centre; Nijmegen, the Netherlands); Dr HESKAMP, Sandra (Radiology and Nuclear Medicine, Radboud university medical centre; Nijmegen, the Netherlands)

Presenter: Dr DE KRUIJFF, Robin (Delft University of Technology)

Contribution ID: **25** Type: **not specified**

The therapeutic potential of anti-HER2 2Rs15d nanobody labeled with 225Ac –an in vitro and in vivo evaluation

Objectives: Nanobodies (Nbs) are the smallest antibody-derived fragments with beneficial pharmacokinetic properties for molecular imaging and radionuclide therapy. Human Epidermal Growth Factor Receptor type 2 (HER2) is overexpressed in numerous carcinomas and portends a poor prognosis. Therefore, HER2-targeting nanobodies are very attractive vectors for TRT, especially when labeled with α-particle emitters. The aim of this study was to evaluate the therapeutic potential of the anti-HER2 Nb 2Rs15d labeled with 225Ac.

Methods: Anti-HER2 Nb 2Rs15d was coupled with the bifunctional chelate p-SCN-Bn-DOTA and further was labeled with 225Ac. Its binding affinity and specificity for HER2, together with immunoreactive fraction (IF), were evaluated on SKOV-3 (HER2+) and MDA-MB-231 (HER2-) cells. Its in vitro cytotoxicity was assessed using MTS and clonogenic assays. In vivo, 225Ac-DOTA-Nb 2Rs15d and a non-targeting control 225Ac-DOTA-Nb R3b23 were evaluated in female athymic nude mice subcutaneously xenografted with SKOV-3 and MDA-MB-231 tumors, both alone and with molar excess of unlabeled 2Rs15d. After determination of maximum tolerated dose (MTD), the therapeutic efficacy of 225Ac-DOTA-Nb 2Rs15d was investigated in mice bearing intraperitoneal SKOV-3.IP1/luciferase+ xenografted metastases against several controls, a trastuzumab regimen and a combination of both 225Ac-DOTA-Nb 2Rs15d and trastuzumab.

Results: The yield of DOTA-Nb 2Rs15d labeling was high (>90%), with radiochemical purity ≥95%. 225Ac-DOTA-Nb 2Rs15d bound specifically to HER2+ cells with ~75% IF, a KD of 3.50±0.17nM and lack of competition with trastuzumab or pertuzumab in vitro. Cytotoxicity studies demonstrated that 225Ac-DOTA-Nb 2Rs15d significantly reduced SKOV-3 cell viability in a dose-dependent and HER2-mediated manner, compared to 225Ac-DOTA or 225Ac-DOTA-Nb R3b23 as controls. Tumor uptake in SKOV-3 xenografted mice was high and specific (~8%), whereas in MDA-MB-231 was <0.5% already 1h pi. Its accumulation in kidneys was reduced almost 3-fold by coinjection 225Ac-DOTA-Nb 2Rs15d with 150 mg/kg Gelofusine. Therapy studies indicated that 225Ac-DOTA-Nb 2Rs15d increased Median Survival significantly, which measured 83 days compared to about 49 days for animals treated with controls PBS and 225Ac-DOTA-Nb R3b23, and to 72 days in case of trastuzumab regimen. The most extensive therapeutic effect (MD~97 days) was observed for the combination of both 225Ac-DOTA-Nb 2Rs15d and trastuzumab.

Conclusions: 225Ac-DOTA-Nb 2Rs15d efficiently targets HER2+ cells both in vitro and in vivo. Strong signs of therapeutic potential were observed in vitro, which were confirmed also at in vivo setting in mice bearing SKOV-3 xenografts. This study underlines the strong potential of 225Ac-DOTA-Nb 2Rs15d as a new radioconjugate for TAT and supports its further development towards the clinic.

Acknowledgments: This work was supported by the National Science Center Poland under grant 2013/09/D/ST4/03791. Matthias D'Huyvetter is a postdoctoral researcher and Tony Lahoutte a senior clinical investigator of the Research Foundation –Flanders (FWO), Belgium.

Email Address

m.pruszynski@ichtj.waw.pl

Presentation Type

Contributed Oral

Primary author: Dr PRUSZYNSKI, Marek (Institute of Nuclear Chemistry and Technology)

Co-authors: Prof. MORGENSTERN, Alfred (Joint Research Centre –Department for Nuclear Safety and Security, Karlsruhe, GERMANY); Mrs CEDROWSKA, Edyta (Institute of Nuclear Chemistry and Technology, Warsaw, POLAND); Prof. BRUCHERTSEIFER, Frank (Joint Research Centre –Department for Nuclear Safety and Security, Karlsruhe, GERMANY); Ms RODAK, Magdalena (Institute of Nuclear Chemistry and Technology, Warsaw, POLAND); Dr D'HUYVETTER, Matthias (In Vivo Cellular and Molecular Imaging Lab, Vrije Universiteit Brussel, Brussels, BELGIUM); Prof. LAHOUTTE, Tony (In Vivo Cellular and Molecular Imaging Lab, Vrije Universiteit Brussel, Brussels, BELGIUM); Ms DEKEMPENEER, Yana (In Vivo Cellular and Molecular Imaging Lab, Vrije Universiteit Brussel, Brussels, BELGIUM)

Presenter: Dr PRUSZYNSKI, Marek (Institute of Nuclear Chemistry and Technology)

Contribution ID: **26** Type: **not specified**

Combining Bismuth-213 with Nanobodies: finding the perfect match for Targeted Alpha Therapy

This study investigates a novel targeted therapy which combines the α-emitter Bismuth-213 (213Bi) and HER2-targeting nanobodies (Nbs) to selectively kill HER2+ metastases in breast- and ovarian cancer. The use of nanobodies as vehicles in TAT is promising due to their excellent in vivo properties, high target affinity and specificity, fast diffusion and clearance kinetics. Moreover, Nbs show good tumor penetration due to their small size. The aim of this study is to develop and evaluate the in vitro binding characteristics on HER+ SKOV-3 cells, the in vitro stability using radio-ITLC and HPLC and the in vivo biodistribution of 213Bi-DTPA HER2 targeting Nb.

First, a 213Bi-labeled-Nb was developed using 225Ac obtained from an historical 229Th-source of SCK•CEN. A classical diethylenetriaminepentaacetic acid (DTPA) derivative was used as bifunctional chelator for complexing 213Bi and conjugating the complex to the anti-HER2 Nb. Due to the 46 min half-life, the 213Bi labeling reaction and quality control of the resulting radioconjugate was performed in a very short time frame to limit significant radioactivity losses. Under optimized labeling conditions, the 213Bi-DTPA-Nb remained stable up to 2 h after labeling with a radiochemical purity ≥ 95% in PBS at room temperature and at 37 ℃ and in serum at 37 ℃. In vitro, the 213Bi-DTPA-Nb bound HER2+ SKOV-3 cells in a HER2-specific way and with an affinity of 3.79 +/- 0.96 nM (Figure 1A and 1B).

In a second part, mice were injected with 213Bi-DTPA-Nb using 225Ac obtained from the Institute for Transuranium Elements in Karlsruhe. Extremely low uptake values were observed in normal tissues at all time points (Figure 1C). 213Bi-DTPA-Nb was excreted via the kidney into the urine, leading to a significant kidney retention of the compound of 40% ID/g at 15 min postinjection (p.i.). Coinfusion of 150 mg/kg Gelofusin resulted in a 50% reduction of the kidney retention at 15 min and 30 min p.i.. No significant difference in tumor uptake was observed between the two groups.

Future work will aim at optimizing 213Bi-labeled Nbs regarding optimal in vivo pharmacokinetic properties: high in vivo stability, sufficiently high tumor accumulation, fast clearance of the unbound fraction and limited radiation exposure to healthy risk organs.

Funding Agency

Belgian Nuclear Research Center (SCK•CEN)

Email Address

yana.dekempeneer@sckcen.be

Presentation Type

Contributed Oral

Primary author: Ms DEKEMPENEER, Yana (1992)

Co-authors: Prof. MORGENSTERN, Alfred (European Commission, Joint Research Centre, Department for Nuclear Safety and Security); Prof. XAVIER, Catarina (Vrije Universiteit Brussel (VUB), In

vivo Cellular and Molecular Imaging Laboratory); Mr MAERTENS, Dominic (Belgian Nuclear Research Center (SCK•CEN), Institute for Nuclear Materials Science); Prof. BRUCHERTSEIFER, Frank (European Commission, Joint Research Centre, Department for Nuclear Safety and Security); Dr OOMS, Maarten (Belgian Nuclear Research Center (SCK•CEN), Institute for Nuclear Materials Science); Prof. D'HUYVETTER, Matthias (Vrije Universiteit Brussel (VUB), In vivo Cellular and Molecular Imaging Laboratory); Dr GYSEMANS, Mireille (Belgian Nuclear Research Center (SCK•CEN), Institute for Nuclear Materials Science); Prof. CARDINAELS, Thomas (Belgian Nuclear Research Center (SCK•CEN)); Prof. LAHOUTTE, Tony (UZ Brussel, Department of Nuclear Medicine); Prof. CAVELIERS, Vicky (Vrije Universiteit Brussel)

Presenter: Ms DEKEMPENEER, Yana (1992)

Contribution ID: **27** Type: **not specified**

212Pb-NNV003 as a novel targeted alpha therapy for CD37 positive B-cell chronic lymphocytic leukemia (CLL) and non-Hodgkin lymphoma (NHL)

Background

Chronic lymphocytic leukemia (CLL) is the most common leukemia in adults in western countries, accounting for approximately one quarter of all leukemias and Non-Hodgkin lymphoma (NHL) caused an estimated 200,000 cancer deaths worldwide in 2014. More than 90,000 cases of chronic lymphocytic leukemia (CLL) and non-Hodgkin lymphoma (NHL) are expected in the US each year. Immuno-chemotherapy using anti-CD20 monoclonal antibodies (mAb) in combination with DNA alkylating agents is the front-line therapy of CLL and NHL. Despite promising initial results, relapses after repeated administration of immuno-chemotherapy are frequent and relapsed/refractory patients show poor prognosis. As CD37 is strongly and selectively expressed on the surface of mature B lymphocytes and B-cell malignancies, the development of new therapies targeting CD37 expressing cells may prove useful for relapsed or refractory patients as an alternative to CD20 targeting agents. We have developed a targeted alpha therapy (TAT) where the CD37-specific antibody NNV003 is coupled to the *in-vivo* alpha-particle-generator, 212Pb. When treated with alpha radiation, targeted cancer cells are exposed to high linear energy transfer (LET). LET acts over a short range (50–100 μm), causing double strand breaks in the DNA of targeted cells while sparing adjacent normal tissues

Materials and Methods

The efficacy of a single escalating 212Pb-NNV003 administration was evaluated on disseminated models of human Burkitt's lymphoma (Daudi) and CLL (MEC-2). 10 million Daudi cells or 2.5 million MEC-2 cells were intravenously injected in CB17-SCID or R2G2 mice and 212Pb-NNV003 was given two days later. Unspecific, 212Pb-labeled antibody was used as control. Dose range finding and tolerability studies were performed in CB17-SCID and R2G2 tumor-free mice to define the maximum tolerated dose prior to the efficacy studies.

Results

212Pb-NNV003 displays a favorable toxicity profile after a single intravenous injection in tumor-free mice. No acute hematological toxicity was observed, and animals presented only a slight initial reduction in their platelets (PLT) counts which was fully recovered 4-weeks after injection. A single intravenous dose of 10, 15 or 20 μCi of 212Pb-NNV003 led to 70 %, 90 % and 100 % of mice injected with MEC-2 cells being tumor free 20 weeks post cell injection. Control animals that received saline, cold antibody or 212Pb-cetuximab presented a median survival of 4.9, 5.4 and 9.3 weeks, respectively.
A single intravenous dose of 2.5, 5 and 7.5 μCi 212Pb-NNV003 led to over 80% tumor-free mice injected with Daudi cells 15 weeks post cell injection. Control animals that received saline, cold antibody or 212Pb-cetuximab presented a median survival of 7, 7.8 and 7.7 weeks, respectively.

Conclusion

The results of preclinical studies suggest that TAT using 212Pb-NNV003 may have positive clinical implication for the treatment of CD37 positive CLL and NHL.

Email Address

amal.saidi@oranomed.com

Presentation Type

Contributed Oral

Primary author: Dr SAIDI, Amal (Orano Med)

Co-authors: Dr MAALAND, Astri (Nordic Nanovector); Dr HEYERDAHL, Helen (Nordic Nanovector); Dr DAHLE, Jostein (Nordic Nanovector); Dr TORGUE, Julien (Orano Med)

Presenter: Dr SAIDI, Amal (Orano Med)

Track Classification: Preclinical

Contribution ID: **28** Type: **not specified**

Increased uptake of At-211 in thyroid gland by the preparation with ascorbic acid for targeted alpha therapy of thyroid cancer

Objectives: Astatine-211 (²¹¹At) is an alpha-emitting radionuclide suitable for targeted alpha therapy. Because At is a heavier homolog of iodine, astatide ion (At^-) is expected to be applied to the treatment of thyroid cancer. In this study, ²¹¹At was treated by ascorbic acid (AA) as reducing agent to prepare At^-. We aimed to evaluate the uptake change in the thyroid after the preparation of ²¹¹At solutions with AA and demonstrate the treatment effect in the differentiated thyroid cancer xenograft mice.

Method: Astatine-211 was produced in the ²⁰⁹Bi(α, 2n) reaction and supplied through Short-lived RI Supply Platform. Produced ²¹¹At was then separated from the target materials by a dry distillation method and dissolved in pure water. The aliquot of ²¹¹At solution was mixed with 1% AA solution to prepare At^-. The radiochemical yield was checked by radio-TLC. The crude ²¹¹At solution or ²¹¹At with AA solution was administered to normal rats (n=3 for both solution) through tail vein under isoflurane anesthesia. In vivo imaging of ²¹¹At in the normal rats was then carried out using a gamma camera at 0.5, 3, 6 and 24 hrs after administration. The ²¹¹At solution with AA was also administered to mice with implanted K1 cells (human papillary thyroid carcinoma) expressing sodium iodide symporter (NIS). Mice were divided into 4 groups according to the injected dose [1 MBq (n=6), 0.4 MBq (n=6), 0.1 MBq (n=6), control (n=6)]. Distribution of ²¹¹At administered in the mice was investigated at 3 and 24 hrs after administration by the gamma camera.

Results: The radiochemical yield of At^- checked by radio-TLC increased from approximately 20% to 90% after treatment of the crude ²¹¹At solution with AA. In vivo imaging of ²¹¹At in the normal rats showed high uptakes in the thyroid, the stomach, and the bladder. Uptake of At with AA in thyroid gland was 2–3 times higher compared to crude ²¹¹At solution. In the xenograft mice, there was a stable accumulation in the thyroid tumor at 3 and 24 hrs post administration (23 ± 11 %ID and 13 ± 7 %ID, respectively). Tumor growth was immediately inhibited after administration of ²¹¹At in a dose-dependent manner. Suppression of tumor growth was maintained until 17, 31, and 41 days after administration of ²¹¹At in 0.1, 0.4, and 1 MBq groups, respectively.

Conclusion: Uptake of ²¹¹At can be enhanced in the normal thyroid by increasing the radiochemical purity of At^-. The administered ²¹¹At showed good treatment effect in thyroid cancer xenograft, suggesting that ²¹¹At solution with AA is promising for the targeted alpha therapy for the thyroid cancer.

Email Address

ooe@tracer.med.osaka-u.ac.jp

Presentation Type

Contributed Oral

Primary author: Dr OOE, Kazuhiro (Department of Nuclear Medicine and Tracer Kinetics, Osaka

University Graduate School of Medicine)

Co-authors: Dr SHINOHARA, Atsushi (Department of Chemistry, Graduate School of Science, Osaka University); Dr TOYOSHIMA, Atsushi (Institute for Radiation Sciences, Osaka University); Dr SHIMOSEGAWA, Eku (Department of Molecular Imaging in Medicine, Osaka University Graduate School of Medicine); Dr HATAZAWA, Jun (Department of Nuclear Medicine and Tracer Kinetics, Osaka University Graduate School of Medicine); Dr KANEDA-NAKASHIMA, Kazuko (Project Research Center for Fundamental Sciences, Graduate School of Science, Osaka University); Dr FUKUDA, Mitsuhiro (Rsearch Center for Nuclear Physics, Osaka University); Dr WATABE, Tadashi (Department of Nuclear Medicine and Tracer Kinetics, Osaka University Graduate School of Medicine); Dr SHIRAKAMI, Yoshifumi (Department of Nuclear Medicine and Tracer Kinetics, Osaka University Graduate School of Medicine); Ms LIU, Yuwei (Department of Nuclear Medicine and Tracer Kinetics, Osaka University Graduate School of Medicine)

Presenter: Dr OOE, Kazuhiro (Department of Nuclear Medicine and Tracer Kinetics, Osaka University Graduate School of Medicine)

Contribution ID: **29** Type: **not specified**

Development of actinium-225 production method using liquid target

To prepare the radioisotope Ac-225 using the liquid target of the Ra-226 chloride, and to evaluate the durability of the liquid target for this purpose. We will use Barium, a family like Radium.
The Ba target was prepared by dissolving BaCl2 in DI water. An amount of 20 g/100 mL was prepared considering the solubility of BaCl2 (35.8 g/100 mL, 20 ℃) and the amount of 2 mL was loaded on the liquid target.
The beam test was carried out using CYCLON 30 Cyclotron (Korea Institute of Radiological & Medical Sciences, IBA, 2001). The target was a large-volume liquid target of IBA and irradiated with energy of 15 - 30 MeV. To optimize irradiation energy and current conditions.
To confirm the nuclear transformation, the irradiated target was analyzed using the HPGe detector for γ-spectrum.

Email Address

kyochul@kirams.re.kr

Presentation Type

Poster

Primary author: Dr OH, Se Young (KIRAMS)

Co-authors: Dr JUNG, Haijo (KIRAMS); Dr LIM, Ilhan (KIRAMS); Dr LEE, Kyo Chul (KIRAMS); Dr LIM, Sang Moo (KIRAMS)

Presenter: Dr LEE, Kyo Chul (KIRAMS)

Contribution ID: **30** Type: **not specified**

Implementation of Single Alpha-Particle Traversal Microdosimetric Model

Background:
Radiotherapy is one of the commonly used approaches to treat cancer. Current research trend and breakthroughs in radiotherapy are focusing on high linear energy transfer (LET) radiation such as alpha particles. Targeted Alpha Therapy (TAT) is the most important application of alpha particles in the development of radiotherapy in the past decade. This paper highlights the research work done on computational modelling of TAT at Canadian Nuclear Laboratories (CNL).

Methods:
• Develop a single-event, computational alpha-particle traversal microdosimetric model based on commercial spreadsheet developed by Roseke [1] using Monte Carlo method.
• Modify the single event alpha-particle traversal microdosimetric model to calculate the energy deposited within the cellular nucleus with known location of alpha particle (provided by the CFD simulation), and
• Integrate the single event alpha-particle traversal microdosimetric model and CFD model to calculate the energy deposited on cellular nucleus of an alpha particle in blood flow.

Results:
A coupled model based on the Monte Carlo micro-dosimetry technique and Computational Fluid Dynamics analysis was established. Transient drug delivery process and background dose to the cells along the pathway were investigated. A mesoscale numerical simulation in a simplified 2D capillary was performed to determine the transient toxicity of the Alpha-Immuno-Conjugate to the targeted cell.

Conclusions:
The paper demonstrates the feasibility of coupling CFD simulations and microdosimetic modeling to evaluate the efficacy of the TAT methodology realistically and accurately.

Reference:
[1] John C Roeske and Mark Hoggarth, "Alpha-particle Monte Carlo simulation for microdosimetric calculations using a commercial spreadsheet", Phys. Med. Biol. 52 (2007) 1909–1922.

Funding Agency

Canadian Nuclear Laboratories

Email Address

tong.liu@cnl.ca

Presentation Type

Poster

Primary author: Ms LIU, Tong (Candadian Nuclear Laboratories)

Co-authors: Mr DUGAL, Clifford (CNL); Dr LI, Gang (CNL); Dr XU, Tong (CNL)

Presenter: Ms LIU, Tong (Candadian Nuclear Laboratories)

Contribution ID: **31** Type: **not specified**

Synthesis of 4-[^{211}At]astato-L-phenylalanine via electrophilic demetallation from a silylprecursor

Background: Astatine-211 (^{211}At) labeled compound, 4-[^{211}At]astato-L-phenylalanine, is one of the promising amino acid derivatives for targeted alpha therapy (TAT) for various cancers. Electrophilic demetallation of stannyl precursor is the most widely used approach for labeling biomolecules with ^{211}At. However, the low acid-resistance of the stannyl precursor necessitates the use of a N- and C-terminus protected precursor, which causes low overall radiochemical yield (RCY) due to the multiple synthetic steps involved. A deprotected organosilyl compound, 4-triethylsilyl-L-phenylalanine, was employed for direct synthesis of the astatinated phenylalanine in this study.
Methods: ^{211}At was produced by irradiating $^{4}He^{2+}$ beams with 28.1 MeV to a bismuth-209 (^{209}Bi) target. ^{211}At was isolated from the irradiated target and recovered with $CHCl_3$ or *N*-chlorosuccinimide-methanol (NCS-MeOH) solution. The ^{211}At solution was evaporated to dryness with the gentle flow of N_2 gas. After adding 4-triethylsilyl-L-phenylalanine (200 μg/5μL MeOH), NCS (400 μg/20 μL MeOH), and 0.3 M of methanol-acetic acid solution (20 μL), the mixture was evaporated to dryness again. For the synthesis of 4-[^{211}At]astato-L-phenylalanine using ^{211}At in NCS-MeOH solution, extra NCS addition to the residue was excluded in this step. Trifluoroacetic acid (20 μL) was then added to the mixture and heated at 70 ℃ for 10 min in both cases. A human colon adenocarcinoma cell line, LS180, was incubated with synthesized 4-[^{211}At]astato-L-phenylalanine at 37 ℃ for up to 30 min. For the inhibition assay, LS180 was incubated with some amino acid derivatives for 10 min., followed the incubation of 4-[^{211}At]astato-L-phenylalanine.
Results: The radiochemical yields obtained from the triethylsilane precursor with ^{211}At in $CHCl_3$ and MeOH-NCS solution, were 75% and 64% respectively. In both cases, the retention time of the desired compound was found to be 20 min, which showed reasonable correlation with the retention time of non-radioactive halogenated phenylalanines. It should be noted that the one step reaction involved mild reaction conditions (70 ℃) and a short time (10 min) compared to the other currently reported procedures for astatination. Uptake of 4-[^{211}At]astato-L-phenylalanine by LS180 was time-dependently increased and then plateaued at about 20 min after incubation. Inhibition assays using several amino acid derivatives demonstrated that uptakes in the presence of BCH, Leu, Phe, and Tyr were significantly reduced compared to uptake of the control. These results clearly showed that 4-[^{211}At]astato-L-phenylalanine was successfully synthesized in this study. In addition, In vitro study would give us valuable information for the characterization of astatinated compounds with no stable isotopes.
Conclusion: Electrophilic desilylation was found to be very effective for the labeling of amino acids with ^{211}At. This method is also applicable to the synthesis of astatinated peptides for TAT.

Email Address

watanabe.shigeki@qst.go.jp

Presentation Type

Poster

Primary author: Dr WATANABE, Shigeki (QST, Japan)

Co-authors: Dr MOHAMMAD ANWAR-UL, Azim (QST Japan; NINMAS, BAEC, Bangladesh); Dr NISHINAKA, Ichiro (QST, Japan); Mr SASAKI, Ichiro (QST, Japan); Dr YAMADA, Keiichi (Gunma Univ. Graduate School of Science and Technology, Japan); Dr ISHIOKA, Noriko, S. (QST, Japan); Dr OHSHIMA, Yasuhiro (QST, Japan)

Presenter: Dr WATANABE, Shigeki (QST, Japan)

Contribution ID: **32** Type: **not specified**

Novel Neuromorphic Computing based Monte Carlo Simulation of Alpha Particles Penetration into Tumor Cells in Targeted Alpha Therapy

Recent breakthrough of radiotherapy to cancers focuses on the high linear energy transfer (LET) radiation, e.g., the alpha particles. Targeted Alpha Therapy (TAT) is an important option of radiotherapeutic method for the treatment of cancers. TAT uses an alpha-immuno-conjugate (AIC) comprising a tumor selective molecule, which attaches to the surface of specific tumor cells selectively and then undergoes alpha decay to destroy the tumor cells. Monte Carlo (MC) calculations are a well-suited method to accurately simulate the energy deposited by ionizing radiation in very small biological structures such as DNA. Thus, MC simulation is the essential technology to estimate Alpha particles penetration into tumors and to accurately determine the optimum therapeutic dose of TAT. However, the computation complexity of MC in the TAT scenario is extremely expensive and then it is impractical to estimate the optimum therapeutic dose under the clinical setting. Consequently, it is very necessary to explore a highly effective computation solution to make alpha particle penetration simulation practical for TAT.

MC method is usually based on massive parallel computing, and neuromorphic computing-based solution is a promising solution to achieve large speed-up of computing effectiveness for the MC simulation. By simply mimicking computing mechanism of human brain, the neuromorphic 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.

Email Address

chliu@clarkson.edu

Presentation Type

Contributed Oral

Primary author: Dr LIU, Yu (Clarkson University)

Co-author: Dr LIU, Chenchen (Clarkson University)

Presenter: Dr LIU, Yu (Clarkson University)

Contribution ID: **33** Type: **not specified**

Isolation of At-211 by dry-distillation under oxidative conditions for targeted alpha therapy in Osaka University

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 ²¹¹At which can be produced in nuclear reactions using an accelerator. At present, cyclotron production, chemical separation, radiopharmaceuticals preparation, and pre-clinical trials of ²¹¹At are under study. In this contribution, our cyclotron production and chemical purification of ²¹¹At are presented.

Astatine-211 was produced in the ²⁰⁹Bi(α, 2n)²¹¹At 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 μA for a few hours. The Bi target was set at 45^o 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 ²¹¹At 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 840^oC. Vapored At species were transported to a Teflon tube cooled with ice water. During accumulation of ²¹¹At in the trap, a trapped amount of ²¹¹At was monitored with a CdTeZn detector. After a few tens of minutes, trapped ²¹¹At was stripped with 100 μL of distilled water at a flow rate of 250 μL/min. The radioactivity of ²¹¹At was determined by γ-ray spectrometry using a Ge detector. The ²¹¹At solution was supplied to pharmaceutical preparations, pre-clinical tests, and/or our chemical analysis. Recovery yield of ²¹¹At 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.

Email Address

toyoshima@chem.sci.osaka-u.ac.

Presentation Type

Contributed Oral

Primary author: Dr TOYOSHIMA, Atsushi (Institute for Radiation Sciences, Osaka University)

Co-authors: Mr KANDA, Akimitsu (Graduate School of Science, Osaka University); Prof. SHINOHARA, Atsushi (Graduate School of Science, Osaka University); Dr OOE, Kazuhiro (Department of Nuclear Medicine and Tracer Kinetics, Osaka University Graduate School of Medicine); Dr NAGATA, Kojiro (Institute for Radiation Sciences, Osaka University); Mr ICHIMURA, Soichiro (Graduate School

of Science, Osaka University); Prof. YOSHIMURA, Takashi (Institute for Radiation Sciences, Osaka University); Mr IKEDA, Takumi (Graduate School of Science, Osaka University); Dr ZHANG, Zijian (Graduate School of Science, Osaka University)

Presenter: Dr TOYOSHIMA, Atsushi (Institute for Radiation Sciences, Osaka University)

Contribution ID: **34** Type: **not specified**

Nanoparticles for the treatment of metastatic non small cell lung cancer with 225Ac

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 5-year 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 α-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 α radiations from the in vivo α-generator 225Ac at biologically relevant receptor sites while also containing the radioactive daughters at those sites. The layered nanoparticles (NP) consist of an 225Ac-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, 225Ac-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, 213Bi, 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 225Ac nanoparticles to A549 NSCLC grown in a mouse orthotopic lung cancer model, while a spontaneous cancer model in canine patients is also being explored.

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)

Email Address

maitzc@missouri.edu

Presentation Type

Contributed Oral

Primary author: Dr MAITZ, Charles (University of Missouri)

Co-authors: Prof. ROBERTSON, J. David (University of Missouri); EMBREE, Mary (University of Missouri); KUMAR, Senthil (University of Missouri)

Presenter: Dr MAITZ, Charles (University of Missouri)

Contribution ID: **35** Type: **not specified**

Optimization of dosimetry in alphatherapy: microlocalisation of 223Ra in mouse models of metastasis from prostate cancer and renal cell carcinoma.

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 223Ra, 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 223Ra (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 223Ra.
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 223Ra uptakes between the healthy tibia and the diseased one. In both tibias, 223Ra is homogeneously distributed in the cortical and trabecular bone. Moreover, there is an important uptake of 223Ra in the growth plate, in both tibias. This uptake is higher in the healthy tibias than in the diseased ones. 223Ra does not localize directly to the tumor, regardless of type. Instead, activity accumulates at the apposite bone surface surrounding the lesion.
The differences of 223Ra 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 223Ra, 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

Email Address

benabdallah.nadia@live.fr

Presentation Type

Contributed Oral

Primary author: Dr BENABDALLAH, Nadia (Institute for Radiological Protection and Nuclear Safety)

Co-authors: Dr CHAUCHEREAU, Anne (INSERM U981, Gustave Roussy Institute); Dr DESBRÉE, Aurélie (Institute for Radiological Protection and Nuclear Safety); Ms SAI-MAUREL, Catherine (Nantes-Angers Cancer Research Center CRCINA INSERM, University of Nantes); Dr DE LABRIOLLE--VAYLET, Claire (Trousseau Hospital); Dr FRANCK, Didier (Institute for Radiological Protection and Nuclear Safety); Mr KERESELIDZE, Dimitri (Institute for Radiological Protection and Nuclear Safety); Dr BERTHO, Jean-Marc (Institute for Radiological Protection and Nuclear Safety); Dr DONNARD, Jérôme (Ai4r); Dr CHEREL, Michel (Nantes-Angers Cancer Research Center CRCINA INSERM, University of Nantes); Mrs BERNARDINI, Michela (European Georges Pompidou Hospital); Dr CHOUIN, Nicolas (Nantes-Angers Cancer Research Center CRCINA INSERM, University of Nantes); Dr LERONDEL, Stéphanie (Imaging Department CIPA PHENOMIN-TAAM-UPS44, CNRS Orléans); Mr GOUARD, Sébastien (Nantes-Angers Cancer Research Center CRCINA INSERM, University of Nantes)

Presenter: Dr BENABDALLAH, Nadia (Institute for Radiological Protection and Nuclear Safety)

Contribution ID: **36** Type: **not specified**

Evaluation of novel antibodies to Centrin-1 for radioimmunotherapy of pancreatic cancer

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 213Bi, an alpha emitter, or with 177Lu, 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 microSPECT/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 213Bi 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, 177Lu-labeled antibody was not very effective in slowing down tumor growth with no difference from 177Lu-IgG control (P=0.06) and was several folds less effective than 213Bi-labeled antibody. Both 213Bi and 177Lu 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.

Email Address

jiaorubin9712@hotmail.com

Presentation Type

Poster

Primary author: Dr JIAO, Rubin (University of Saskatchewan)

Co-authors: Dr RICKLES, David (RadImmune Therapeutics); Dr DADACHOVA, Ekaterina (University of Saskatchewan); SMART, K (Albert Einstein College of Medicine); Dr ALLEN, Kevin (University Of Saskatchewan); Mrs MALO, Mackenzie (University of Saskatchewan); Dr BRYAN, Ruth (Albert Einstein College of Medicine); BUHL, S (Albert Einstein College of Medicine); Mr JIANG, Zewei (Albert Einstein College of Medicine)

Presenter: Dr JIAO, Rubin (University of Saskatchewan)

Contribution ID: **37** Type: **not specified**

Evaluation of inorganic ion exchange materials for purification of 225Ac from thorium and radium radioisotopes

Targeted alpha therapy with Actinium-225 (225Ac) or its daughter Bismuth-213 (213Bi) is an emerging and promising treatment for various types of cancers. 225Ac can be produced from a 229Th/225Ra generator system or from proton irradiated 232Th at high or 226Ra at low proton energies. Several types of inorganic ion exchange materials were synthesized to aid in chemical separations. Distribution coefficients (Kd) were determined for 225Ac, 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 227Th and 223Ra while 225Ac passed through. Further 227Th and 223Ra were recovered by eluting with different pH solution. In the optimized purification method >90% of 225Ac was recovered with radiopurity >99% (calculated from 225Ac, 227Th and 223Ra). The studies further showed the material could be used for a single column separation of 225Ac from the 229Th/225Ra generator. The capacity of the inorganic ion exchange materials for Barium and 232Th 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 225Ac from a ~300 mg production scale 226Ra target. However, the material would not have the capacity needed for a 50-100 g production scale 232Th 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

Email Address

jfitzsimmons@bnl.gov

Presentation Type

Contributed Oral

Primary authors: YOUNES, Ali (Medical Isotope Research & Production Program, Collider-Accelerator Department, Brookhaven National Laboratory, NY, 11973, USA); ABRAHAM, Alyson (Department of Chemistry, Stony Brook University, Stony Brook, NY 11794); CUTLER, Cathy S. (Medical Isotope Research & Production Program, Collider-Accelerator Department, Brookhaven National Laboratory, NY, 11973, USA); CATALANO, Dametra (Biochemistry Department, Stony Brook University, Stony Brook, NY 11794); MEDVEDEV, Dmitri (Medical Isotope Research & Production Program, Collider-Accelerator Department, Brookhaven National Laboratory, NY, 11973, USA); FITZSIMMONS, Jonathan

(Medical Isotope Research & Production Program, Collider-Accelerator Department, Brookhaven National Laboratory)

Presenter: FITZSIMMONS, Jonathan (Medical Isotope Research & Production Program, Collider-Accelerator Department, Brookhaven National Laboratory)

Contribution ID: **38** Type: **not specified**

Coordination Chemistry of +3 Actinium

Targeted alpha therapy (TAT) represents an emerging technology that has potential in treatment of disease. Amongst many isotopes showing promise in TAT, 225-actinium (225Ac) 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

Email Address

stosh@lanl.gov

Presentation Type

Contributed Oral

Primary author: Dr KOZIMOR, Stosh (Los Alamos National Laboratory)

Co-authors: Dr MORGENSTERN, Amanda (LANL); Dr STEIN, Benjamin (LANL); Dr BATISTA, Enrique (LANL); Dr BIRNBAUM, Eva (LANL); Dr JOHN, Kevin (LANL); Dr LILLEY, Laura (LANL); Dr MOCKO, Veronika (LANL)

Presenter: Dr KOZIMOR, Stosh (Los Alamos National Laboratory)

Track Classification: Targeting

Contribution ID: **39** Type: **not specified**

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

Thorium-229 Generator Production of Actinium-225 at Oak Ridge National Laboratory
Shelley Van Cleve, Paul Benny, Thomas Dyke, Jay Kehn, Kayla Phillips, Rose Boll
Oak Ridge National Laboratory, Oak Ridge, TN 37831
Background and Objective: Oak Ridge National Laboratory (ORNL) is a major producer of 225Ac and supplies research and clinical trials for the treatment of various forms of cancer with this promising radioisotope. Actinium-225 (t1/2 = 10 days) has nuclear properties well suited for use in targeted alpha therapy, emitting four α-particles in a decay cascade via short half-life daughters. It can also be used as a generator for 213Bi (t1/2 = 45.6 min.). ORNL has been producing and shipping 225Ac for research and clinical applications since 1997. During the first year of production, a total of 135 mCi was shipped. Since then, production levels have steadily increased, and in 2018, ORNL produced ~800 mCi of 225Ac in 13 processing campaigns. From 1997 through the end of calendar year 2018, ORNL conducted 145 production campaigns and provided 11.2 Ci in over 1,200 shipments. ORNL's objective is to continually improve quality and quantity of product to meet the increasing demand for 225Ac using the limited amount of high-purity 229Th currently available.
Separation and Purification: The chemical separation process consists of anion exchange separation using hydrochloric and nitric acids followed by cation exchange separation for the final purification. Gamma spectroscopy is used for quality control analysis of the final product before shipping, and mass spectroscopy data is used to evaluate chemical purity.
Results: Various processing schedules have been used for the production of the 225Ac, depending on the needs of the scientific community, staffing, and funding. This presentation will review various production sequences and present ways to optimize production from ORNL's current 229Th cow. ORNL's goal is to continue to produce high-quality 225Ac for use in research and clinical trials.
Research supported by the U.S. Department of Energy (DOE) Office of Science, Office of Nuclear Physics, under contract DE-AC05-00R22725 with UT-Battelle, LLC.

Funding Agency

DOE Isotope Program

Email Address

bollra@ornl.gov, eov@ornl.gov

Presentation Type

Poster

Primary author: Ms VAN CLEVE, Shelley (Oak Ridge National Laboratory)

Co-authors: Mr KEHN, Jay (ORNL); Ms PHILLIPS, Kayla (ORNL); Dr BENNY, Paul (ORNL); Dr

BOLL, Rose (ORNL); Mr DYKE, Thomas (ORNL)

Presenters: Dr BOLL, Rose (ORNL); Ms VAN CLEVE, Shelley (Oak Ridge National Laboratory)

Contribution ID: **40** Type: **not specified**

Glycoprotein 41 targeted radioimmunotherapy as a novel treatment for neuroHIV/AIDS

The HIV epidemic is a major global health threat. Nowadays HIV-infected individuals live much longer due to the inhibition of the viral replication by combined anti-retroviral therapy (cART). However, cART fails to eradicate the residual HIV-infected cells, therefore, virus persists and continues to cause damage both systemically and to central nervous system (CNS). HIV enters the CNS in infected monocytes shortly after peripheral exposure. The infection of CNS poses a challenge due to strict regulation of the entry of molecules into the brain by the blood brain barrier (BBB) which limits many cART regimens from reaching effective levels in the brain. Radioimmunotherapy (RIT) uses antigen-specific monoclonal antibodies (mAbs) for targeted delivery of cytocidal ionizing radiations to cells. The distinct advantages of RIT are its relative independence from the immune status of the patient and secondly, it is not subject to drug resistance mechanisms. These features are very useful in the management of HIV-infected individuals. The challenge in extending the RIT approach to the elimination of HIV in the CNS lies in the difficulty of the therapeutic molecules to penetrate through the BBB. Recently we have demonstrated that an antibody 2556 to gp41 was able to penetrate the in vitro human BBB and to kill infected cells in the brain compartment of the BBB model (McFarren et al AIDS 2016). In this study we have identified six human mAbs with higher pI (> 8.5) that recognizes a conserved region of HIV gp41. The penetration of these antibodies through in vitro human BBB model was pI dependent. We are now using these novel gp41-binding human mAbs conjugated with three different radioisotopes (213Bi, 188Re or 177Lu) enabling their more efficient penetration into the CNS through the intact BBB. To achieve this, monocytes are infected with HIV and then treated with radiolabelled mAbs. Finally, to validate these novel radiolabeled molecules, we will use a human in vitro BBB model to assess the ability of these mAbs to penetrate the BBB and to kill the HIV infected monocytes in the brain compartment of the BBB model. This study will provide a novel treatment option for the eradication of HIV-1 infection and will also be useful for treatment of drug-resistant HIV strains.

Funding Agency

National Institutes of Health

Email Address

ravendra.garg@usask.ca

Presentation Type

Poster

Primary author: Mr GARG, Ravendra (University of Saskatchewan)

Co-authors: Dr EKATERINA, Dadachova (University of Saskatchewan); Ms MILLS, Kienna (University of Saskatchewan)

Presenter: Mr GARG, Ravendra (University of Saskatchewan)

Contribution ID: **41** Type: **not specified**

FLUKA simulation of Ac-225 production with a medical cyclotron

Alpha-emitting Ac-225 is a radionuclide being developed and used in the treatment of some cancers [1]. Currently, the Department of Energy (DOE) isotope program's Tri-Lab Effort (Brookhaven National Laboratory, Oak Ridge National Laboratory, Los Alamos National Laboratory) effort provides Ac-225 from a Thorium target irradiated with a high energy proton beam [2]. We have a plan to make Ac-225 from Ra-226 target using the relatively low energy proton beam from a medical cyclotron.
FLUKA is a general-purpose Monte Carlo simulation code used to model the interaction and transport of particles from a few KeV to thousands of TeV in arbitrary materials. It is built and maintained with the aim of including the best possible physical models in terms of completeness and precision [3]. In this study, we are using the RESNUCLEi card to score the residual isotopes and activities from the Ra-226 target irradiated in the EBCO TR19 cyclotron.
For the simulation, we used 300 mg of Ra-226 (5.0 g/cm3) which is 8.0E+20 atoms. These atoms can be deposited as a 0.0086 cm thick layer on a 1.58 X 4.45 X 0.234 cm aluminum plate. The Ra-226 target geometry is specially designed to fit the solid target holder for the EBCO TR19 cyclotron. The EBCO TR19 cyclotron proton beam energy range is from 13 to 19 MeV and the beam current is 200 μA (1.248E+15 protons/s). At 19 MeV, the highest proton beam energy, protons can penetrate 0.198 cm of Ra-226 (13 MeV, 0.106 cm) and 0.192 cm of aluminum. Thus, the proton beam penetrates the radium layer and is completely stopped in the aluminum plate. Ra-226 target irradiations were simulated using a 40 hours irradiation time using a varied particle energy from 13 to 19 MeV and 200 μA proton beam currents to find the best conditions for Ac-225 production in the EBCO TR19 cyclotron.
The maximum yield for the Ac-225 production was obtained at the beam energy 14.5 MeV. The amount of the produced Ac-225 from Ra-226 target is about 340 mCi at EOB.

References

[1] David A. Scheinberg and Michael R. McDevit. Actinium-225 in targeted alpha-particle therapeutic applications. Curr Radiopharm. 2011 Oct; 4(4): 306–320.
[2] The Journey of Actinium-225: How Scientists Discovered a New Way to Produce a Rare Medical Radioisotope. DOE News. https://science.energy.gov/news/featured-articles/2018/06-20-18/
[3] Giuseppe Battistoni et al. Overview of the FLULA code. Annals of Nuclear Energy. 2015 Aug. Vol 82, Pages 10-18.

Acknowledgments

This research supported by the Department of Energy Office of Science's Isotope Program.

Email Address

dohkim@bnl.gov

Presentation Type

Poster

Primary author: Dr KIM, Dohyun (Collider-Accelerator Department, Brookhaven National Laboratory, Upton, NY 11973, USA)

Co-authors: Dr CUTLER, Cathy S. (Collider-Accelerator Department, Brookhaven National Laboratory, Upton, NY 11973, USA); Dr BENMERROUCHE, Mohamed (Radiological Control Division / National Synchrotron Light Source II, Brookhaven National Laboratory, Upton, NY 11973, USA)

Presenter: Dr KIM, Dohyun (Collider-Accelerator Department, Brookhaven National Laboratory, Upton, NY 11973, USA)

Contribution ID: **42** Type: **not specified**

Production of 211At at the Copenhagen University Hospital, Denmark.

Production of At-211 at the Copenhagen University Hospital, Denmark.

Holger J. Jensen, PET and Cyclotron Unit, Copenhagen University Hospital, DK-2100, Copenhagen, Denmark.

Objective
There is a great interest in At-211 for alpha radio immunotherapy. However the production of At-211 is difficult and it can only be produced in few accelerator facilities worldwide. In Copenhagen we have produced At-211 for more than 18 years at our Scanditronix MC32 cyclotron. The special features of this cyclotron will be discussed together with a presentation of results, data and experience from our more than 500 productions.

Method
The general accelerator production route of At-211 is via the 209Bi(α,2n)211At reaction using beam energies of 28-29 MeV, but only very few cyclotrons worldwide are capable of making α- beams with the necessary energies. Most cyclotrons today are build for acceleration of only negative ions and in many cases only H-. The Scanditronix MC32 cyclotron at the Copenhagen University Hospital, Copenhagen, Denmark, is a negative-ion cyclotron for dual beam irradiation at two beam lines with variable proton and deuteron energies of 16-32 and 8-16 MeV respectively. A special feature of this cyclotron enables all magnetic elements of the cyclotron to be reversed. Combined with the design of our RF system, this allows in addition the acceleration of positive ions and α-particles for internal target bombardment.

Targets are prepared on 30×28×5 mm aluminium backings, at the Department of Physics, Chalmers University of Technology, Gothenburg, Sweden, using highly enriched (99.999%) Bi-209 layers of 24±2 mg/cm2. To stabilize the Bi-209 layer and to prevent diffusion of produced 211At out of the target surface during irradiation, an additional layer of 0,5±0,3 mg/cm2 pure aluminium are added on top of the Bi-209 layer. Irradiations are done at an internal water-cooled probe using beam energies of 28-29 MeV. Shortly after irradiation the target are transported to our only collaborator - the Department of Radiation Physics, Göteborg University, Sweden - by car within 4 hours for the final refinement of At-211. Upon arrival to Göteborg the At-211 are isolated using a dry distillation procedure previously described by Lindegren et al. (Appl. Radiat. Isot. 2001, 55(2), 157-160).

Results
With irradiation times of 3,8±0,2 hours and beam currents of 16,4±1,1 μA, we have produced activities of 1,23±0,19 GBq EOB in average over the last 10 years. This corresponds to a saturation yield of 246±31 MBq/μA, which corresponds very well with the expected yield of 240 MeV/μA given by Lambrecht et al (Appl. Radiat. Isot. 1985, 36, 443-450).

Conclusion
We have established a stable and reliable production of At-211, with activities relevant for both research and therapy. With only one production every second week we clearly have the capacity for more costumers.

Email Address

Holger.Jan.Jensen@regionh.dk

Presentation Type

Contributed Oral

Primary author: Dr JENSEN, Holger J. (Copenhagen University Hospital)

Presenter: Dr JENSEN, Holger J. (Copenhagen University Hospital)

Contribution ID: **43** Type: **not specified**

Safety profile and therapeutic efficacy of one cycle of [177Lu] PSMA in end stage metastatic castration resistant prostate cancer patients with low performance status

Introduction
Prostate cancer patients with distant metastasis have a poor prognosis and developed resistance to all standard drugs at various time intervals. A therapeutic option which can alleviate symptoms and prolong survival is in-search for these patients. [177Lu] prostate specific membrane antigen ([177Lu]PSMA) is a novel drug based on the theranostic concept. Here, we have presented the safety and efficacy profile of one cycle of [177Lu]PSMA in metastatic castration-resistant prostate cancer (mCRPC) patients who have exhausted all standard therapeutic options.
Methods
Twenty-two patients treated with at least first line anti-androgens and docetaxel were treated with one cycle of [177Lu]PSMA therapy on a compassionate basis. Haemoglobin, total leukocyte counts, platelets and serum creatinine for toxicity profile while prostate-specific antigen (PSA), eastern co-operative oncology group (ECOG) performance status, visual analogue scale (VAS) and analgesic quantification scale (AQS) for therapeutic efficacy were recorded pre and 8 weeks post-therapy. Wilcoxon signed-rank and ANOVA tests were used for statistical analysis.
Results
Partial response (PR), stable disease (SD) and progressive disease (PD) for PSA were seen in 5 (22.7%), 13 (59.1%) and 4 (18.2%) patients respectively treated with mean 6.88GBq dose of [177Lu]PSMA. 8/22 (36.4%) patients showed ≥ 30% drop in PSA. Grade 3 haemoglobin toxicity was seen in 5/22 (22.7%) patients. No patient developed grade 4 haemoglobin toxicity. No patients had grade 3 or 4 leukocytopenia or thrombocytopenia. Wilcoxon signed-rank test showed statistical significant ($p < 0.05$) difference in pre and post-treatment ECOG, VAS, AQS scores while it was insignificant for PSA ($P > 0.05$). ANOVA test showed a statistically significant difference in mean doses of [177Lu]PSMA used in three PSA response group while the difference was non-significant for other variables.
Conclusion
We concluded that [177Lu]PSMA therapy has adequate pain palliation in all end-stage mCRPC patients and it has the potential to become an effective therapeutic option in properly selected patients.

Keywords: [177Lu]PSMA, Safety, efficacy, mCRPC

Funding Agency

None

Email Address

docmanojgupta@yahoo.com

Presentation Type

Contributed Oral

Primary author: Dr GUPTA, Manoj (Rajiv Gandhi Cancer Institute and Research Centre, Delhi, India)

Co-authors: Mrs GUPTA, Amita (Rajiv Gandhi Cancer Institute and Research Centre, Delhi, India.); Dr SINGH, Amitabh (Rajiv Gandhi Cancer Institute and Research Centre, Delhi, India.); Prof. GOEL, Harish Chandra (Amity centre for radiation biology, Amity University, Noida, Uttar Pradesh India); Dr DUTTA, Kumar Deep (Rajiv Gandhi Cancer Institute and Research Centre, Delhi, India.); Dr CHOUDHURY, Partha (Rajiv Gandhi Cancer Institute and Research Centre, Delhi, India); Dr RAWAL, Sudhir (Rajiv Gandhi Cancer Institute and Research Centre, Delhi, India,); Dr TALWAR, Vineet (Rajiv Gandhi Cancer Institute and Research Centre, Delhi, India.)

Presenter: Dr GUPTA, Manoj (Rajiv Gandhi Cancer Institute and Research Centre, Delhi, India)

Contribution ID: **44** Type: **not specified**

High-Purity Actinium-225 Production from Radium-226 using a Superconducting Electron Linac

Niowave is operating a closed-loop cycle to domestically produce high-purity Ac-225 and other alpha emitters from Ra-226 using a superconducting electron linear accelerator. The commercial-scale system will produce 10 Ci per week of Ac-225 from a nitrate-based solution of Ra-226. The electron beam impinges on a photon converter to irradiate the Ra-226, inducing a photon-neutron reaction to Ra-225, which decays to Ac-225. Ac 225 is eluted continuously from the target vessel then centrifugal contactors are used to harvest and purify Ac 225 through a separation cascade. Unlike other production methods, including proton linacs (spallation of Th-232) and proton cyclotrons (Ra-226 bombardment), Niowave's method does not generate any Ac-227 contamination in the Ac-225 product. Niowave's superconducting linacs can handle higher production output (>500 Ci per year using a 20 MeV, 210 kW beam) than any other method. Demonstration-scale production of 10 mCi batches of Ac-225 at Niowave's HQ has begun and will be complete in April 2019. Niowave is in a unique position to quickly take the lead in alpha-emitters for cancer therapy because they have expertise in superconducting electron linacs and an NRC materials license to possess and irradiate Ra-226 while capturing gaseous radioisotopes and progeny. This presentation will focus on Niowave's scale up plans to full production including radium acquisition, NRC and FDA licensing strategies, and a path to profitability.

Email Address

grimm@niowaveinc.com

Presentation Type

Contributed Oral

Primary author: Dr GRIMM, Terry (Niowave, Inc.)

Co-authors: GRIMM, Amanda (Niowave, Inc.); ZAMIARA, Mike (Niowave, Inc.); Dr PETERS, William (Niowave, Inc.)

Presenter: Dr GRIMM, Terry (Niowave, Inc.)

Contribution ID: **45** Type: **not specified**

Proton Beam Production of Curie Scale Ac-225 at 100 MeV and Below

The DOE National Isotope Program for radionuclide production operates two intermediate energy, high intensity accelerator-based production facilities: The 100 MeV Isotope Production Facility (IPF) at Los Alamos National Laboratory and the 200 MeV Brookhaven Linac Isotope Producer (BLIP). They are two of only eight intermediate energy production facilities worldwide and often operate with record breaking beam intensities on target. These two facilities will be used for year-round Ci-scale batch production of Ac-225 via proton bombardment of thorium targets. High power targetry for this purpose is being developed as part of the US DOE Tri-Lab production development effort.

Production cross sections measured in recent years dictate that Ci-scale production at a 100 MeV facility such as IPF requires much higher beam currents than at higher energy facilities such as BLIP. As a result, targets used for production at these lower energies must withstand power levels that are higher by a factor that approaches an order of magnitude. While existing target designs have been used to successfully produce up to ~200 mCi at end-of-bombardment, improvements are needed to achieve Ci-scale production. As part of the US DOE Tri-Lab effort, ultra-high power thorium targets are being developed to withstand 100 MeV proton beam currents up to 450 μA. Based on thermal model predictions, a major emphasis is placed on the enhancement of thermal contact between the thorium target and its containment. Several enhancement approaches and techniques are being explored with the goal to down select and integrate the most appropriate technique into a procedure for the routine fabrication of IPF targets.

This presentation will provide a status update on the ongoing targetry R&D effort to achieve Ci-scale production. In the context of recent upgrades at IPF, updated Ac-225 production projections will also be presented based on expected target thermal performance at ultra-high beam currents and yields obtained from recent pilot Ac-225 production campaigns.

Funding Agency

DOE Office of Science, Office of Nuclear Physics

Email Address

Presentation Type

Contributed Oral

Primary author: Dr NORTIER, Meiring Nortier (Los Alamos National Laboratory)

Co-authors: Dr STEIN, Benjamin (Los Alamos National Laboratory); MARTINEZ, Chris (Los Alamos National Laboaratory); Dr VERMEULEN, Christiaan (Los Alamos National Laboratory); O'BRIEN, Ellen (Los Alamos National Laboratory); OLIVAS, Eric (Los Alamos National Laboratory); BIRNBAUM, Eva

(Los Alamos National Laboratory); COOLEY, Jason (Los Alamos National Laboratory); JOHN, Kevin (Los Alamos National Laboratory); Mr BHANDIA, Rishi (Los Alamos National Laboratory)

Presenter: Dr NORTIER, Meiring Nortier (Los Alamos National Laboratory)

Contribution ID: **46** Type: **not specified**

Mechanistic modelling of Radium-223 treatment of bone metastases

Despite the effectiveness of 223RaCl2 for treating castration resistant prostate patients with symptomatic bone metastatic disease, its mechanisms of action are still unclear. Even established dosimetric approaches differ considerably in their conclusions. With the rapid growth in the interest of alpha-targeted radionuclide approaches, in silico tumour models bring a new perspective to this as they can quantitatively simulate the interaction of α-particles with the predicted target(s). Here, we investigated three different mathematical models of tumour growth that take into account the radiation effect of Radium-223 treatments and compare the results to existing clinical data from the ALSYMPCA trial [1].

The well-established Gompertz growth model was applied to simulate metastatic tumour burden. Based on published measurements of Radium-223 uptake, we have incorporated the radiation effect of α-particles into the model and investigated three radium distribution scenarios - uniform exposure, exposure of only an outer layer, and exposure of a constant volume of the tumour. For each scenario, the times for various tumour stages to progress to the first symptomatic skeletal event were calculated.

Uniform and outer-layer exposure scenarios showed very poor agreement with the Kaplan-Meier patient curves from clinical data. However, the constant volume effect predicted very similar outcomes to the observed clinical results, suggesting that only relatively small fractions of the cell population see damage from Radium-223.

The commonly-used assumption of uniform Radium-223 distribution does not accurately reflect clinical responses. The suggestion that only a sub-population of the tumour might be affected by Radium-223 shows that there is a pressing need to further study the tumour and drug kinetics in order to schedule more effective treatments in the future. Given the clinical efficacy, even under these conditions additional preclinical studies are also required to test different radium distributions and their biological efficacy. This will ultimately aid in the design and implementation of future alpha-radionuclide targeted therapies.

[1] Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med. 2013;369:213-223.

Funding Agency

Movember/Prostate Cancer UK

Email Address

k.prise@qub.ac.uk

Presentation Type

Contributed Oral

Primary author: Prof. PRISE, Kevin (Queen's University Belfast)

Co-authors: Mr LIBERAL, Francisco (Queen's University Belfast); Mr MORIERA, Hugo (Queen's University Belfast); Prof. O'SULLIVAN, Joe (Queen's University Belfast); Dr MCMAHON, Stephen (Queen's University Belfast)

Presenter: Prof. PRISE, Kevin (Queen's University Belfast)

Contribution ID: **47** Type: **not specified**

Consideration toward Safety Guidance for Targeted Alpha Therapy in Japan

Targeted alpha therapy (TAT) was reported both decreasing side effects and significant therapeutic efficacies in comparison with several conventional anti-tumor treatments. Although the TAT research project has also started in Japan to proceed with drug development, there is still no concrete evaluation standard to conduct non-clinical studies for TAT drug toward human clinical studies. Regulatory science for translational research of drug product under international standard is very important now. While watching the current progress on the TAT drug development and the several subjects clarified by the former TAT research, we have recently published our report on evaluation standard for non-clinical studies which is essentially necessary for first-in-human TAT studies in Japan1). We focused on both astatine 211At and actinium 225Ac as the alpha-emitters.
We also discuss on initial human-dose and dose escalation, organ identification to suspect toxicity and evaluation items for monitoring upon considering physical half-lives, drug stabilities and accumulation into targeted cells. Both biodistribution analysis by PET or SPECT using complementary nuclide labeling agents and localization analysis by auto-radiography imaging for animal tissues using alpha-camera are very important for these purposes1). We also propose the selection method of TAT drug candidates which is satisfied with safety profile including delayed-type toxicities under our new evaluation system with histopathological examination in animal tissues which is also very important to deepen our understanding1).
Furthermore, dose escalation studies and their verification of accuracy using animal models will be established by our newly proposed dosimetric simulation which adopts reliable extrapolation to human trials2).
We expect this report can provide how to think about the non-clinical safety issues for development of new TAT drugs in advance.
Acknowledgement; This research is supported by the Program on Open Innovation Platform with Enterprises, Research Institute and Academia (OPERA) from Japan Science and Technology Agency (JST).
1)Tsuneo Yano, Koki Hasegawa, Akiko Hachisuka, Koichi Fukase, Yoko Hirabayashi, Discussion on Translational Research of Drug Product for Targeted Alpha Therapy –Part 1 –, PMDRS, 49(10), 676-684 (2018).
2)Tsuneo Yano, Koki Hasegawa, Tatsuhiko Sato, Akiko Hachisuka, Koichi Fukase, Yoko Hirabayashi, Discussion on Translational Research of Drug Product for Targeted Alpha Therapy –Part 2 –, PMDRS, 50(3), March 10th (2019).

Funding Agency

Japan Science and Technology Agency (JST)

Email Address

tyano@rcnp.osaka-u.ac.jp

Presentation Type

Contributed Oral

Primary author: Prof. YANO, Tsuneo (Osaka University)

Presenter: Prof. YANO, Tsuneo (Osaka University)

Contribution ID: **48** Type: **not specified**

Separation of Ac-225 from lanthanide fission products using a reverse phase chromatographic process incorporating a solvent impregnated resin

Targeted α-particle therapy (TAT) has been shown in recent years to be a promising route for the treatment of various forms of cancer, and may serve as an alternative to more traditional cancer treatment options. TAT takes advantage of an α-emitting radionuclide's ability to deliver cytotoxic doses of radiation to tumor cells while causing minimal damage to surrounding healthy tissue. This is possible because of the short path length and high linear energy transfer associated with α -particles, which are on the order of 100 μm or less and around 100 keV/μm, respectively. To this end, a number of α-emitting radionuclides have explored for therapeutic applications including Ac-225, Bi-213, Bi-212, At-211, and Ra-223 with others currently in development. Of these, Ac-225 in particular has proven itself to be an especially appealing isotope for the treatment of some cancers.

The value of Ac-225 is derived in part from its four alpha decay chain, which includes Bi-213 (t1/2 = ~46 minutes), which is in itself a desirable isotope for TAT. The targeted delivery of Ac-225 to tumor sites has been shown in a number of instances to be highly effective for the treatment of several forms of cancer when a conjugate with an antibody, peptide, or protein is produced which can carry the isotope to the target site. One of the more notable instances of the successful treatment of human cancer with Ac-225 has been in the treatment of prostate cancer, for which Ac-225 may be conjugated with Prostate Specific Membrane Antigen for targeted doses to prostate cancer tumor cells. Because of the proven efficacy of Ac-225-containing conjugate species in anticancer treatment applications, demand for this isotope is expected to rise above current production capabilities.

The work presented herein describes a new method for the separation of Ac-225 from radiolanthanide impurities resulting from fission of proton irradiated Th-232 target foils. The process incorporates a solvent impregnated resin to achieve the separation, and is the first in a series of resins to be tested as alternatives to current technologies incorporating branched DGA resin. The current resin is comprised of an Amberlite XAD7HP resin that has been loaded with the ionic liquid 1-butyl-3-methylimidazolium bis(trifluoromethane)sulfonamide ([Bmim][NTf2]) and the extractant N,N-dioctyldiglycolamic acid (DODGAA). Going forward, the resin will be tuned to achieve optimum results by loading the Amberlite scaffold with varying combinations of ionic liquids and extractants. Data presented will include batch extraction experiments including the solvent impregnated resin with complex matrices of metals (La-Lu, Sc, Y, U, Th, Ac) in HCl, HNO3, and citrate-phosphate buffer media over a range of pH. Additionally, results of dynamic column experiments will be presented, and comparisons will be made to separations technologies currently in use.

Funding Agency

US DOE Office of Science

Email Address

tgparker@lanl.gov

Presentation Type

Contributed Oral

Primary author: Dr PARKER, Gannon (Los Alamos National Laboratory)

Co-author: Dr FASSBENDER, MICHAEL (Los Alamos National Laboratory)

Presenter: Dr PARKER, Gannon (Los Alamos National Laboratory)

Contribution ID: **49** Type: **not specified**

A production challenge of Ac-225 from RaCO3 target activated by vertical beam

[Introduction] Ac-225 (T1/2 = 10 d) is regarded as a promising alpha emitter for the targeted alpha therapy (TAT). Considering biodistribution of conjugated antibodies, as well as logistics in worldwide supply, a physical half-life of 10 days would be tolerable for keeping certain radioactivity in each case. Actinium shows a good compatibility to DOTA that is favorable in radiochemistry to enhance the fusion of diagnosis and therapeutic studies including novel radiopharmaceuticals development. However, the current capability of Ac-225 supply is very limited at around 2 Ci/year that mainly relies on the natural source of Th-229 stocked in a few institutes; therefore, any artificial production ways of Ac-225 would be highly desired. Among possible channels of Ac-225 production, protons on Ra-226 (T1/2 = 1600 y) is the sole option we can employ practically, due to the accessibility of target material under the current regulation in our country/institute and high cross-section of this reaction that can be performed on medical cyclotron platforms.
[Methods] Radium-226 used in this study was originated from 1–4 mCi of 'legacy needles', presumably being filled as sulfate or bromide with or without carrier Ba, and we successfully collected soluble Ra in HCl followed by the Ref [1]. Then, enriched 40CaCO3 (as carrier), ammonium solution (to make pH>9) and (NH4)2CO3 (to precipitate) in turn were added into 100–500 μCi of Ra/HCl to obtain practically insoluble radium carbonate. The sediment contained RaCO3 was isolated on a filter made of silicon carbide to make Ra target disk, which can be activated directly at our vertical beam station owing to the heat and chemical resistance of SiC, as well as gravity-supported target holding.
Irradiations were performed with 18 MeV protons at 3 μA for 3 h (on target 16.7 MeV). The activated target, allowed to decay for about 3 days, was dissolved in 1 M HCl, and then purified to obtain Ac-225 fraction as the final product.
[Results and Discussion] Production yield of Ac-225 was roughly estimated to be about 1/200 of Ra-226 activity by this activation condition (1.6 μCi of Ac-225 at the EOB from 360 μCi of Ra-226, in average). Ac-226 (T1/2 = 29 h) was the primal impurity found in our sample that was about 30% with regards to the activity of Ac-225, corrected to the EOB.
Although our study is still in development, we concluded that the Ac-225 production from Ra-226 target is feasible that could give sufficient quantity and quality of Ac-225 also in a scaled-up condition with appropriate energy window, cooling time and chemical separation processes.
[Acknowledgement] This work was partially supported by JSPS Grant-in-Aid for Scientific Research (C), Grant Number 17K10384.
[Reference] [1] Matyskin, A.V. et al. J. Radioanal. Nucl. Chem. 310 (2016) 589–595

Email Address

nagatsu.kotaro@qst.go.jp

Presentation Type

Poster

Primary author: Dr NAGATSU, Kotaro (Nat. Inst. for Quantum and Radiological Science and Technology)

Co-authors: Dr TSUJI, Atsushi (Nat. Inst. for Quantum and Radiological Science and Technology); Mr SUZUKI, Hisashi (Nat. Inst. for Quantum and Radiological Science and Technology); Mr MINEGISHI, Katsuyuki (Nat. Inst. for Quantum and Radiological Science and Technology); Mr FUKADA, Masami (Nat. Inst. for Quantum and Radiological Science and Technology); Mr MATSUMOTO, Mikio (Japan Radioisotope Association); Dr ZHANG, Ming-Rong (Nat. Inst. for Quantum and Radiological Science and Technology); Dr HIGASHI, Tatsuya (Nat. Inst. for Quantum and Radiological Science and Technology)

Presenter: Dr NAGATSU, Kotaro (Nat. Inst. for Quantum and Radiological Science and Technology)

Contribution ID: **50** Type: **not specified**

NorthStar Program for Production of Ac225

Ac-225 and its daughter Bi-213 have become increasingly important in clinical research for potential treatment of various diseases. The current US production of Ac-225 is limited to about 900 mCi annually from Oak Ridge National Laboratory. While there are limited sources of the stock material used to produce Ac-225, there are options available to meet this need. NorthStar has previously described a high-energy proton spallation of Th-232 approach. This route is capable of supplying daily quantities equivalent to the current annnual supply. This presentation will describe the current development effort that is underway during started in 2017 and continuing toward a goal to continuing development efforts to approach 100mCi+ of Ac-225 per run by the end of 2019, with the ultimate target to achieve sufficient capability in the future to meet market demands.

Funding Agency

NorthStar funded

Email Address

jharvey@northstarnm.com

Presentation Type

Contributed Oral

Primary author: Dr HARVEY, James (NorthStar Medical Technologies, LLC)

Presenter: Dr HARVEY, James (NorthStar Medical Technologies, LLC)

Contribution ID: **51** Type: **not specified**

Selective Separation of Radium and Actinium from Bulk Thorium Target Material

A complete scheme for the selective separation of actinium and radium isotopes from bulk 232Th target material will be presented. The process may be applicable to the production of 225Ac and 227Ac via proton spallation on thorium targets. Thorium metal is dissolved in sulfuric acid with small amounts of HF. Actinium and radium are retained on cation exchange resin from the sulfate medium, while neutral and anionic thorium sulfate complexes are rejected. Targeting the minor components (Ac,Ra) allows use of much smaller chromatographic columns than traditional nitrate based systems which target the bulk thorium. Additionally, the primary separation is performed from 0.1M Th, 0.6M sulfate, pH 1-2 instead of the more corrosive 3-8M HNO3 typically employed in solvent extraction or anion exchange based thorium separations.
Actinium and radium are recovered from the cation exchange resin in a small volume of 5M HNO3 and directly purified via extraction chromatography with UTEVA and DGA resins without feed adjustment or evaporation. The radium fraction can be further processed following ingrowth of 225Ac from 225Ra to produce additional 225Ac free from any potential 227Ac impurity. The flow-sheet has been tested at the Canadian Nuclear Laboratory (CNL) on 25 gram solid thorium targets irradiated at Fermi Lab.

Bond, A.H., Horwitz, E.P., McAlister, D.R., 2006. A Multicolumn Selectivity Inversion Generator for the Production of High Purity Actinium-225 for Use in Therapeutic Nuclear Medicine, United States patent number 7,087,206. (Licensed to NorthStar Medical Radioisotopes)
D.R. McAlister, E.P. Horwitz, "Selective Separation of Radium and Actinium from Bulk Thorium Target Material on Strong Acid Cation Exchange Resin from Sulfate Media,"Applied Radiation and Isotopes, 140, 18-23 (2018).

Email Address

dmcalister@eichrom.com

Presentation Type

Contributed Oral

Primary author: MCALISTER, Daniel (Eichrom TEchnologies, LLC/PG Research Foundation, Inc.)

Co-authors: GENDRON, Denise (Canadian Nuclear Laboratory); HORWITZ, E. Philip (Eichrom Technologies, LLC/PG Research Foundation, Inc.); HARVEY, James T. (NorthStar Medical Radioisotopes); CAUSEY, Patrick (Canadian Nuclear Laboratory); PERRON, Randy (Canadian Nuclear Laboratory)

Presenter: MCALISTER, Daniel (Eichrom TEchnologies, LLC/PG Research Foundation, Inc.)

Contribution ID: **52** Type: **not specified**

Evaluation of 225Ac-anti-VLA-4 for targeted α-therapy for treatment of metastatic melanoma

Background.
Very late antigen 4 (VLA-4; also called integrin α4β1) is overexpressed in melanoma tumors with an active role in tumor growth, angiogenesis, and metastasis. This makes VLA-4 an ideal antigenic target for targeted alpha therapy. The expression of VLA-4 on primary melanomas in human correlates with the development of metastasis and has been associated with high risk of metastasis and tumor progression. Furthermore, up-regulation of VLA-4 in melanoma is associated with a more aggressive, metastatic phenotype. Here in we evaluated an 225Ac-anti-VLA-4 conjugate as well as its 111In-labeled companion imaging agent for targeted radiotherapy in an aggressive mouse melanoma model.

Methods.
An anti-VLA-4 antibody was conjugated to DOTA for 225Ac-labeling and DTPA for 111In-labeling. The resulting agents, 225Ac- or 111In-labeled anti-VLA-4 were evaluated in vitro, including binding affinity, internalization, and clonogenic assays as well as in vivo biodistribution studies. Furthermore, the therapeutic efficacy of 225Ac-anti-VLA-4 was evaluated in a subcutaneous and disseminated disease mouse model of melanoma.

Results.
111In-DTPA-anti-VLA-4 demonstrated high affinity for VLA-4 in B16F10 cells, having a Kd of 0.18 ± 0.05 nM and approximately 20% internalized at 8 hours. For delivery of an α-emitting radionuclide to VLA-4 positive tumor cells, the DOTA conjugate was labeled with 225Ac with specific activity of 3.5 MBq/nmol and >95% radiochemical purity, and demonstrated selective uptake in VLA-4 positive B16F10 cells. Clonogenic assays demonstrated a decrease in the surviving fraction of B16F10 cells treated with 225Ac-DOTA-anti-VLA-4 compared to controls. Biodistribution studies demonstrated uptake in the VLA-4 positive tumor in addition to VLA-4 rich organs. A blocking dose highlighted the potential of blocking uptake in VLA-4 rich organs without a significant impact on tumor uptake. Therapeutic efficacy studies demonstrated significant increases survival in mice treated with 225Ac-DOTA-anti-VLA-4 compared to saline and cold antibody controls. In addition, a single mouse (subcutaneous model) remained tumor-free until the study end-point, 6-months post-treatment.

Conclusion.
111In- and 225Ac-labeled anti-VLA-4 antibody conjugates are capable of selectively delivering radionuclides for SPECT imaging and targeted alpha therapy to melanoma tumor cells that overexpresses VLA-4. The biodistribution studies highlighted the uptake in VLA-4 rich organs, including the spleen and bone, could be potentially reduced without significantly impacting the uptake in the tumor. The agents presented here with future dose optimization have the potential to identify and treat patients who have metastatic melanoma.

Acknowledgments.
The 225Ac used in this research was supplied by the Isotope Program within the Office of Nuclear Physics in the Department of Energy's Office of Science.

Email Address

jnedrow1@jhmi.edu

Presentation Type

Contributed Oral

Primary authors: CORTEZ, Angel (Johns Hopkins University); Dr NEDROW, Jessie (Johns Hopkins University)

Co-authors: SHTEKLER, Abigail (Johns Hopkins University); RAO, Akhila (Johns Hopkins University); Dr JOSEFSSON, Anders (Johns Hopkins University); Dr SGOUROS, George (Johns Hopkins University); Dr HOBBS, Robert (Johns Hopkins University); AUSTIN, Zachery (Johns Hopkins University)

Presenter: Dr NEDROW, Jessie (Johns Hopkins University)

Track Classification: Preclinical

Contribution ID: **53** Type: **not specified**

Radium Targets for the Reactor Production of Alpha-emitting Medical Radioisotopes

Radium 226 (t1/2 = 1600 years) can be irradiated in a reactor to produce a variety of important medical radioisotopes. These isotopes can be chemically separated and purified after irradiation, and the radium can be recycled for future use. Since radium is highly radioactive, there are unique challenges with using radium as a target material. Also, the chemical properties of radium are not yet fully explored, so stable surrogate materials, such as barium, are used to develop the process. To irradiate radium at the Oak Ridge National Laboratory (ORNL) High Flux Isotope Reactor, it must be in a stable chemical form and in a safe and thoroughly certified target configuration.

Recent efforts at ORNL have focused on the identification and preparation of several radium compounds to be used as target material for irradiation followed by chemical processing to extract the desired product and recover the radium material. Radium in a stable chemical form can be blended into an aluminum pellet cermet and contained within a welded aluminum capsule. Due to the radioactive properties of radium, the material must be handled in a hot cell, which required design, testing, and construction of in-cell welding and certification capability to seal and certify target capsules. The development of a suitable radium target material, pellet fabrication process and capsule welding will be discussed.

Email Address

coppingr@ornl.gov

Presentation Type

Contributed Oral

Primary author: Dr COPPING, Roy (Oak Ridge National Laboratory)

Co-authors: Mr MARCUS, Chris (ORNL); Dr STRACENER, Daniel (ORNL); Mr DENTON, David (ORNL); Ms HICKMAN, Eva (ORNL); Mr WRIGHT, Joseph (ORNL); Ms MURPHY, Karen (ORNL); Dr MIRZADEH, Saed (ORNL)

Presenter: Dr COPPING, Roy (Oak Ridge National Laboratory)

Contribution ID: **54** Type: **not specified**

Separation of Actinium-225 from Lanthanides Using High Pressure Ion Chromatography

Actinium-225 is an important radioisotope for targeted alpha therapy applications and can be used for the treatment of several different cancer types such as, gliomas, leukemias, lymphomas, and melanomas. The 225Ac decay chain yields a net of four α particles, which have a high linear energy transfer. The α particles deposit their energy in 70 100 μm tracks, effectively targeting the binding site while limiting the destruction of surrounding healthy tissue. The high energy and large particle size also make α particles likely to cause double strand breaks in DNA. Current methods of production of 225Ac include 229Th derived material and chemical processing of irradiated thorium targets. This results in the production of 225Ac that has a high level of contaminating radiometals. Separation of 225Ac from the contaminating lanthanides is particularly challenging due to their similar chemical properties and charge. The goal of this research is to use high pressure ion chromatography to develop an effective separation of lanthanides and organic media from 225Ac at tracer level activity. After loading 225Ac and Ln(III) onto a sulfonated polystyrene divinylbenzene resin, α hydroxyisobutyric acid (α HIBA) and HCl are serially used to separate Ln(III) from 225Ac. The organic acid complexes with Ln(III) preferentially over Ac(III). After the Ln(III) is removed from the resin, low molarity HCl is introduced to the resin to flush the organic acid. When the eluent matrix has been fully converted to HCl, the molarity of HCl is increased to elute the 225Ac from the resin. We have developed a successful method that achieves 225Ac separation of >99% with minimal α HIBA contamination.

Funding Agency

DOE Office of Nuclear Physics

Email Address

davernsm@ornl.gov

Presentation Type

Poster

Primary author: Dr DAVERN, Sandra (ORNL)

Co-authors: Dr STRACENER, Daniel (ORNL); Dr GRISWOLD, Justin (ORNL); Mr GADDIS, Kevin (ORNL); Dr COPPING, Roy (ORNL); Dr MIRZADEH, Saed (ORNL)

Presenter: Dr DAVERN, Sandra (ORNL)

Contribution ID: **55** Type: **not specified**

Production of 230Pa from proton-irradiated thorium and developing 230Pa/230U/226Th tandem generator

Targeted alpha-therapy of various oncology diseases is based on the coupling of alpha-emitting radionuclides to tumour-selective carrier molecules. 230U (T1/2=20.8 d) is accumulated via decay of 230Pa and has strong potential for alpha-therapy due to 5 emitting alpha - particles with total energy 33.5 MeV. It can be used directly or as a parent of 226Th in a generator system.
A prospective way for production of 230Pa/ 230U is irradiation of natural thorium with medium-energy protons. Curie amounts of 230Pa can be generated in one irradiation run together with other useful alpha-emitters 225Ac and 223Ra.
After dissolving Th-target in 6M nitric acid with the addition of catalytic amounts of hydrofluoric acid Pa was isolated by liquid extraction with octanol. The water phase may be further used for isolation of 225Ac and 223Ra according the method, proposed in [1, 2]. Namely, the most part of thorium was removed by liquid extraction with di(2-ethylhexyl)phosphoric acid in toluene. Organic phase was kept for accumulation 223Ra from parent 227Th. 225Ac and 223Ra were concentrated from aqueous phase and then separated and purified by extraction chromatography. After re-extraction 230Pa was purified on silica gel using different oxalic acid solutions. Up to 85% of 230Pa with radionuclidic purity >99% was recovered and stored for 230U accumulation.
Basing on distribution coefficients 230U was separated from 230Pa in diluted nitric acid solution on DGA resin. Obtained 230U may be used for development of 230U/226Th –generator. Distribution coefficients for U and Th were obtained for a wide range of extraction chromatographic resins. TEVA (mixture of trioctyl and tridecyl methyl ammonium chloride as an extractant) and WBEC (based on a mixture of tertiary octyl and decylamines) resins are most suitable for this purpose.
REFERENCES
1. R.A. Aliev, S.V. Ermolaev, A.N. Vasiliev, V.S. Ostapenko, E.V. Lapshina, B.L. Zhuikov, N.V. Zakharov, V.V. Pozdeev, V.M. Kokhanyuk, B.F. Myasoedov, S.N. Kalmykov. Isolation of medicine-applicable actinium-225 from thorium targets irradiated by medium-energy protons. Solvent Extraction and Ion Exchange, 2014, v. 32, p. 468-477.
2. A.N. Vasiliev, V.S. Ostapenko , E.V. Lapshina, S.V. Ermolaev, S.S. Danilov, B.L. Zhuikov and S. N. Kalmykov. Recovery of Ra-223 from natural thorium irradiated by protons. Radiochimica Acta, 2016, v. 104, N.8, p. 539-547.

Email Address

lapshina@inr.ru

Presentation Type

Contributed Oral

Primary author: Dr LAPSHINA, Elena (Institute for Nuclear Research of Russian Academy of Sciences)

Co-authors: Dr VASILIEV, Aleksandr (Institute for Nuclear Research of Russian Academy of Sci-

ences); Dr ZHUIKOV, Boris (Institute for Nuclear Research of Russian Academy of Sciences); Dr ERMOLAEV, Stanislav (Institute for Nuclear Research of Russian Academy of Sciences); Ms OSTAPENKO, Valentina (Institute for Nuclear Research of Russian Academy of Sciences)

Presenter: Dr LAPSHINA, Elena (Institute for Nuclear Research of Russian Academy of Sciences)

Contribution ID: **56** Type: **not specified**

The role of IAEA in the development of radiopharmaceutical sciences with focus on alpha emitters

The Radioisotope Products and Radiation Technology (RPRT) Section of IAEA has been implementing several activities focusing on the production and quality control of alpha emitter radioisotopes and radiopharmaceuticals as well as capacity building in the field, through Technical Meetings, Workshops, Publications and Conference Supports and the IAEA-Technical Cooperation projects. As interest to targeted therapy grows, the demand of alpha emitting radioisotope and radiopharmaceuticals continues to raise. As a result, several Member States worldwide are seeking to develop/adapt technologies for the preparation of radiopharmaceuticals labelled with various alpha-emitters. Currently Bi-213 has shown more clinical applications, thanks to its generator availability at hospital radiopharmacy. On the other hand, successful results of recent worldwide clinical trials of Ac-225 radiopharmaceuticals opened a new area for radiopharmaceutical sciences. Harmonisation and coordination of large scale production of alpha emitters with desired quality and adequate safety for human application is an important activity that IAEA has initiated. Several important events took place recently including; "The workshop on the supply of actinium-225"held at IAEA, Vienna in October 2018; "Regional Workshop on Preparation and Clinical Utilization of Radiolabelled Therapeutic Peptides"held in Poland June 2018 [1]; an IAEA publication covering quality control procedures for alpha emitter radiopharmaceuticals [2]; and the support and activities related to Technical Cooperation projects at national and regional levels aiming the production and/or application of alpha emitter radiopharmaceuticals worldwide [3].

References:
[1] https://www.iaea.org/newscenter/news/new-technique-to-fight-prostate-cancer-iaea-organizes-first-of-a-kind-training-for-radiopharmacists
[2] Quality Control in the Production of Radiopharmaceuticals: IAEA-TECDOC-1856; (ISBN:978-92-0-107918-3);(https://www-pub.iaea.org/books/IAEABooks/13422/Quality-Control-in-the-Production-of-Radiopharmaceuticals)
[3] Asia-Pacific Regional Training course on "Preparation and clinical utilization of radiolabelled therapeutic peptides (under RAS/6/082), Singapore, May 2017.

Email Address

a.jaliliab@iaea.org

Presentation Type

Contributed Oral

Primary author: Mr JALILIAN, Amirreza (IAEA)

Co-authors: Ms KORDE, Aruna (IAEA); Mr OSSO JR., Joao Alberto (IAEA); Ms VALERIIA, Starovoitova (IAEA)

Presenter: Mr JALILIAN, Amirreza (IAEA)

Contribution ID: **57** Type: **not specified**

Numerical Investigation of Th-229 Production in an Accelerator Driven System Reactor

Abstract
The expected increase in radionuclide demand for treatment of various tumor diseases has led to the investigation of alternative production routes to provide sufficient amount of medical isotopes[1]. In Targeted Alpha Therapy (TAT), there is a present and future need for the Ac-225 and Bi-213, as the most promising alpha emitting isotopes, one of the limited ways to provide these radioisotopes is by production of Th-229 in reactor route[2][3]. The present study conducted to investigate the production of Th-229 to expand the availability of Ac-225 and Bi-213 in innovative nuclear reactor concept like Accelerator Driven System reactor (ADS)[4], which is a subcritical reactor and currently in development that predict to play an important role in the transmutation process of heavy elements and isotopes production. The possibility of producing Th-229 from neutron transmutation of Ra-226 are numerically investigated for simple model of ADS reactor consist of two zones, inner region with fast neutron spectra and outer region with thermal neutron spectra, and the subcritical core coupled with external neutron source. The calculations of transmutation behavior and mass ratio for the produced isotopes are conducted by using Monte Carlo N-particle Transport (MCNPX) code.

Acknowledgements
This research was supported by International Center for Theoretical Physics and The Institute of International Education Scholar Rescue Fund. My deep thanks to colleagues from Institute for Safety Problems of Nuclear Power Plants, Ukraine who provided expertise that assisted the research.

References
[1] E. R. Birnbaum, L. J. Bitteker, A. Couture, and M. E. Fassbender, "Ac and Ra-223 Production via 800 MeV Proton Irradiation of Natural Thorium Targets,"vol. 836.
[2] J. R. Griswold et al., "Large scale accelerator production of Ac-225: Effective cross sections for 78–192 MeV protons incident on Th-232 targets,"Appl. Radiat. Isot., 2016.
[3] S. Hogle et al., "Reactor production of Thorium-229,"Appl. Radiat. Isot., vol. 114, pp. 19–27, 2016.
[4] H. Aït Abderrahim, P. Baeten, D. De Bruyn, and R. Fernandez, "MYRRHA - A multi-purpose fast spectrum research reactor,"in Energy Conversion and Management, 2012, vol. 63, pp. 4–10.

Funding Agency

International Center for Theoretical Physics (ICTP) and The Scholar Rescue Fund (IIE-SRF)

Email Address

aalqaaod@gmail.com

Presentation Type

Poster

Primary author: Dr AL QAAOD, Amer A. (Postdoctoral fellowship)

Presenter: Dr AL QAAOD, Amer A. (Postdoctoral fellowship)

Track Classification: Nuclide Production Supply

Contribution ID: **58** Type: **not specified**

Safe use of Ra-223 radium dichloride (223Ra) across a wide-range of clinical scenarios: A 10-year single-institution radiation safety experience.

Objectives: 223Ra is an effective therapeutic radiopharmaceutical for the treatment of prostate cancer metastatic to bone. As an institutional participant in the ALSYMPCA trial, and early adopter of Xofigo as a clinical modality, our facility has accrued over 10 years'experience in the regulatory-compliant use of this radiopharmaceutical. Because 223Ra is a pure alpha emitter, there is negligible concern regarding external exposure from injected patients. However, several radiation safety related factors still need to be considered when treating patients with 223Ra. Our presentation will discuss a number of these concerns, based on first-hand experience gained from navigating several specific scenarios and additional information gathered from the medical literature, to provide guidance on the safe usage of 223Ra in the treatment of patients with boney metastases.

Methods: Personnel involved in the clinical care and radiation safety oversight of patients treated with 223Ra were canvassed to recall cases with radiation safety concerns. By drawing upon our institution's experience, and reviewing the relevant world-wide literature, we have provided guidance for various scenarios in the radiation-safety compliant treatment of patients with 223Ra.

Results: Physical, biological and regulatory aspects of 223Ra form the basis of understanding radiation safety concerns. We describe the potential of internal contamination from patient excreta, body fluids, and tissue samples based on a number of clinical scenarios, and the ensuing exposures that may result. Adherence to Universal Precautions is paramount in avoiding internal contamination. Of particular interest is our first-hand experience with a patient who underwent hip replacement surgery following 223Ra therapy, including the proper handling and storage of radioactive bone fragments. Handling of a deceased patient, and the associated guidelines regarding 223Ra decedents, is a potential outcome that should be familiar to physicians administering 223Ra therapy.

Conclusion: While the lack of a gamma emission greatly reduces exposure and radiation concerns when treating patients with therapeutic levels of 223Ra activity, there are still several regulatory and safety concerns that need to be addressed in the course of potential patient scenarios. We will review appropriate solutions to these scenarios in a radiation-safety compliant manner.

Email Address

lzuckier@toh.ca

Presentation Type

Contributed Oral

Primary author: Mr ARO, Jon (The Ottawa Hospital)

Co-authors: Dr LEUNG, Eugene (University of Ottawa Faculty of Medicine); Dr ZUCKIER, Lionel (University of Ottawa Faculty of Medicine); Dr DINNING, Stephen (University of Ottawa Faculty of Medicine)

Presenter: Mr ARO, Jon (The Ottawa Hospital)

Contribution ID: **59** Type: **not specified**

Sensitivity to a poly(ADP-ribose) polymerase 1 (PARP-1) targeting alpha particle therapeutic in neuroblastoma is characterized by increased relative biological effectiveness (RBE) compared to gamma irradiation

Introduction:
Neuroblastoma is the most common extracranial solid malignancy in childhood, with only up to 50% 5-year survival in high-risk cases. Neuroblastoma overexpresses the nuclear enzyme PARP-1, which can be targeted for specific delivery of alpha particles to DNA using an astatine-211 radiolabeled small molecule PARP-1 inhibitor called [211At]MM4.

Methods:
Using a panel of twenty human neuroblastoma cell lines previously screened *in vitro* for sensitivity to [211At]MM4, IMR5 and NLF were chosen as examples of a sensitive and a resistant cell line to assess RBE.
Next, radiopharmacologic properties of the two cell lines were characterized by performing radioligand saturation binding assays to measure the maximum number of binding sites for [211At]MM4 and to directly measure bound [211At]MM4.
For self-dose calculation, the geometric dimensions of the cells were measured by immunofluorescence microscopy. For cross-dose calculation, the cellular arrangements in the sensitivity screening condition was modeled with hexagonal circle packing.
Then, Monte Carlo simulation was performed with MIRDcell v2.0 to calculate the total radiation dose to the cell nucleus from astatine-211 and its daughters at 50% cell kill (D50). RBE against gamma rays was calculated using D50 for gamma irradiation with a cesium-137 source.
Finally, mouse tumor xenograft models were imaged with 18F-fluorthanatrace (FTT), a [211At]MM4 analog for positron emission tomography (PET), for correlative *in vivo* dosimetry.

Results:
In IMR5 cells, [211At]MM4 demonstrated 3 and 9 orders of magnitude greater cytotoxic potency compared to free 211At and its non-radioactive analog respectively, whereas the differences were 2 and 8 orders of magnitude in NLF.
IMR5 had more PARP-1 binding sites compared to NLF (Bmax= 2.3 vs 1.4 million sites/cell), but similar binding affinity of [211At]MM4 was seen (IMR5: Kd=2.7 nM, NLF: Kd=2.4 nM).
The nuclear and cell radii were measured at 6 μm and 8 μm respectively in IMR5, and 9 μm and 12 μm in NLF. The mean distance between adjacent cells was determined to be 86 μm.
The D50 in IMR5 was 0.076 Gy for [211At]MM4, 0.34 Gy for free 211At, and 0.7 Gy for gamma irradiation, yielding RBE of 9.2 for [211At]MM4. The D50 in NLF was 3.8 Gy for [211At]MM4, 4.6 Gy for 211At, and 3.6 Gy for gamma irradiation, yielding RBE of 1.0.
Using 18F-FTT mouse PET images, the tumor radiation dose from [211At]MM4 based on tumor size and amount of [211At]MM4 administered were modelled.

Conclusion:
Delivery of an alpha emitter directly to the neuroblastoma nuclear DNA by the astatinated PARP-1 inhibitor [211At]MM4 results in variable levels of enhanced cytotoxicity. Sensitivity to [211At]MM4 is characterized by increased RBE against gamma irradiation, warranting investigation of the underlying biological factors. Tumor dosimetry results from mouse models can be applied to future *in vivo* therapy experiments with [211At]MM4 for correlation between tumor dose and therapeutic efficacy.

Funding Agency

National Institutes of Health

Email Address

Hwan.Lee@uphs.upenn.edu

Presentation Type

Contributed Oral

Primary author: Dr LEE, Hwan (University of Pennsylvania)

Co-authors: Mr MANSFIELD, Adam (University of Pennsylvania); Dr PRYMA, Daniel A. (University of Pennsylvania); Dr MARIS, John M. (Children's Hospital of Philadelphia); Dr XU, Kuiying (University of Pennsylvania); Dr MAKVANDI, Mehran (University of Pennsylvania); Dr SAMANTA, Minu (Children's Hospital of Philadelphia); Dr MACH, Robert H. (University of Pennsylvania); Dr CARLIN, Sean D. (University of Pennsylvania); Dr REILLY, Sean W. (University of Pennsylvania)

Presenter: Dr LEE, Hwan (University of Pennsylvania)

Contribution ID: **60** Type: **not specified**

IGF-1R Targeted Alpha Therapeutic FPI-1434 causes DNA double-stranded breaks and induces regression in preclinical models of human cancer

Objectives:
Insulin-like growth factor-1 receptor (IGF-1R) is an oncogenic protein that is over-expressed in multiple solid tumors. IGF-1R targeted therapeutics have not demonstrated clinical efficacy for treating cancers either as stand-alone agents or in combination with other therapies. Despite this, targeted alpha therapeutic agents (TATs) may be ideal for treating IGF-1R expressing cancers due to their high potency and lower protein mass dose. Herewith we describe the preclinical efficacy of FPI-1434 in several solid tumor models and provide insight into its mechanism of action.
Methods: FPI-1434 was produced by conjugating with a lysine directed bifunctional chelated to AVE1642
and radiolabeled with Ac-225. Single dose radiotherapeutic efficacy studies were carried out using Colo-205 (colorectal), A549 (radioresistant lung), or LNCaP (prostate) xenografts inoculated into immunodeficient mice. Animals received single doses ranging from 0.05 µCi to 0.4 µCi with a corresponding dose of total protein typically less than 10 µg (0.5 mg/kg). Study endpoints included tumor volume measurement and/or impact to animal health status.
Results: Colo-205 xenograft bearing mice received single doses of FPI-1434 at 0.05, 0.2, and 0.4 µCi or vehicle and radiotherapeutic efficacy was followed for 178 days. FPI-1434 caused suppression of tumor growth at the 0.05 µCi dose and the 0.2 and 0.4 µCi doses caused durable tumor regression. In addition, FPI-1434 caused regression in large Colo-205 tumors grown to a volume of greater than 400 mm prior to dosing. FPI-1434 was also efficacious in the LNCaP and A549 models following single doses of radioimmunoconjugate. To elucidate the mechanism of action, COLO205 tumors treated with 400 nCi FPI-1434 were isolated at 24h, 96h and 168h post treatment, fixed, paraffin-embedded and stained with γH2AX (S139), a marker of double-stranded DNA breaks and Cleaved Caspase 3 (CC3), an early/intermediate apoptosis marker. γH2AX phosphorylation (S139) was almost undetectable at 24h but became more prominent at 96h and 168h post treatment. CC3 followed a similar pattern to γH2AX, highlighting cell nuclei actively undergoing apoptosis because of double-stranded DNA breaks. Current efforts are focusing on confirming the role of apoptosis and investigating the contribution of necrosis, autophagy and senescence to FPI-1434 mechanism of action.
Conclusion: Single doses of FPI-1434 as a standalone agent in pre-clinical models demonstrate a high degree of durable anti-tumor efficacy in multiple tumor xenograft types. The mechanism of action involves induction of DNA double-stranded breaks and progression into apoptosis. These results strongly support the use of FPI-1434 in IGF-1R overexpressing cancers.

Email Address

grinshtein@fusionpharma.com

Presentation Type

Contributed Oral

Primary author: Dr GRINSHTEIN, Natalie (Fusion Pharmaceuticals)

Co-authors: Dr BURAK, Eric (Fusion Pharmaceuticals); Dr FORBES, John (Fusion Pharmaceuticals); Prof. VALLIANT, John (Fusion Pharmaceuticals); Dr MORAN, Matthew (Fusion Pharmaceuticals); Dr HU, Meiduo (Fusion Pharmaceuticals); Dr SIMMS, Ryan (Fusion Pharmaceuticals); Mrs STOROZHUK, Yaryna (Fusion Pharmaceuticals)

Presenter: Dr GRINSHTEIN, Natalie (Fusion Pharmaceuticals)

Contribution ID: **61** Type: **not specified**

Ac-225 production using TRIUMF's 500 MeV cyclotron

TRIUMF has begun production of Ac-225 (t_{1/2} = 9.9 d) by irradiation of thorium metal with 480 MeV protons and has developed new methods for separating Ac-225 from these targets.

At TRIUMF's 500 MeV Isotope Production Facility, targets containing thorium metal (8 g, 60 mm diameter, 0.25 mm thickness) welded inside an Inconel capsule are irradiated by 480 MeV protons to an integrated current of 2640 μA*h, producing at end of bombardment (502 ± 11) MBq of Ac-225 and (64 ± 4) MBq of its parent Ra-225, (n = 2).

After irradiation the thorium is dissolved in 60 mL of 10 M HNO₃ + 12.5 mM HF and evaporated to a thorium nitrate salt. After redissolution in 80 mL of 1 M HNO₃, thorium is precipitated as thorium peroxide by addition of 56 mL of 30% H₂O₂ (>98% of thorium is precipitated). The resulting precipitate is easily filtered. The filtrate is diluted to 0.5 M HNO₃ and loaded onto a 10 mL cation exchange column (DOWEX 50WX8, 200-400 mesh). Washing the column with 450 mL of 1 M citric acid (pH 2.0-2.2) removes residual thorium and other spallation products. After washing with 50 mL of 0.5 M HNO₃, Ra and Ac are then eluted in 60 mL of 8 M HNO₃. This Ac and Ra fraction is then diluted to 4 M HNO₃ with 60 mL of deionized water and passed through a column containing 200-205 mg of DGA-normal resin. While Ra-225 passes through the column, Ac-225 is later removed from the column using 13 mL of 12 M HNO₃. This initial "reagent-grade"Ac-225 product contains other Ac isotopes, most notably long-lived (t_{1/2} = 22 y) Ac-227 (~0.2% relative to ²²⁵Ac by activity).

However, after allowing the Ra-225 fraction to generate additional Ac-225, repassing this fraction through another DGA column produces a second "analytical-grade"Ac-225 product with reduced Ac-227 content. Both the reagent- and analytical-grade Ac-225 have demonstrated high radiolabeling ability (labeling at DOTA concentrations of 10⁻⁵ M at 85 C and macropa concentrations of 10⁻⁷ M at ambient temperature). Efforts to label bifunctional constructs are currently underway. This presentation will provide detailed results of these Ac-225 production efforts with a focus on a comparison of the reagent- and analytical-grade products in terms of radioactive and stable impurities.

In addition, anticipated production scale-up will be described. As the IPF is located immediately in front of the TRIUMF cyclotron's main beam dump, this facility continuously receives >80 μA of 480 MeV protons for >7 months per year and has potential as a potent future Ac-225 source.

Email Address

arobertson@triumf.ca

Presentation Type

Contributed Oral

Primary author: ROBERTSON, Andrew (Life Sciences Division, TRIUMF; Dept. of Physics and Astronomy, University of British Columbia)

Co-authors: LOBBEZOO, Andrew (Life Sciences Division, TRIUMF); Dr HOEHR, Cornelia (Life Sciences Division, TRIUMF; Dept. of Physics and Astronomy, University of Victoria); YANG, Hua (Life Sciences Division, TRIUMF); MOSKVEN, Louis (Applied Technology Group, TRIUMF); Dr SCHAFFER, Paul (Life Sciences Division, TRIUMF); ZEISLER, Stefan (Life Sciences Division, TRIUMF); Dr RADCHENKO, Valery (Life Sciences Division, TRIUMF)

Presenter: ROBERTSON, Andrew (Life Sciences Division, TRIUMF; Dept. of Physics and Astronomy, University of British Columbia)

Contribution ID: **62** Type: **not specified**

Alpha-Particle Therapy for Acute Myeloid Leukemia

Early studies using the humanized anti-CD33 monoclonal antibody lintuzumab labeled with β-emitters showed significant activity against acute myeloid leukemia (AML) but produced prolonged myelosuppression necessitating hematopoietic cell transplantation (HCT). Targeted α-particle therapy may produce more efficient tumor killing while sparing normal cells. An initial phase I trial of bismuth-213 (213Bi)-lintuzumab in relapsed and refractory (R/R) AML provided proof-of-principle for systemically administered α-particle therapy (Jurcic, Blood 2002). 213Bi-lintuzumab demonstrated rapid targeting of disease sites without significant extramedullary toxicity. Target-to-whole body dose ratios were greatly enhanced compared to β-emitting immunoconjugates. Anti-leukemic effects were seen across all dose levels with a decrease in marrow blasts in 78% of patients. In a subsequent phase I/II trial, 213Bi-lintuzumab was administered following partial cytoreduction with cytarabine (Rosenblat, Clin Cancer Res 2010). Among patients receiving the maximum tolerated dose of 37 MBq/kg or higher, responses were seen in 24% of patients. The 46-minute half-life of 213Bi, however, remained an obstacle to its widespread use. Therefore, a more potent second-generation construct containing actinium-225 (225Ac) ($t_{½}$ = 10 days), which generates four α-particle emissions, was developed. A phase I study demonstrated that a single dose of 225Ac-lintuzuamb was safe at doses of 111 kBq/kg or less and produced marrow blast reductions in 67% of evaluable patients with R/R AML (Jurcic, ASH 2011). Dose-limiting toxicity was prolonged myelosuppression, and no evidence of radiation-induced nephrotoxicity was seen. Based on these findings, 225Ac-lintuzumab was investigated in a multicenter phase I/II trial in combination with low-dose cytarabine for older patients with untreated AML (Jurcic, SNMMI 2017). During the first cycle of therapy, two fractions of 225Ac-lintuzumab (18.5-74 kBq/kg/fraction) were administered one week apart after completion of chemotherapy. Five of 18 patients (28%) had objective responses. All responses occurred after the first cycle. The baseline peripheral blood blast count was a strong predictor of outcome, as responses were seen only in patients with peripheral blast counts < 200/μL. This is most likely explained by preferential antibody binding to peripheral sites in patients with higher circulating blast counts, leading to decreased marrow targeting. Because of this observation, a multicenter phase II trial of 225Ac-lintuzumab monotherapy using hydroxyurea to lower peripheral blast counts if needed was undertaken in older AML patients (Finn, ASH 2017). Objective responses were seen in nine of 13 patients (69%) after two doses of 225Ac-lintuzumab (74 kBq/kg) administered one week apart. Myelosuppression, however, was considered to be longer than acceptable in this population, and additional patients were treated with two fractions of 55.5 kBq/kg each. 225Ac-lintuzumab has shown significant activity in AML both alone and in combination with chemotherapy. Future development of 225Ac-lintuzumab includes combinations with standard chemotherapy and novel targeted agents for R/R AML, treatment for measurable residual disease in AML, and conditioning before HCT in patients with high-risk myelodysplastic syndromes.

Email Address

jgj2110@cumc.columbia.edu

Presentation Type

Contributed Oral

Primary author: Dr JURCIC, Joseph (Columbia University Medical center)

Presenter: Dr JURCIC, Joseph (Columbia University Medical center)

Contribution ID: **63** Type: **not specified**

Biodistribution and dosimetry of free 211At and meta-[211At]astatobenzylguanidine (MABG) in normal mice

Alpha particle emitting radionuclides are suitable for targeted radionuclide therapy (TRT), because of their short range in the tissue and high linear energy transfer. 211At is considered to be one of the ideal nuclides for TRT. A new generation of alpha particle compounds for TRT including meta-211At-astato-benzylguanidine (211At-MABG) are expected to have strong therapeutic efficacy with acceptable side effects [1]. 211At-MABG has been proposed for therapy of pheochromocytoma. 211At is a halogen and probably has similar characteristics to radioiodine [1-3]. However, the activity concentration of radioiodine was higher in the thyroid and lower in other organs as compared with free 211At [3]. Therefore, it is important to know the biodistribution and absorbed dose to normal tissues for free 211At and 211At-labelled compounds to predict potential risk organs when these compounds will be used for TRT. The aim of this study is to perform dosimetry of free 211At and 211At-MABG to various organs in normal mice.
Male C57BL/6N mice were injected via tail vein with free 211At (0.13MBq) or 211At-MABG(0.2MBq), and the absolute uptake of these compounds in the organs (%ID/g) were determined at 5 min, and 1, 3, 6, and 24 h after the injection. Number of disintegrations per unit activity administered (μCi-hr/μCi or Bq-hr/Bq) is known as 'Residence time'. It is the integral of a time activity curve for a source region. The absorbed radiation dose for each compound was calculated by OLINDA ver.2.0 by inputting residence time.
Biodistribution study showed that high uptake of free 211At was observed in the lungs, spleen, salivary glands, stomach, and thyroid, while 211At-MABG was observed in the heart and adrenals. The absorbed dose of free 211At was higher in the thyroid and that of 211At-MABG was higher in the adrenals, heart, and liver. The higher mean absorbed dose from 211At-MABG in the specific organs was characteristic to the biochemical property of this compound.
Absorbed dose evaluation of free 211At and 211At-MABG would help to predict potential risk organs and therapeutic strategy when 211At-labelled compounds are used for TRT.

[1] Ohshima Y, et al. Antitumor effects of radionuclide treatment using α-emitting meta-211At-astato-benzylguanidine in a PC12 pheochromocytoma model. Eur J Nucl Med Mol Imaging 2018;45:999–1010
[2] Stocklin G, et al. The impact of radioactivity on medicine. Radiochim Acta. 1995;70/71:249–72.
[3] Spetz J, et al. Biodistribution and Dosimetry of Free 211At, 125I - and 131I - in Rats. Cancer Biother Radiopharm. 2013;28:657–64.

Email Address

ukon@fmu.ac.jp

Presentation Type

Poster

Primary author: Dr UKON, Naoyuki (Fukushima Medical University)

Co-authors: Dr TAN, Chengbo (Fukushima Medical University); Prof. ITO, Hiroshi (Fukushima

Medical University); Prof. KUBO, Hitoshi (Fukushima Medical University); Prof. TAKAHASHI, Kazuhiro (Fukushima Medical University); Dr NISHIJIMA, Ken-ichi (Fukushima Medical University); Dr WASHIYAMA, Kohshin (Fukushima Medical University); Ms AOKI, Miho (Fukushima Medical University); Prof. ORI-UCHI, Noboru (Fukushima Medical University); Ms SHIMOYAMA, Saki (Fukushima Medical University); Prof. ZHAO, Shongji (Fukushima Medical University)

Presenter: Dr UKON, Naoyuki (Fukushima Medical University)

Contribution ID: **64** Type: **not specified**

225Ac-PSMA617 for therapy of prostate cancer – where do we stand?

225Ac-PSMA617 is a novel and highly promising compound for treatment of prostate cancer. Since treatment of the first patient in early 2014, to date more than 330 prostate cancer patients have received a total of approximately 800 therapeutic applications through collaboration of the European Commission's Joint Research Center with hospitals in Heidelberg (Germany), Pretoria (South Africa), Munich (Germany) and Warsaw (Poland). This lecture will give an overview on the current state of clinical development of 225Ac-PSMA617, focusing on its benefits and limitations for treatment of patients suffering from late-stage prostate cancer that have exhausted available established therapies, for patients that have also failed therapy with 177Lu-PSMA617 and for patients that have received fewer pre-treatments, e.g. chemo-naive patients. The safety and efficacy of various dosing regimes, e.g. administration of fixed activities, dose de-escalation strategies and combination therapies with 177Lu-PSMA617 as well as strategies for mitigation of xerostomia, the main toxicity associated with 225Ac-PSMA617 therapy will be reviewed.

Email Address

alfred.morgenstern@ec.europa.e

Presentation Type

Contributed Oral

Primary author: Prof. MORGENSTERN, Alfred (European Commission, Joint Research Centre (JRC), Karlsruhe, Germany)

Presenter: Prof. MORGENSTERN, Alfred (European Commission, Joint Research Centre (JRC), Karlsruhe, Germany)

Contribution ID: **65** Type: **not specified**

Investigating the potential of 212Pb-rituximab as an alpha-radioimmunotherapy for the treatment of Non-Hodgkin's Lymphoma

Background: Non-Hodgkin's Lymphoma (NHL) is the 8th most commonly diagnosed cancer in men and 11th in women. Immunotherapy with anti-CD20 monoclonal antibody rituximab in combination with chemotherapy is used as a first line treatment and significantly improves response rate and survival. However, many relapses are observed. Radioimmunotherapy (RIT) is then an emerging second line option for NHL. RIT with beta-emitters (Bexxar®, Zevalin®) has been developed but hematological toxicity was observed (1). The development of RIT with alpha-emitters is attractive because of the high linear energy transfer (LET) and short path length of alpha-radiation in tissues, resulting in higher tumor cell killing and lower toxicity to surrounding tissues.
In this study, we investigated the potential of alpha-RIT with 212Pb-rituximab in both in vitro and in vivo models. 212Pb is used as an in vivo generator of the high-energy alpha-particle emitting radionuclide 212Bi (2).
Results: Inhibition of proliferation of the mouse lymphoma EL4-hCD20-Luc cell line was correlated with a dose-dependent increase in apoptosis after incubation with 212Pb-rituximab compared to 212Pb-irrelevant mAb or cold antibodies.
Dose range finding (DRF) and acute toxicity studies were performed in order to determine the safety profile and safe administration doses. To evaluate in vivo efficacy of 212Pb-rituximab, 8-week-old C57BL/6JRj mice were injected intravenously with 25 x 103 EL4-hCD20-Luc cells and treated either 11 days or 20 to 30 days post cell injection with 277.5 kBq 212Pb-rituximab or relevant controls (including 277.5 kBq 212Pb-irrelevant mAb, cold rituximab and saline). Therapeutic efficacy was monitored by bioluminescence imaging (BLI) and overall survival. Mice treated with 212Pb-rituximab 20 to 30 days post cell injection (BLI-detectable tumors) exhibited marked tumor growth inhibition compared to controls, with a median survival of 28 days for 212Pb-rituximab-treated group instead of 9 to 13 days for control groups.
Strongly improved median survival (above 105 days) was observed for mice treated with 212Pb-rituximab 11 days after cell injection, whereas median survival was reached 36.5 days post-treatment for 212Pb-irrelevant mAb, 64 days for cold rituximab and 27 days for saline control.
Conclusion: These results show 212Pb-rituximab efficacy on a murine syngeneic lymphoma model with significant tumoral regression and increased survival. This study highlights alpha-RIT potency in B-NHL treatment.

References:
(1) C. Bodet-Milin et al., Frontiers in Oncology, 2013
(2) K. Yong and M.W. Brechbiel, Dalton Trans. 2011

Acknowledgments:
This project received funding from French Public Investment Bank Bpifrance

Funding Agency

French Public Investment Bank Bpifrance

Email Address

isabelle.quelven@unilim.fr

Presentation Type

Contributed Oral

Primary author: Dr DURAND-PANTEIX, Stephanie (CRIBL, CNRS UMR 7276, INSERM 1262, University of Limoges, France)

Co-authors: Dr SAIDI, Amal (Orano Med, Plano, Texas, USA); Dr QUELVEN, Isabelle (CRIBL, CNRS UMR 7276, INSERM 1262, University of Limoges, France ; Nuclear Medicine Department, Limoges University Hospital, France); Prof. MONTEIL, Jacques (CRIBL, CNRS UMR 7276, INSERM 1262, University of Limoges, France ; Nuclear Medicine Department, Limoges University Hospital, France); Dr TORGUE, Julien (Orano Med, Plano, Texas, USA); Prof. COGNE, Michel (CRIBL, CNRS UMR 7276, INSERM 1262, University of Limoges, France)

Presenter: Dr QUELVEN, Isabelle (CRIBL, CNRS UMR 7276, INSERM 1262, University of Limoges, France ; Nuclear Medicine Department, Limoges University Hospital, France)

Contribution ID: **66** Type: **not specified**

Poly-L Lysine based Approaches for Pretargeted Radioimmunotherapy with Astatine-211

Pretargeted radioimmunotherapy (PRIT) has the potential to increase activity uptake in tumors relative to normal tissue compared with conventional radioimmunotherapy. In pretargeting there is preferably a three step administration of agents with different properties. Firstly the pretargeting molecules (usually antibody conjugates) are administered allowing for maximum tumor targeting during the course of several hours. Secondly, a clearing agent is injected in order to clear unbound pretargeting molecules from the blood circulation. When administering antibody-based pretargeting molecules systemically, they will exhibit a relatively slow clearance from the blood why the clearing agent reduce the absorbed dose to normal tissue and thereby maximize the absorbed dose to the tumors. Thirdly, a radiolabeled effector molecule with high affinity for the pretargeting molecule is administered. The effector is a small molecule that therefore exhibits rapid circulation and blood clearance allowing more of the injected radioactivity to reach the tumor compared with conventional radioimmunotherapy. In addition the small effector molecule also distribute faster within the tumor, rendering a more homogenous activity distribution compared with directly radiolabeled antibodies.

Homogenous activity distribution is especially important within Targeted Alpha Therapy where particles ranges in tissue are short (< 100μm). One of the best alpha particle emitters for curative therapies is astatine-211 that have a 7.21 h half-life and one alpha emission per decay.

Several different pretargeting approaches exists where two of the most important ones are the biological (strept)Avidine(SA)<->Biotin system and the chemical Tetrazine (Ttz)<->Tetracyclooctane (TCO) system. In either case the pretargeting molecule is functionalized with one of the ingoing components in each system while both the clearing agent and the effector molecule is functionalized with the other. Poly-L Lysine is a versatile scaffold that can be modified in order to function both as effector molecule and as clearing agent in either one of the mentioned pretargeting systems.

In this work, different approaches using Poly-L Lysine within pretargeted radioimmunotherapy with astatine-211 are explored. For use as clearing agent, Poly Lysine is functionalized with galactose amine to steer clearance to the liver and succinic anhydride for charge modification. Charge modification is also necessary for use as effector molecule where the poly Lysine in addition is functionalized with a molecule e.g. N-succinimidyl-3-(trimethylstannyl)benzoate, in order to allow for incorporation of the radionuclide, astatine-211. Poly-L Lysine is also available in different chain-lengths in order to change circulation and clearance properties.

Email Address

emma.aneheim@radfys.gu.se

Presentation Type

Contributed Oral

Primary author: Dr ANEHEIM, Emma (University of Gothenburg, Sweden)

Presenter: Dr ANEHEIM, Emma (University of Gothenburg, Sweden)

Contribution ID: **67** Type: **not specified**

212Pb Production and Investigation of a Preparation Based on this Radionuclide for Therapy of Neuroendocrine Tumors

Targeted alpha therapy is actually one of the most promising and rapidly progressing method of treatment of oncological diseases. Of certain interest for radionuclide therapy is 212Pb beta emitter with its daughter nuclides (212Bi and 212Po) undergoing α-decay which allows one to regard 212Pb as an in vivo generator of alpha-particles.

In this connection, a new method of 212Pb radionuclide production has been developed and implemented for studies in the field of nuclear medicine. Besides, a method of synthesizing a 212Pb-labeled complex based on synthetic peptide Tyr3-octreotate conjugated with bifunctional DOTA chelating agent (DOTATATE) has been implemented. Such compound is specific to SSTR2 type somatostatin receptors whose overexpression is observable in cells of a number of tumors.

Radionuclide 212Pb was produced with the designed 228Th/212Pb generator. The operation principle of the generator is based on the transfer of gaseous 220Rn by airflow from a vessel with the 228Th-containing ion exchange resin into a separate collector vessel. The 220Rn decay results in the formation of 212Pb which is washed out from the collector by 0.1M HCl solution. Such phase separation ensures high radionuclide purity of the preparation which is of high significance for its application in nuclear medicine. 228Th/212Pb generator design allows generating 10-20 mCi of 212Pb in small volume. Every cycle of the 212Pb radionuclide production lasts for 72 h.

Dependences of the yield of the DOTATATE labeling reaction with 212Pb radionuclide have been studied in cases of different peptide masses in the reaction mixture. The specific activity of preparation varied starting from 0.025 MBq/nmol of peptide and higher. The results of the 212Pb-DOTATATE synthesis efficiency depending on the synthesis duration and pH variety will also be presented. In particular, in case of low specific activities one can attain high labeling yield (>95%) at the synthesis temperature of 90 ℃, the synthesis duration of 30 min and pH values of 6.0-6.5.

Dissociative stability of the synthesized preparation in isotonic solution has also been studied. It was shown that the complex retains its integrity at the level of more than 90% throughout the 212Pb half-life (10.64 h). Also experiments to determine the complex stability in human blood serum were made. Serum was sampled from blood of a healthy volunteer. After holdup of the preparation in blood serum during different time intervals, serum proteins were denatured followed by centrifugal protein precipitation. The degree of stability was estimated from the ratio of protein-unbound activity to the initial activity in corresponding aliquot. The experiments have proven that throughout all of time up to 10 h the stability is at the level of 80-85%.

Researches of the 212Pb-DOTATATE cytotoxicity were also performed on rat pancreas cancer cells (Rin-m5F cell line) by MTT assay. Receptor binding studies of the synthesized complex are also intended to perform. In the long term, biodistribution investigations and other preclinical studies are also planned to carry out.

Funding Agency

National Research Center Kurchatov Institute, Moscow, Russia

Email Address

kvkokov@yandex.ru

Presentation Type

Contributed Oral

Primary authors: Ms DEMCHENKO, Anna (Sechenov University, Moscow, Russia); Dr CHUVILIN, Dmitry (National Research Center "Kurchatov Institute", Moscow, Russia); Dr RESHETOV, Igor (Sechenov University, Moscow, Russia); Mr KOKOV, Konstantin (National Research Center "Kurchatov Institute", Moscow, Russia)

Co-authors: Dr LYUNDUP, Alexey (Sechenov University, Moscow, Russia); Dr EGOROVA, Bayirta (Lomonosov Moscow State University, Moscow, Russia); Dr PROSHIN, Mikhail (National Research Center "Kurchatov Institute", Moscow, Russia); Mr PERMINOV, Yury (National Research Center "Kurchatov Institute", Moscow, Russia)

Presenter: Mr KOKOV, Konstantin (National Research Center "Kurchatov Institute", Moscow, Russia)

Contribution ID: **68** Type: **not specified**

Depleting the latent HIV-1 cell population using 225Ac-labeled anti-CD4+ targeted radioimmunoconjugates

Barreto K¹, Causey P², Solomon VR³, Bernhard W¹, Sutherland A¹, Wilson JJ⁴, Geyer CR¹, Sadowski I⁵, Fonge H^{3,6}.

¹Department of Pathology and Laboratory Medicine, University of Saskatchewan
²Canadian Nuclear Lab, Chalk River, ON
³Department of Medical Imaging, University of Saskatchewan
⁴Department of Chemistry & Chemical Biology, Cornell University
⁵Department of Biochemistry and Molecular Biology, University of British Columbia
⁶Department of Medical Imaging, Royal University Hospital Saskatoon

Overview: A cure for HIV-1 has been elusive. Antiretroviral therapies eliminate the circulating viral load, but upon cessation of treatment the viral load rebounds from latent reservoirs. The Berlin patient is the only known patient cured of HIV-1 and underwent an aggressive ablation/transplant strategy where all T-cells were purged and replaced with T-cells resistant to infection. We present a targeted ablation strategy using a radioimmunotherapy (RIT). Anti-CD4 antibodies ibalizumab, recently FDA approved, and zanolimumab with a significant clinical track record are conjugated to an eight-membered macrocyclic chelator SCN-macropa, and then complexed with Actinum-225 to obtain ²²⁵Ac-ibalizumab or ²²⁵Ac-zanolimumab that specifically targets CD4+ T-cells. This RIT will be used to treat patient blood ex vivo. The amount of latent HIV in treated versus non-treated samples is compared. The objective of this research is to eliminate the latently infected HIV population.

Research methodology & results: SCN-macropa has been synthesized. Anti-CD4 antibodies zanolimumab and ibalizumab were obtained from a commercial source and found to be 93% and 74% pure respectively. Flow cytometry was used to determine their affinity for CD4+ cells isolated from PBMCs as 420 ± 60 pM and 520 ± 20 pM respectively. Conjugation with SCN-macropa resulted in constructs with purities of 83% and 95% and similar binding constants of 400 pM and 200 pM to CD4+ cells isolated from PBMCs. In vitro experiments will be performed using live-cell imaging to determine specific cell killing of CD4+ versus CD4- cells. Depletion on CD4+ cells in PBMCs will be measured using flow cytometry and the amount of HIV DNA in patient blood samples before and after treatment will be quantified by specifically amplifying and quantifying the amount of proviral HIV DNA using real-time PCR.

Significance: HIV-1 hides from treatment in resting immune cells, which means treatment must continue indefinitely. This preliminary study will allow us to determine if we can reduce or eliminate cells harboring latent HIV from patients'blood sample using ²²⁵Ac-ibalizumab or ²²⁵Ac-zanolimumab. Combined with other therapies this strategy could result in a cure for HIV-1.

Funding Agency

CIHR

Email Address

dr.barreto@gmail.com

Presentation Type

Poster

Primary author: Dr BARRETO, Kris (University of Saskatchewan)

Presenter: Dr BARRETO, Kris (University of Saskatchewan)

Contribution ID: **69** Type: **not specified**

Chemical Purification of Actinium-225 from Proton-Irradiated Thorium Targets

The chemical separation of actinium from proton-irradiated 232Th targets is being performed as part of a tri-laboratory (Oak Ridge National Laboratory, Brookhaven National Laboratory, and Los Alamos National Laboratory) effort focused on the accelerator production of 225Ac. Actinium-225 (t1/2 = 9.92 days) is produced by proton irradiation of a thorium metal target via the 232Th[p,x]225Ac reaction and can be used in targeted alpha therapy applications. The irradiation produces a suite of radioisotopes, including fission products, that must be chemically separated from actinium, as well as a vast excess of thorium. This separation is achieved by chemically processing irradiated thorium targets through a series of ion separation and extraction chromatography columns. This effort has produced purified 225Ac over 15 campaigns, providing material for use in targeted alpha therapy research and development.

Funding Agency

DOE, Office of Nuclear Physics, Isotope Program

Email Address

damean@ornl.gov

Presentation Type

Poster

Primary author: Dr DAME, Ashley (Oak Ridge National Labratory)

Co-authors: Ms PEACOCK, Allison (Oak Ridge National Laboratory); Dr CUTLER, Cathy (Brookhaven National Labraotry); Mr STRACNER, Daniel (Oak Ridge National Laboratory); Mr DENTON, David (Oak Ridge National Labratory); Mr MEDVEDEV, Dmitri (Brookhaven National Labratory); Dr BIRNBAUM, Eva (Los Alamos National Labraotry); FITZSIMMONS, Jonathan (Brookhaven National Laboratory); Mr WRIGHT, Joseph (Oak Ridge National Laboratory); Dr GRISWOLD, Justin (Oak Ridge National Labraotry); Ms MURPHY, Karen (Oak Ridge National Laboratory); Mr GADDIS, Kevin (Oak Ridge National Labratory); JOHN, Kevin (Los Alamos National Laboratory); Mr WYANT, Lance (Oak Ridge National Laboratory); Mr MAUSNER, Leonard (Brookhaven National Laboratory); Dr FASSBENDER, MICHAEL (Los Alamos National Laboratory); Dr NORTIER, Meiring Nortier (Los Alamos National Laboratory); Dr COPPING, Roy (Oak Ridge National Laboratory); Dr MIRZADEH, Saed (Oak Ridge National Laboratory); Dr DAVERN, Sandra (Oak Ridge National Laboratory); Dr MASTREN, Tara (Los Alamos National Labratory); Dr RADCHENKO, Valery (TRIUMF); Dr BOLL, rose (ORNL)

Presenter: Dr DAME, Ashley (Oak Ridge National Labratory)

Contribution ID: **70** Type: **not specified**

Safety and efficacy of Ac-225-PSMA-617 in mCRPC after failure of Lu-177-PSMA

Aim: Despite the approval of several new agents metastatic castration resistant prostate cancer is still a major medical challenge. The beta-emitting Lu-177-PSMA radioligand therapy (RLT) is a new option but its antitumor effect can decrease over time. The aim of this retrospective analysis was to investigate safety and efficacy of the alpha emitting Ac-225-PSMA-617 RLT in mCRPC after Lu-177-PSMA failure.

Methods: 15 patients underwent Ac-225-PSMA-617 RLT between 10/17 and 08/18. All patients had previously received second line antihormonal treatment, as well as chemotherapy and had shown progression after Lu-177-PSMA therapy (median 2 cycles).Repeat PSMA-PET/CT before Ac-225-PSMA-617 therapy indicated continued high PSMA-expression. Patients were treated at 8 weekly intervals until progression or intolerable side effects. Prostate-specific antigen (PSA) and blood cell count were measured every 2-3 weeks. We report hematological and non-hematological side effects (Common Terminology Criteria for Adverse Events) and biochemical response.

Results: A total of 27 cycles of Ac-225-PSMA-617 (median dose 8 MBq, range 6–12.8) were applied. 5 patients received only 1 cycle, 8 patients 2 cycles and 2 patients 3 cycles. Baseline PSA was 758 ng/ml (range 49–4073). ECOG score was grade 0, 1 and 2 in 3, 10 and 2 patients, respectively. 10/15 patients showed any PSA-decline, 5/15 a PSA-decline of more than 50% and 3 patients no PSA-decline at any time. Grade 1-2 xerostomia occurred in 14 and 1 patient, respectively. 5/15 patients requested to stop treatment due to xerostomia. Two patients developed grade 2 renal insufficiency, 4 patients grade 3-4 anemia, 2 patients grade 3 thrombocytopenia. No grade 3-4 leucopenia was observed. 7/15 patients died during the observation period (median overall survival 8 months).

Conclusion: In this small cohort Ac-225-PSMA-617 RLT showed antitumor effect in mCRPC after Lu-177-PSMA failure. However, treatment had to be stopped in one third of the patients due to xerostomia.

Email Address

benedikt.feuerecker@tum.de

Presentation Type

Contributed Oral

Primary author: Dr FEUERECKER, Benedikt (Klinikum rechts der Isar, department of nuclear medicine, Technical University of Munich, Munich, Germany)

Co-authors: Dr MORGENSTERN, Alfred (European Commission, Joint Research Centre (JRC), Karlsruhe, Germany); Mr BEHESHTI, Ali (Klinikum rechts der Isar, department of nuclear medicine, Technical University of Munich, Munich, Germany); Dr D'ALESSANDRIA, Calogero (Klinikum rechts der Isar, department of nuclear medicine, Technical University of Munich, Munich, Germany); Dr SEIDL, Christof (Klinikum rechts der Isar, department of nuclear medicine, Technical University of Munich, Munich, Germany); Dr BRUCHERTSEIFER, Frank (European Commission, Joint Research Centre (JRC), Karlsruhe); Dr KNORR, Karina (Klinikum rechts der Isar, department of nuclear medicine, Technical

University of Munich, Munich, Germany); Prof. RETZ, Margitta (Klinikum rechts der Isar, department of urology, Technical University of Munich, Munich, Germany); Prof. EIBER, Matthias (Klinikum rechts der Isar, department of nuclear medicine, Technical University of Munich, Munich, Germany); Dr TAUBER, Robert (Klinikum rechts der Isar, department of urology, Technical University of Munich, Munich, Germany); Prof. WEBER, Wolfgang (Klinikum rechts der Isar, department of nuclear medicine, Technical University of Munich, Munich, Germany)

Presenter: Dr FEUERECKER, Benedikt (Klinikum rechts der Isar, department of nuclear medicine, Technical University of Munich, Munich, Germany)

Contribution ID: **71** Type: **not specified**

Various chromatographic schemes for separation of 213Bi from 225Ac

Among alpha emitters suitable for targeted alpha-therapy, 225Ac (T1/2 = 9.9 days) and the product of its decay 213Bi (46 min.) are the most promising. Clinical trials are confirming higher efficacy and less toxicity of the radiopharmaceuticals labeled with these radionuclides in comparison with similar beta-emitting ones. A prospective method of producing 225Ac (more than 1 Ci for a 10-day run) by irradiation of natural thorium with medium-energy protons followed by chemical isolation has been developed at the Institute for Nuclear Research of the Russian Academy of Sciences (INR RAS). A long-lived 227Ac (21.7 years) is also formed (~0.1% of 225Ac at the end of irradiation), and direct medical application of the product seems questionable. However, 225Ac with small impurity of 227Ac is appropriate as a mother radionuclide for 225Ac/213Bi generator.

225Ac/213Bi generators based on ion exchange (AG MP-50, AG 1, BioRad) and extraction chromatography resins (Actinide Resin, UTEVA Resin, Triskem Int.) are well described.

All the proposed generator systems can be classified as follows:
1. The «direct» generator, where Ac-225 is firmly retained by the sorbent, and Bi-213 is eluted with various complexing agents. Such generator based on the cation-exchange resin of the type AG MP-50 is commonly applied for clinical trials;

1. The «direct» generator, where Ac-225 is firmly retained by the sorbent, and Bi-213 is accumulated and concentrated due to the separation and decay of the short-lived Fr-221 on the second sorbent. This type of generators is under development at INR RAS;
2. A «reverse» generator, where periodically accumulating Bi-213 is selectively adsorbed from solution of Ac-225, and then desorbed for use. Systems of so-called multicolumn selective inversion generators (MSIG) was developed at PNNL, USA. Generators of this type based on inorganic sorbents is also under development at INR RAS.

The «direct» generator is most convenient for clinical application, however, in the presence of Ac-227 in Ac-225, the content of Ac-227 and its decay products in Bi-213 eluate may be important. Generators developed at INR RAS can provide higher degree of purification from these radionuclides.

The initial activity of generator (not more than 50-100 mCi) is limited not only by 225Ac production capabilities but also by the radiation resistance of the sorbents used in the generator. Since the developed method of 225Ac production allows increasing the activity of 213Bi injected into a patient (at least to 4 GBq (100-150 mCi)), both radiation and radiolytic destruction of the sorbent also grow up. In this case, generators assigned to the 2nd and 3rd categories will have an advantage.

Funding Agency

This work has been supported by the Russian Science Foundation under Contract № 17-73-10465.

Email Address

vasiliev@inr.ru

Presentation Type

Contributed Oral

Primary author: Dr VASILIEV, Aleksandr (Institute for Nuclear Research Russian Academy of Sciences)

Co-authors: Dr ZHUIKOV, Boris (Institute for Nuclear Research of the Russian Academy of Sciences); Dr LAPSHINA, Elena (Institute for Nuclear Research of Russian Academy of Sciences); Dr DENISOV, Evgeniy (Ural Federal University named after the first President of Russia B.N.Yeltsin); Prof. BETENEKOV, Nikolay (Ural Federal University named after the first President of Russia B.N.Yeltsin); Dr ERMOLAEV, Stanislav (Institute for Nuclear Research Russian Academy of Sciences)

Presenter: Dr VASILIEV, Aleksandr (Institute for Nuclear Research Russian Academy of Sciences)

Contribution ID: **72** Type: **not specified**

Development of a new method for the microbiological analysis of radiopharmaceuticals case of Iodine 131

OBJECTIVE:
The main aim of this study is to develop a new microbiological control method for the solution of iodine 131 in a closed system for radiopharmacy services not equipped with a class A Hot Cell dedicated to microbiological analysis according to GMP requirements.

METHODS:
The method is based on the preparation of perforated petri dishes containing three culture media. The perforation of the Petri dishes was realized under a class A laminar flow hood using a heated metal cylindrical rod. A sterile magnetic stir bar was then placed in each Petri dish before closing the hole and sealing Petri dishes with autoclaving adhesive.
First, the method was tested inside a class C room then inside an unclassified area by perforating the adhesive with a sterile syringe and injecting a volume of sterile water before the perforation was closed by a second sterile adhesive. Seeding was performed by moving each Petri dish on a magnet. Then the Petri dishes were incubated inside the Hot Cell at room temperature for Yeast and Mold at 32.5 ℃ and for Total Aerobic Microbial and Total Coliform.
A positive control (bacterial suspension) and a negative control (sterile water) were performed for each culture medium.
Finally, the method was tested inside a class C Hot Cell for three production batches of sterile iodine-131.

RESULTS:
After 5 days incubation at 32,5℃ and 7 days at room temperature, The Petri dishes was sterile for both tests performed in class C room and for the unclassified room. The same result was obtained with the solution of iodine131 in the three production batches.

CONCLUSION:
This new method has shown good efficiency to keep the sterility of culture medium during the microbiological analysis independently of the environmental class. It could be adopted by radiopharmacy services for the control of the solution of iodine131 and other radiopharmaceuticals. This method would make it possible to carry out the microbiological analysis of radiopharmaceuticals quickly without waiting for the decay. Moreover, it allows to minimize the risk of exposure of the laboratory technicians by iodine inhalation.

Email Address

aiboud.abdelmjid@gmail.com

Presentation Type

Poster

Primary author: Mr AIBOUD, abdelmjid (National Energy Center of Nuclear Science and Technology (CNESTEN)- Morocco)

Co-authors: Mr ETTABIA, abdellah (National Energy Center of Nuclear Science and Technology (CNESTEN)- Morocco); Mr FLLOAUI, aziz (National Energy Center of Nuclear Science and Technology (CNESTEN)- Morocco); Mr BENHAMOU, kaddour (National Energy Center of Nuclear Science and Technology (CNESTEN)- Morocco); Mr AIT SAID, mouhsine (National Energy Center of Nuclear Science and Technology (CNESTEN)- Morocco); Mr BENTALEB, naoual (National Energy Center of Nuclear Science and Technology (CNESTEN)- Morocco); Mr GHAMAD, younes (National Energy Center of Nuclear Science and Technology (CNESTEN)- Morocco); Mr AYAZ, zine el abidine (National Energy Center of Nuclear Science and Technology (CNESTEN)- Morocco)

Presenter: Mr AIBOUD, abdelmjid (National Energy Center of Nuclear Science and Technology (CNESTEN)- Morocco)

Contribution ID: **73** Type: **not specified**

In vitro radiobiological effects of Radium-223

α-particle emitting radionuclides have been increasingly used in cancer treatment with particular interest for the treatment of micrometastases, due to the recently demonstrated survival benefit of Radium-223 (223Ra) in the treatment of bone metastases [1]. However, the reasons for its efficacy in comparison to previous beta emitters remains poorly understood. There is a pressing need to model and quantify α-emitter effects in pre-clinical models so the next generation of trials utilizing 223Ra can be optimally designed.

It is often assumed that the higher lethality of α-particles is related with the higher propensity for complex DNA double-strand breaks (DBSs) and clustered DNA damage in the irradiated cells. The present investigation was carried out to evaluate the radiobiological effect of 223Ra in 3 different prostate cell models (PC-3, U-2OS metastatic lines, and normal RWPE) by assays of clonogenic survival and DNA damage.
Clonogenic cell survival curves were analyzed for different cell lines after irradiation with 225 kVp X-rays from 0 to 8 Gy (dose rate 0.594 Gy/min), external α-particles (241 Americium) from 0 to 2 Gy (dose rate 1.579 Gy/min) and 223Ra from 0 to 0.5 Gy (dose rate 1.389 mGy/min).

The results showed a superior efficacy of 223Ra in comparison with the external α source in all cell lines but with a cell type dependency. The Relative Biological Effectiveness (RBE) for 50% survival for RWPE is 6.07 and 7.97, for external α- particles and 223Ra respectively. For U-2OS is 6.36 and 8.9 and finally for PC-3 the values are 3.63 and 7.47.

Lastly, the induction and repair of DNA damage by different radiation qualities was analyzed by immunofluorescence (53BP1) for doses up to 2 Gy and recovery times of 1, 4, 24 and 96h. For all irradiation setups there is a linear relationship between the number of foci and the absorbed dose. The level of induction and the shape of the kinetics curves are radiation- and cell-specific with the highest induction of foci observed after X-ray irradiation, the lowest after external α irradiation, and 223Ra being slightly higher than external α particles. In terms of repair, foci induced by external α source or 223Ra are repaired approximately 3.5 times slower than the X-ray induced breaks in the same cell line. These observations support the higher propensity for complex DNA-damage induced by heavy particles as reported in the literature.
Interestingly, exposure to 223Ra severely affects the nuclear structure with a significant number of giant nuclei, and a large fraction of cells undergoing mitotic catastrophe, features not seem to the same extent with external beam irradiation.

In conclusion, our results suggest that response to Radium-223 is cell-specific and that better effectiveness does not solely depend on the DNA damage complexity.

[1] Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med. 2013;369:213-223.

Funding Agency

Fundação para a Ciência e Tecnologia (FCT-MCTES) and Movember/Prostate Cancer UK

Email Address

f.liberal@qub.ac.uk

Presentation Type

Contributed Oral

Primary author: Mr LIBERAL, Francisco (Queen's University Belfast)

Co-authors: Mr MOREIRA, Hugo (Queen's University Belfast); Prof. O'SULLIVAN, Joe (Queen's University Belfast); Dr REDMOND, Kelly (Queen's University Belfast); Prof. PRISE, Kevin (Queen's University Belfast); Dr MCMAHON, Stephen (Queen's University Belfast)

Presenter: Mr LIBERAL, Francisco (Queen's University Belfast)

Track Classification: Preclinical

Contribution ID: **74** Type: **not specified**

Safety and therapeutic efficacy of 225Ac-DOTA-Substance P for therapy of brain tumors

Leszek Krolicki1, Frank Bruchertseifer2, Jolanta Kunikowska1, Henryk Koziara3, Bartosz Królicki3, Maciej Jakuciński4, Dariusz Pawlak 5, Christos Apostolidis2, Rafał Rola6, Adrian Merlo7, Alfred Morgenstern2
1 Department of Nuclear Medicine, Medical University of Warsaw, Warsaw, Poland
2 European Commission, Joint Research Centre, Directorate for Nuclear Safety and Security, Karlsruhe, Germany
3 Department of Neurosurgery, National Cancer Institute, Warsaw, Poland
4 Department of Nuclear Medicine, Brodnowski Hospital, Warsaw, Poland
5 Radioisotope Centre POLATOM, National Centre for Nuclear Research, Otwock, Poland
6 Department of Neurology, Military Institute of Aviation Medicine. Warsaw, Poland
7 Neurosurgery, Spitalgasse 32, Bern and University of Basel, Switzerland

Glioblastoma multiforme (GBM) is the most common, aggressive and devastating malignant primary brain tumor in humans. Treatment options for recurrent glioblastoma multiforme (GBM) are very limited. For many years, no significant progress in the treatment of tumors was monitored. Local treatment with radiopharmaceuticals is a promising method of treatment. GBM cells express high levels of the GPCR neurokinin type 1 receptor (NK-1R) and modified substance P can be used as its ligand for tumor cell targeting. Targeted alpha therapy with DOTA-Substance P (SP) labeled with the short range alpha emitter allows for selective irradiation and killing of tumor cells. In the first step 213Bi with a short half-time (45 min) was used for labeling of SP and local injection to the tumor and promising results were described. It seems that this radioisotope can be use in treatment of small tumors. The relatievly short half-live of 213Bi and a slow diffusion process limit the optimal distribution of the tracer in the larger tumors. A radioisotope with longer half time might be preferred in this group of patients. Therefore 225Ac with a half live of 9.9 days has been applied. 21 patients with histologically confirmed recurrence of the glia tumor grade II-IV were included in the study: grade II - 1 patient, grade III, - 8 patients. grade IV -12 patients. All patients received standard treatment (surgery + radio-chemo-therapy). When recurrence of disease was diagnosed, resection of the tumor and implantation of the cat-cap system intratumoral or to the postsurgical cavity were performed. Few weeks later 20-40 MBq 225Ac-DOTA-SP was given. 68Ga-DOTA-Substance P (68Ga-DOTA-SP) was co-injected with 225Ac-DOTA-SP to assess biodistribution using PET/CT. Therapeutic response was monitored with performance status and MRI imaging. In the group of patients with primary glioblastoma multiforme (grade IV) PFS was 4-112 weeks; OS from primary diagnosis was 32-128 weeks; OS from recurrence was 28-62 weeks; and OS from radioisotopic treatment was 8-48 weeks.
Intracavitary / intratumoral injection of 225Ac-substance P was well tolerated. Only mild, temporary adverse effects observed (edema, epileptic seizures, aphasia). Patient recruitment and dose escalation is ongoing.

Funding Agency

Department of Nuclear Medicine, Medical University of Warsaw, Warsaw, Poland

Email Address

leszek.krolicki@WUM.edu.pl

Presentation Type

Contributed Oral

Primary author: Prof. KROLICKI, Leszek (Medical University, Warsaw)

Co-authors: Prof. MERLO, Adrian (Neurosurgery, Spitalgasse 32, Bern and University of Basel, Switzerland); Dr MORGENSTERN, Alfred (European Commission, Joint Research Centre, Directorate for Nuclear Safety and Security, Karlsruhe, Germany); Dr KRÓLICKI, Bartosz (Department of Neurosurgery, National Cancer Institute, Warsaw, Poland); APOSTOLIDIS, Christos (European Commission, Joint Research Centre, Directorate for Nuclear Safety and Security, Karlsruhe, Germany); Dr PAWLAK, Dariusz (Radioisotope Centre POLATOM, National Centre for Nuclear Research, Otwock, Poland); Dr BRUCHERTSEIFER2, Frank (European Commission, Joint Research Centre, Directorate for Nuclear Safety and Security, Karlsruhe, Germany); Dr KOZIARA, Henryk (Department of Neurosurgery, National Cancer Institute, Warsaw, Poland); KUNIKOWSKA1, Jolanta (Department of Nuclear Medicine, Medical University of Warsaw, Warsaw, Poland); Dr JAKUCIŃSKI, Maciej (Department of Nuclear Medicine, Brodnowski Hospital, Warsaw, Poland); ROLA, Rafał (Department of Neurology, Military Institute of Aviation Medicine. Warsaw, Poland)

Presenter: Prof. KROLICKI, Leszek (Medical University, Warsaw)

Contribution ID: **75** Type: **not specified**

Radiohalogenated neopentyl derivatives: A novel scaffold for radioiodinated and astatinated compounds of high stability to in vivo dehalogenation

Objectives: Astatine-211 (²¹¹At) is an α-emitting radionuclide appropriate for medical use. To expand the application of ²¹¹At-labeled compounds to radiotheranostics, we developed neopentyl derivatives as a novel scaffold for radioiodination and astatination. The stability, biodistribution, and metabolism of ¹²⁵I-labeled neopentyl derivatives were evaluated. The biodistribution of a ²¹¹At-labeled compound was compared with its ¹²⁵I-labeled counterpart.

Methods: Two iodinated neopentyl derivatives with a nitroimidazole group were synthesized; *N*-[2,2-bis(hydroxymethyl)-2-(iodomethyl)ethyl]-2-nitroimidazole (BHIN) and *N*-[2,2-diethyl-2-(iodomethyl)ethyl]-2-nitroimidazole (DEIN). The radioiodination was conducted by reacting their sulfonyl precursors with Na[¹²⁵I]I. The stability to the nucleophilic substitution was evaluated in a 10 mM glutathione solution at pH 7.4 for 24 h. The biodistribution of [¹²⁵I]BHIN or [¹²⁵I]DEIN was evaluated in normal male mice. Urine samples collected for 6 h after injection were analyzed by a reversed-phase HPLC. [²¹¹At]*N*-[2,2-bis(hydroxymethyl)-2-(astatomethyl)ethyl]-2-nitroimidazole ([²¹¹At]BHAN) was prepared under the procedure similar to [¹²⁵I]BHIN and was subjected to biodistribution study in normal male mice.

Results: Both ¹²⁵I-labeled compounds were obtained in 40 to 90% radiochemical yields and over 98% radiochemical purities after HPLC purification. Both ¹²⁵I-labeled compounds remained stable after incubation in a glutathione solution for 24 h (>95%), indicating that the two radioiodinated compounds possess high stability to the nucleophilic substitution reaction. In biodistribution study, while [¹²⁵I]DEIN showed high radioactivity levels in the neck (10.60 ± 0.03 %ID at 24 h), such radioactivity was hardly observed with [¹²⁵I]BHIN (0.03 ± 0.02 %ID at 24 h). Both radioiodinated compounds were mainly excreted into urine. The analysis of urine samples indicated that while the majority of the radioactivity was present as [¹²⁵I]I⁻ for [¹²⁵I]DEIN, [¹²⁵I]BHIN showed the majority of the radioactivity as the glucuronide-conjugate. [²¹¹At]BHAN was obtained in about 14% radiochemical yields and over 98% radiochemical purities after HPLC purification. [²¹¹At]BHAN exhibited the pharmacokinetics similar to [¹²⁵I]BHIN with low radioactivity levels in the neck and the stomach.

Conclusions: Both ¹²⁵I-labeled compounds possessed high stability to the nucleophilic substitution. The presence of the hydroxyl groups in BHIN provided further stabilization to the enzymatic dehalogenation reaction. [¹²⁵I]BHIN and [²¹¹At]BHAN exhibited similar pharmacokinetics each other with dehalogenation being hardly observed. These findings indicate that the neopentyl derivatives would serve as a useful scaffold to develop a radiotheranostic pair consisting of radioiodinated and ²¹¹At-labeled compounds.

Email Address

h.suzuki@chiba-u.jp

Presentation Type

Contributed Oral

Primary author: Dr SUZUKI, Hiroyuki (Graduate School of Pharmaceutical Sciences, Chiba University)

Co-authors: Dr TOYOSHIMA, Atsushi (Institute for Radiation Sciences, Osaka University); Dr TANAKA, Hiroshi (Graduate School of Chemical Science and Engineering, Tokyo Institute of Technology); Prof. HATAZAWA, Jun (Graduate School of Medicine, Osaka University); Dr OOE, Kazuhiro (Graduate School of Medicine, Osaka University); Ms TATSUTA, Maho (Graduate School of Chemical Science an Engineering, Tokyo Institute of Technology); Ms WASHIYA, Nana (Graduate School of Pharmaceutical Sciences, Chiba University); Dr ISHIOKA, Noriko (Quantum Beam Science Research Directorate, National Institutes for Quantum and Radiological Science and Technology); Dr WATANABE, Shigeki (Quantum Beam Science Research Directorate, National Institutes for Quantum and Radiological Science and Technology); Dr WATABE, Tadashi (Graduate School of Medicine, Osaka University); Dr UEHARA, Tomoya (Graduate School of Pharmaceutical Sciences, Chiba University); Prof. ARANO, Yasushi (Graduate School of Pharmaceutical Sciences, Chiba University); Dr SHIRAKAMI, Yoshifumi (Graduate School of Medicine, Osaka University); Ms SATO, Yui (Graduate School of Pharmaceutical Sciences, Chiba University); Mr KAIZUKA, Yuta (Graduate School of Pharmaceutical Sciences, Chiba University)

Presenter: Dr SUZUKI, Hiroyuki (Graduate School of Pharmaceutical Sciences, Chiba University)

Contribution ID: **76** Type: **not specified**

ISOL technique for the production of 225Ac at CERN-MEDICIS

Over the last few years, several studies have proven the effect of targeted alpha therapy using 225Ac and 213Bi[1,2,3]. One of the crucial bottlenecks in upscaling current studies and moving to clinical trials is the availability of these isotopes. The current production methods cannot provide sufficient quantities of 225Ac or its daughter 213Bi. Furthermore, some of these production techniques result in batches of 225Ac with a lot of impurities which require advanced radiochemical separation techiques to be purified. Therefore, a new technique for the production of 225Ac and other radioisotopes is proposed. The new CERN-MEDICIS facility, which is under development, uses the Isotope Separation On-Line (ISOL) technique to produce a range of medical radioisotopes, e.g. 225Ac, 149Tb, etc[4]. This techique uses a combination of element selective and mass selective processes which result in a very pure, carrier-free batch of the isotope of interest. First a target material, e.g. UCx or Ta, is irradiated with high energy protons of 1.4 GeV. Afterwards, the target it heated to extract the produced isotopes. These isotopes are selectively ionized using a resonant ionisation laser ion source[5]. This allows to selectively ionize Ac isotopes. This ion beam passes through a mass separating magnetic field to result in an ion beam which is very pure in mass. As a final step this ion beam will be collected in a metallic foil or a salt. Afterwards, the radioisotopes can be separated from the collection material using dissolution and simple radiochemical purifications. Resonant laser ionisation of actinium has recently been achieved during a proof-of-concept experiment at CERN while the upscaling towards routine production is under investigation.

In this contribution, we shall introduce the ISOL technique and its possible application in the production of alpha-emitting radioisotopes for medical applications. The CERN-MEDICIS facility will be introduced and the recent results on the production of 225Ac at CERN will be presented.

[1] M. Sathekge et al. 225Ac-psma-617 in chemotherapy-naive patients with advanced prostate cancer: a pilot study. European Journal of Nuclear Medicine and Molecular Imaging, Sep 2018.

[2] L. Finn et al. A phase 2 study of actinium-225 (225Ac)-lintuzumab in older patients with previously untreated acute myeloid leukemia (aml) unt for intensive chemotherapy. Blood, 130(Suppl 1):2638-2638, 2017.

[3]L. Krolicki et al. Prolonged survival in secondary glioblastoma following local injection of targeted alpha therapy with 213Bi-substance p analogue. European Journal of Nuclear Medicine and Molecular Imaging, 45(9):1636-1644, Jul 2018.

[4] R. dos Santos Augusto et al. CERN-MEDICIS (Medical Isotopes Collected from ISOLDE): A New Facility. Applied Sciences, 4(2):265-281, may 2014.

[5] V. Fedosseev et al. Resonance laser ionization of atoms for nuclear physics. Physica Scripta, 85(5):058104, 2012.

Email Address

dockx.kristof@kuleuven.be

Presentation Type

Contributed Oral

Primary author: Mr DOCKX, Kristof (Institute for Nuclear and Radiation Physics, KU Leuven)

Co-authors: Dr STORA, Thierry (CERN); Dr COCOLIOS, Thomas Elias (Institute for Nuclear and Radiation Physics, KU Leuven)

Presenter: Mr DOCKX, Kristof (Institute for Nuclear and Radiation Physics, KU Leuven)

Contribution ID: **77** Type: **not specified**

Actinium Biokinetics and Dosimetry: What is the Impact of Ac-227 in Accelerator-Produced Ac-225?

Among the growing list of alpha-emitting isotopes now available for pharmaceutical development, Ac-225 can act as an in vivo alpha-generator radionuclide and is of great interest for new targeted alpha-therapy applications. To seek further development of Ac-225 bioconjugate therapeutics, ongoing efforts aim at addressing current limitations, including lacking supply of the radioisotope, insufficient understanding of its biodistribution and biodosimetry, poor retention of alpha-emitting daughter products at the target site, as well as inadequate chelation, one of the major drawbacks.

The U.S. Department of Energy's Isotope Program has been exploring new pathways for the production of the radioisotope Ac-225 at accelerator facilities to address a potential increased need for medical applications. However, the presence of co-produced, long-lived Ac-227 (21.8 y half-life) is observed in about 0.15-0.3 activity percent in the accelerator-derived product at the end of target bombardment. Up to 0.5 activity percent values due to Ac-227 could be anticipated in a research/clinical setting. One goal of our work is to delineate the biodistribution of Ac-225, its short-lived daughter products, and potential trace contaminants such as Ac-227 that may be co-produced in new larger-scale accelerator-derived processes. The biokinetics of unchelated, chelated (with classic macrocyclic structures, amino-polycarboxylic acids, or new hydroxypyridinone ligands under development), and bio-conjugated Ac-225 and Ac-227 were determined in several mouse models. The resulting biodistribution and dosimetry profiles highlight significant differences among isotope and ligand combinations that must be considered and addressed in order to ensure bioconjugated Ac-225 is safe for use in the clinic.

Part of the discussed work was supported by the U.S. Department of Energy's Isotope Program in the Office of Nuclear Physics at the Lawrence Berkeley National Laboratory under Contract DE-AC02-05CH11231.

Email Address

abergel@berkeley.edu

Presentation Type

Contributed Oral

Primary author: Prof. ABERGEL, Rebecca (University of California, Berkeley)

Co-authors: Dr LAKES, Andrew (Lawrence Berkeley National Laboratory); AN, Dahlia (Lawrence Berkeley National Laboratory); Dr REES, Julian (Lawrence Berkeley National Laboratory); GAUNY, Stacey (Lawrence Berkeley National Laboratory)

Presenter: Prof. ABERGEL, Rebecca (University of California, Berkeley)

Contribution ID: **78** Type: **not specified**

Estimation of long-term risks for cancer induction following adjuvant targeted alpha therapy with curative intent.

Risks for induction of secondary cancers following radiation or other therapies of advanced cancers are typically not considered since the estimated life-span of these patients is relatively short. This is often the case for patients currently considered for targeted alpha therapy, TAT. However, TAT may hold most promise as an adjuvant therapy following surgery and/or chemotherapy. It will then be delivered to patients possibly already cured by the primary treatment. In this setting, or for any TAT with curative intent, some estimate of long-term risks is therefore needed for an informed decision whether to justify the treatment.

Within the overall aim to base a decision on justification for adjuvant TAT on a sound risk-benefit evaluation, the specific aim of the current work was to translate the, for intraperitoneal TAT, most relevant data on excess cancer induction and mortality to an estimate of what can be expected following adjuvant intraperitoneal TAT.

Methods
A survey of baseline data for risk estimates of alpha-particle irradiation of organs of interest for intraperitoneal TAT was performed. The well-known studies on excess cancer induction and mortality for subjects exposed to either high-dose-rate 224Ra treatment or Thorotrast contrast agent were selected. Dosimetry have been presented for both 224Ra (1) and Thorotrast (2,3). Organ-specific risks from these studies were then applied on our previously reported dosimetry for intraperitoneal TAT patients (4).

Results
We have previously reported that an infusate concentration of 200 MBq/L 211At-mAb would result in 2.6 Sv effective dose (4). This result indicates a life-long lethal cancer risk of around 10%. When directly translating the results from the 224Ra and Thorotrast studies, this risk is reduced. The organs at highest risk for secondary cancer were the kidneys and lungs, which warrants evaluation of the microscopic distribution of the alpha decays even if secondary cancers in these organs have relatively long latency. For intraperitoneal TAT, the risk for hematological malignancies seems very low.

Conclusion
There are obvious and large uncertainties in both excess cancer incidence and dosimetry. Overall, however, the results indicate that some estimate of long-term risk for cancer induction can be derived. For TAT, such data are seldom used, but could strengthen a risk-benefit analysis of use in patient selection and dose optimizations of TAT with curative intent.

1. Radiat Environ Biophys (2002)41:173–178
2. Radiat Res (1993)135:244-248
3. Health Phys (1978)35:113-121
4. Int J Radiat Oncol Biol Phys (2015)93:569-76

Email Address

stig.palm@gu.se

Presentation Type

Contributed Oral

Primary author: Dr PALM, Stig (University of Gothenburg)

Co-authors: Dr HALLQVIST, Andreas (University of Gothenburg); Dr ANEHEIM, Emma (University of Gothenburg, Sweden); Prof. RAGNAR, Hultborn (University of Gothenburg); Dr MIA, Johansson (University of Gothenburg); Prof. JACOBSSON, Lars (University of Gothenburg); Dr ALBERTSSON, Per (University of Gothenburg); Dr LINDEGREN, Sture (University of Gothenburg); Dr BÄCK, Tom (University of Gothenburg)

Presenter: Dr PALM, Stig (University of Gothenburg)

Contribution ID: **79** Type: **not specified**

Therapeutic efficacy and dosimetry of targeted alpha therapy using 225Ac-PSMA-617 in a murine model of prostate cancer

Background and Objective. Targeted alpha therapy shows promise as a treatment in metastatic castration-resistant prostate cancer (mCRPC), owing to the high dose deposition and short range characteristics of alpha particle radiation. Ac-225 decays via multiple alpha particles –each capable of inducing irreparable DNA double-strand breaks in cell nuclei. PSMA-617 is a targeting ligand with specific affinity for prostate-specific membrane antigen (PSMA), a protein that is overexpressed in mCRPC but has low expression in normal tissues. Coupled with the lethal effects of alpha radiation, 225Ac-PSMA-617 is potentially highly cytotoxic to mCRPC while sparing normal tissues. The objective of this study was to evaluate the efficacy of alpha-particle radioligand therapy in a mouse model of mCRPC. Radiation dosimetry analysis was carried out to determine tumor dose as well as dose-limiting organs.

Methods. NSG mice bearing subcutaneous PSMA-expressing C4-2 tumors were injected with escalating activities of 225Ac-PSMA-617: 20, 40, and 100 kBq/mouse (n=8/group). The tumor volumes were assessed over time by weekly low-dose microCT and compared with an untreated control group. In parallel, twenty-five NSG mice were used in a biodistribution study at five time points – 1, 4, 24, 48, and 168 hours post-administration of 40 kBq of the radiopharmaceutical. After sacrifice, percent tumor and organ radioactivity uptake was measured using gamma spectroscopy. Biexponential curve-fitting was used to fit the time-activity curves for the tumor and each organ, and integrated according to standard medical internal radiation dose methods to estimate the tumor and organ doses.

Results. Significant tumor growth retardation was observed in all treatment groups compared with the untreated group. Mice treated with 100 kBq exhibited some weight loss, while the mice treated with lower activities experienced only transient weight loss. There was a significant survival benefit conferred on tumor-bearing mice treated with 225Ac-PSMA-617. The biodistribution over five time points showed high uptake and slow tumor activity clearance, and low uptake with fast clearance in non-target organs. The salivary glands, a dose-limiting organ in humans, did not show high uptake in mice, possibly due to lower PSMA expression. Estimates of the absorbed dose to the tumor and organs are reported.

Conclusion. An administered activity of 40 kBq per mouse of the peptidomimetic 225Ac-PSMA-617 is well-tolerated and results in significant tumor growth retardation and improved survival. This work provides a preclinical foundation for further studies towards a more effective treatment option for advanced castration-resistant prostate cancer.

Email Address

cameyer@mednet.ucla.edu

Presentation Type

Poster

Primary author: MEYER, Catherine (Physics & Biology in Medicine Interdepartmental Graduate

Program, David Geffen School of Medicine, UCLA.)

Co-authors: STUPARU, Andreea (Department of Molecular & Medical Pharmacology, David Geffen School of Medicine, UCLA.); RADU, Caius (Department of Molecular & Medical Pharmacology, David Geffen School of Medicine, UCLA.); CAPRI, Joe (Department of Molecular & Medical Pharmacology, David Geffen School of Medicine, UCLA.); CZERNIN, Johannes (Department of Molecular & Medical Pharmacology, David Geffen School of Medicine, UCLA.); WEI, Liu (Department of Molecular & Medical Pharmacology, David Geffen School of Medicine, UCLA.); DAHLBOM, Magnus (Physics & Biology in Medicine Interdepartmental Graduate Program, David Geffen School of Medicine, UCLA.); SLAVIK, Roger (Department of Molecular & Medical Pharmacology, David Geffen School of Medicine, UCLA.); LE, Thuc (Department of Molecular & Medical Pharmacology, David Geffen School of Medicine, UCLA.)

Presenter: MEYER, Catherine (Physics & Biology in Medicine Interdepartmental Graduate Program, David Geffen School of Medicine, UCLA.)

Contribution ID: **80** Type: **not specified**

Astatine-211: The Chemistry Infrastructure

Introduction

There are a consensus around the clinical potential of astatine-211 (211At), but only a limited number of research facilities work with the nuclide. There are three main reason for this which all are related to the chemistry infrastructure:

• Despite the fairly straight way of producing the rare alpha emitting element 211At, the production is scarce. There are a number of existing cyclotrons that have the capacity of producing 211At but only a few do.

• After cyclotron production there are no systems available for converting astatine into a chemical useful form and this is likely the biggest hurdle for widespread 211At research. Currently the research groups that do work with 211At depend on custom systems for recovering 211At from the irradiated targets. Setting up and implementing such custom units require long lead times to provide a proper working system. This means that even though there are cyclotrons capable of producing 211At, there is lack of research infrastructure that prohibits interested parties to scale up or even start 211At research.

• Another hurdle to overcome is the 211At chemistry. Appropriate chemical synthesis methods for stable bonds between 211At and the tumor specific vector has to be established.
Herein we like to present chemical strategies for overcoming these hurdles in research and clinical trials with 211At. It includes automation of isolation and work up of 211At and chemical synthesis of 211At radiopharmaceuticals.

Method

To increase the chemical infrastructure for 211At research and clinical trials an automatic system for work up of 211At and synthesis of 211At labelled compounds has been developed. To simplify the synthesis of 211At-radiopharmaceuticals prefabricated conjugated molecules has been synthesized. This strategy reduce reaction times, increase radiochemical yields and can effortless be adopted for automatic radiochemical synthesis.

Conclusion

By providing a chemistry infrastructure for work up and chemical synthesis 211At and 211At-radiopharmaceuticals, the main obstacles concerning research and clinical trials of this element could be met and research significantly enhanced.

Funding Agency

Swedish Cancer Society

Email Address

info@cancerfonden.se

Presentation Type

Contributed Oral

Primary author: Dr LINDEGREN, Sture (Radiation Physics Gothenburg University Sweden)

Co-authors: Dr PER, Albertsson (Oncology Gothenburg University Sweden); Dr EMMA, Aneheim (Radiation Physics Gothenburg University Sweden); Dr TOM, Bäck (Radiation Physics Gothenburg University Sweden); Dr HOLGER, Jensen (Rigshospitalet Copenhagen Denmark); Dr STIG, Palm (Radiation Physics Gothenburg University Sweden)

Presenter: Dr LINDEGREN, Sture (Radiation Physics Gothenburg University Sweden)

Contribution ID: **81** Type: **not specified**

Intraperitoneal alpha-emitting radio immunotherapy with Astatine-211 in relapsed ovarian cancer; long-term follow-up with individual absorbed dose estimations

Eliminating microscopic residual disease with α-particle radiation is theoretically appealing. Following extensive preclinical work with α-particle emitting astatine-211 (211At), we performed a phase I trial in epithelial ovarian cancer (EOC). This was a first-in-class intraperitoneal (i.p.) α-particle therapy and the first in human study using the conjugate 211At-MX35, a murine monoclonal F(ab')2 antibody. We now present clinical outcome data and toxicity in a long-term follow-up with individual absorbed dose estimations.

Methods: Twelve patients with relapsed EOC, achieving a second complete or near complete response with chemotherapy received i.p. treatment with escalating (20 to 215 MBq/L) activity concentrations of 211At-MX35 F(ab')2.

Results: The activity concentration was escalated to 215 MBq/L without any dose limiting toxicities. Most toxicities were low-grade and likely related to the treatment procedure, not clearly linked to the α-particle irradiation with no observed hematological toxicity. One grade 3 fatigue, and one grade 4 intestinal perforation during catheter implantation was observed. Four patients had a survival >6 years, one of whom did not relapse. At progression chemotherapy was given without signs of reduced tolerability. Overall median survival was 35 months with a 1-, 2-, 5-, and 10-year survival of 100%, 83%, 50% and 25%.

Calculations of the absorbed doses showed that a lower specific activity is associated with a lower single cell dose, whereas a high specific activity may result in a lower central dose in microtumors. Individual differences in absorbed dose to possible micro-tumors were due to variations in administered activity and the specific activity.

Conclusion: No apparent signs of radiation-induced toxicity, or decreased tolerance to relapse therapy were observed. The dosimetric calculations show that further optimization is advisable to increase the efficacy and reduce possible long-term toxicity.

Funding Agency

Swedish Research Council; the Swedish Cancer Society; the King Gustav V Clinic Research Foundation

Email Address

andreas.hallqvist@gu.se

Presentation Type

Contributed Oral

Primary authors: Dr PER, Albertsson (Department of Oncology, Institute of Clinical Sciences,

Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden); Dr HALLQVIST, Andreas (Dept. of Oncology, Sahlgrenska University Hospital, Gothenburg, Sweden)

Co-authors: Dr HÅKAN, Andersson (Department of Oncology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden); Dr KARIN, Bergmark (Department of Oncology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden); Mr TOM, Bäck (Department of Radiation Physics, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden); Dr PERNILLA, Dahm-Kähler (Department of Obstetrics and Gynecology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden); Dr JENSEN, Holger (PET and Cyclotron unit, Copenhagen University Hospital); Prof. RAGNAR, Hultborn (Department of Oncology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden); Prof. LARS, Jacobsson (Department of Radiation Physics, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden); Dr MIA, Johansson (Department of Oncology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden); PALM, Stig (University of Gothenburg); Dr LINDEGREN, Sture (Departemnt of Radiation Physics, Institute of clinical Sciences Sahlgrenska Academy at Gotehnburg University)

Presenter: Dr PER, Albertsson (Department of Oncology, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden)

Contribution ID: **82** Type: **not specified**

Precision Medicine and Innovation Law –Some Considerations

Precision Medicine and Innovation Law –Some Considerations

This presentation provides an overview of common aspects of Innovation Law in relation to Precision Medicine, and also bears down on legal issues specific to the area of targeted therapies.

The first part narrates the interrelation between Innovation Law and Precision Medicine. *Precision Medicine* alludes to the customisation of healthcare by way of tailoring appropriate and ideal remedial decisions, treatments and products, based on the genetic constitution of the individual patient or groups of patients. Past policy supporting targeted therapy innovation has proven beneficial, such as, *e.g.,* legislation enacted to aid the development of orphan drugs. Should additional interventions be considered?

The second section relates characteristics of main types of legal protection relevant to Precision Medicine innovation, including mainly patent, trade secret, and data protection law. In continuation these will be explained along with associated leading legal cases, and allusions as to the interplay between these classes will also be made. Data protection will be dealt with, as this asset has become a main driver underlying and increasingly affecting the other legal protection categories.

Patent
Recent legal developments restricting patent eligible subject matter in the US have been foreseen to detrimentally influence Precision Medicine innovation. In the European context, the evolving requirements of 'plausibility' and data submission before the EPO appear to pose challenges for antibody and targeted therapy inventions.

Trade secret
Main cases mentioned include those of the company Myriad, which has been using patient related data for commercial applications after patents on BRCA1 and BRCA2 were struck down, citing trade secret law. This legal protection category is thus also an option for data protection.

Data protection
This subsection will consider the increasing availability of aggregate genetic data and its increasing influence on innovation, the important role of data exclusivity, along with associated privacy protection mechanisms such as the EU GDPR.

The third section emphasises the research or experimental use exemption. As part of patent law in most jurisdictions, an instrument has been introduced and placed in the scales to balance out the real or perceived rigidness of the patent system, to a certain extent allowing assessment in relation to patented subject matter in non-commercial settings.

The fourth section will make a number of conclusions and suggestions for potential policy interventions.

Email Address

mattias.dinnetz@ec.europa.eu

Presentation Type

Contributed Oral

Primary author: Dr KARLSSON DINNETZ, Mattias (EC-JRC)

Presenter: Dr KARLSSON DINNETZ, Mattias (EC-JRC)

Contribution ID: **83** Type: **not specified**

Targeted alpha therapy with anti-HER2 thorium-227 antibody-chelator conjugates (HER2-TTCs) in mouse xenograft models with varying levels of HER2 expression and resistance to current state-of-the-art therapies

Targeted thorium conjugates (TTCs) represent a new class of therapeutic radiopharmaceuticals for the targeted alpha therapy (TAT) of cancer. The human epidermal growth factor receptor 2 (HER2) is overexpressed in several cancers and is a validated target for the treatment of breast and gastric cancer, also serving as a prognostic and predictive biomarker. During treatment, many patients become resistant or are not eligible for these therapies, due to low expression levels of the target (~55%). Therefore there exists a high unmet medical need for new drugs with alternative mechanisms of action targeting HER2. We describe an antibody conjugate capable of delivering thorium-227 (227Th) to cancer cells expressing the human epidermal growth factor receptor 2 (HER2). The preclinical pharmacological in vivo characterization of the HER2-TTC, with a focus on trastu¬zumab and T-DM1 (trastuzumab-DM1)-resistant and HER2 low expressing mouse xenograft models, are presented.

Email Address

jenny.karlsson@bayer.com

Presentation Type

Poster

Primary author: Dr KARLSSON, Jenny (Bayer AS)

Co-authors: Dr CUTHBERTSON, Alan S (Bayer AS); Dr KRISTIAN, Alexandr (Bayer AS); Dr ELLINGSEN, Christine (Bayer AS); Dr SCHATZ, Christoph (Bayer AG); Dr GRANT, Derek (Bayer AS); Dr MUMBERG, Dominik (Bayer AG); Dr RYAN, Olav (Bayer AS); Dr BJERKE, Roger M (Bayer AS); Dr HAGEMANN, Urs B (Bayer AG); Dr CRUCIANI, Veronique (Bayer AS)

Presenter: Dr KARLSSON, Jenny (Bayer AS)

Contribution ID: **84** Type: **not specified**

225Ac-labeled girentuximab for targeted alpha therapy of CAIX-expressing renal cell cancer xenografts.

Authors: Robin Merkx, Annemarie Kip, Egbert Oosterwijk, Michael Wheatcroft, Alfred Morgenstern, Frank Bruchertseifer, Peter Mulders, Mark Rijpkema, Sandra Heskamp

Background: Despite progress in the treatment of clear cell renal cell carcinoma (ccRCC), the prognosis of patients with metastasized disease remains poor. Therefore, novel treatment options need to be developed. A rapidly advancing field of interest is targeted radionuclide therapy using α-emitting radionuclides, such as actinium-225 (225Ac). Carbonic anhydrase IX (CAIX) is over expressed in ccRCC and can be targeted effectively using the monoclonal antibody girentuximab. The aim of this preclinical study was to investigate the in vivo tumor targeting properties of 255Ac-labeled girentuximab, and assess the therapeutic efficacy and toxicity in mice.

Methods: Girentuximab was conjugated with DOTA and labeled with 225Ac and its binding to CAIX-expressing SK-RC-52 cells was determined in vitro. Immunodeficient mice bearing subcutaneous SK-RC-52 xenografts were injected intravenously with 30 ug [225Ac]Ac-DOTA-girentuximab (50 kBq). The biodistribution of [225Ac]Ac-DOTA-girentuximab was determined at 24, 72 and 168 hours post injection (p.i.). Subsequently, therapeutic efficacy was evaluated for different doses (3.7, 9.3 and 18.5 kBq) by measuring tumor growth using caliper measurements up to 4 weeks p.i. Toxicity was monitored by measuring body weight. Furthermore, non-tumor bearing mice were used to analyze nephrotoxicity by immunohistochemistry and [99mTc]Tc-DMSA renal imaging, and blood samples were collected to assess hematotoxicity.

Results: Labeling efficiency exceeded 96% and [225Ac]Ac-DOTA-girentuximab demonstrated specific binding to CAIX-expressing SK-RC-52 cells in vitro. In vivo, maximum tumor uptake was reached at 168 hours; 124.2 ± 28.8 %ID/g, while the corresponding blood level was 4.0 ± 2.2 %ID/g. The tumor to blood ratio was 35.5 ± 9.3 at 168 hours p.i. compared to 11.2 ± 3.1 at 72 hours p.i. Mean tumor volume doubling times were 22 ± 11, 33 ± 24 and 31 ± 20 days for 3.7, 9.3 and 18.5 kBq for treated groups respectively, compared to 17 ± 5 days for the control group. Tumor-bearing mice showed no weight loss after treatment. Assessment of nephro- and hematotoxicity is still ongoing.

Conclusion: Girentuximab can be efficiently labeled with actinium-225 and shows excellent tumor targeting. First data indicate that [225Ac]Ac-girentuximab may lead to tumor growth delay without short-term toxicity. However, future experiments in larger groups of animals should be performed to confirm these results and to monitor long term nephro- and hematotoxicity.

Funding Agency

Telix Pharmaceuticals

Email Address

Robin.Merkx@radboudumc.nl

Presentation Type

Contributed Oral

Primary author: Mr MERKX, Robin (Radboudumc, Nijmegen, The Netherlands)

Co-authors: Dr MORGENSTERN, Alfred (Joint Research Centre, Institute for Transuranium Elements); Mrs KIP, Annemarie (Radboudumc, Nijmegen, The Netherlands); Dr OOSTERWIJK, Egbert (Radboudumc, Nijmegen, The Netherlands); Dr BRUCHERTSEIFER, Frank (Joint Research Centre, Institue for Transuranium Elements); Dr RIJPKEMA, Mark (Radboudumc, Nijmegen, The Netherlands); Mr WHEATCROFT, Michael (Telix Pharmaceuticals); Prof. MULDERS, Peter (Radboudumc, Nijmegen, The Netherlands); Dr HESKAMP, Sandra (Radboudumc, Nijmegen, The Netherlands)

Presenter: Mr MERKX, Robin (Radboudumc, Nijmegen, The Netherlands)

Contribution ID: **85** Type: **not specified**

Synergistic Effect of a HER2 Targeted Thorium-227 Conjugate in Combination with olaparib in a BRCA2 Deficient Xenograft Model

Targeted thorium conjugates (TTCs) represent a new class of therapeutic radiopharmaceuticals with the capability of targeting multiple cancer types. The TTCs are comprised of the alpha particle emitter thorium-227 complexed to a 3,2-hydroxypyridinone chelator conjugated to a tumor-targeting monoclonal antibody. When coupled to a suitable targeting moiety the radiation dose can be preferentially delivered to the surface of the tumor cell minimizing unwanted effects on the normal surrounding tissue. This study reports the pre-clinical evaluation of combination therapy comprising a HER2-TTC and the PARP inhibitor olaparib in the human cancer model DLD-1 and the knockout version DLD-1 BRCA2 -/-. As the mode of action of the TTC is based on the induction DNA damage we hypothesized that BRCA2 deficiency would sensitize to TTC treatment, and that the combination with PARP inhibitors would be synergistic.
Methods: The combination treatment was first evaluated in in vitro cytotoxicity assays, followed by analysis of the combination index according to the median-effect model of Chou-Telalay. Next, the HER2 expression and biodistribution of HER2-TTC was determined in DLD-1 xenograft bearing nude mice after a single intravenous dose administration (600 kBq/kg, 0.14 mg/kg, i.v.). In the same models we evaluated the in vivo anti-tumor efficacy of HER2-TTC ± olaparib and the combination effect was analyzed according to the Bliss additivity model. Results: In vitro, HER2-TTC and olaparib induced significantly increased cytotoxicity in the BRCA2 -/- cell line as compared to the parental and the combination treatment was determined to be
synergistic in DLD-1 BRCA2 -/- and additive in DLD-1 parental.
The xenograft models DLD-1 parental and DLD-1 BRCA2 -/- were both determined to be HER2 low expressing and the biodistribution demonstrated significant and specific uptake of HER2-TTC (40-60 % ID/g) as compared to the isotype control (5 % ID/g). The monotherapy treatment with HER2-TTC induced significant and dose dependent tumor inhibition in both xenograft models. Furthermore, based on treatment-over-control ratio the DLD-1 BRCA2 -/- model was more sensitive to the highest dose of HER2-TTC (600 kBq/kg) compared to the DLD-1 parental. The in vivo combination efficacy was determined to be synergistic only in the DLD-1 BRCA2 -/- xenograft model, demonstrating significant tumor growth inhibition from a TTC dose of 120 kBq/kg and 50 mg/kg olaparib (daily, i.p. for 4 weeks), with comparable tumor growth inhibition to a single dose of 600 kBq/kg HER2-TTC. Conclusion: This study supports the further investigation of DNA damage response inhibitors in combination with TTCs as a new strategy for the effective treatment of mutation-associated cancers. Acknowledgments: We would like to thank the Research Council of Norway for funding this study. We would like to thank Pharmatest Services for conducting the animal studies.

Email Address

roger.bjerke@bayer.com

Presentation Type

Poster

Primary author: Dr WICKSTROEM, Katrine (Bayer AS)

Co-authors: Dr CUTHBERTSON, Alan (Bayer AS); Dr KRISTIAN, Alexander (Bayer AS); Dr MUMBERG, Dominik (Bayer AG); Dr KARLSSON, Jenny (Bayer AS); Dr LINDEN, Lars (Bayer AG); Dr BRANDS, Michael (Bayer AG); Dr RYAN, Olav (Bayer AS); Dr BJERKE, Roger (Bayer AS); Dr HAGEMANN, Urs B (Bayer AG); Dr CRUCIANI, Veronique (Bayer AS)

Presenter: Dr BJERKE, Roger (Bayer AS)

Contribution ID: **86** Type: **not specified**

In-vivo comparison of thorium-227 and zirconium-89 labeled 3,2-HOPO mesothelin antibody-chelator conjugate

Targeted thorium conjugates (TTCs) represent a new class of therapeutic radiopharmaceuticals for the targeted alpha therapy (TAT) of cancer. Cell surface glycoprotein mesothelin is highly expressed in many human cancers. Mesothelin targeted thorium-227 conjugate (MSLN-TTC, BAY 2287411), comprising a mesothelin targeted antibody (MSLN-Ab), covalently attached to 3,2-HOPO chelator, enabling specific complexation and delivery of the alpha particle emitter thorium-227 (227Th) to tumor cells, is currently in a phase 1 clinical trial (NCT03507452). 3,2-HOPO systems are also very efficient chelators for zirconium-89 and it has therefore been suggested that positron emission tomography (PET) imaging provides a useful surrogate for understanding 227Th radioimmunotherapy. Hence, we describe the radiolabeling of the conjugated MSLN-Ab conjugate with the PET isotope zirconium-89 (89Zr) and show data from a biodistribution study comparing both thorium and zirconium conjugates.

Email Address

olav.ryan@bayer.com

Presentation Type

Poster

Primary author: Dr RYAN, Olav Benjamin (Bayer AS)

Co-authors: Dr CUTHBERTSON, Alan (Bayer AS); Dr KRISTIAN, Alexander (Bayer AS); Dr INDREVOLL, Baard (Bayer AS); Dr KARLSSON, Jenny (Bayer AS); Dr BJERKE, Roger M (Bayer AS); Dr HAGEMANN, Urs B (Bayer AG)

Presenter: Dr RYAN, Olav Benjamin (Bayer AS)

Contribution ID: **87** Type: **not specified**

Automated Bone Scan Index (aBSI) as an Imaging Biomarker in Castration Sensitive Metastatic Prostate Cancer in a novel clinical trial with Radium-223 and External Beam Radiotherapy

BACKGROUND
The majority (~90%) of patients with metastatic prostate cancer will have multiple bony metastases. Despite being the most common area of metastases in prostate cancer, reliably evaluating the burden of bony metastases at baseline and monitoring response to different therapeutic interventions is challenging and not standardised.

Isotope Bone Scan (IBS) is the most widely utilised imaging modality in staging and initial management decisions in prostate cancer. Presently, the standard interpretation of IBS relies on subjective assessment of the number and geographical distribution of metastases.

Automated Bone Scan Index (aBSI) is a quantitative analysis of IBS reflecting the extension of tumour burden in bone as present of the total skeleton weight calculated from IBS. This method allows a standardised approach to comparing distribution of bony metastatic disease.

Figure 1. Schematic of aBSI methodology

OBJECTIVE
The objective of this study was to evaluate aBSI as an Imaging Biomarker in Metastatic Castration Sensitive Prostate Cancer (mCSPC) in a novel clinical trial with Radium-223 (Ra-223) and External Beam Radiotherapy (EBRT).

METHODS
We present preliminary data from a Phase II trial exploring the use of six cycles of Ra-223 in combination with prostate and pelvic EBRT post-docetaxel in mCSPC (>3 bone metastases, no lymph node or visceral disease T4N0/1M1b). Fifteen of twenty-eight patients enrolled in the trial had baseline and treatment follow-up IBS available for aBSI analysis. The EXINI aBSI software programmed was used to retrospectively analyse the IBS and generate the aBSI value. Alkaline phosphatase (ALP) and Prostate Specific Antigen (PSA) values were collected.

RESULTS
All patients had a reduction or stability in the aBSI reading except one patient had progression disease. There was a median reduction of 71.5% (-350-88.9%) in the aBSI with a number of patients having almost complete resolution of quantifiable disease on IBS as evidenced in Figure 2. All patients had a reduction in ALP from Cycle 1 to Cycle 6 with treatment, median reduction from Cycle 1 90 (65-236U/L) to Cycle 6 59 (37-165U/L). Over a median follow up period of 25.9 months the median overall survival and progression free survival have not yet been reached. Two-thirds of the patients in this study have prolonged reductions in aBSI in excess of 2 years post-commencement of LHRHa.

Figure 2. An illustrative example of aBSI change over the course of treatment on IBS (baseline and follow-up scans) MRI scans also shown depicting response.

CONCLUSION
We present the first documented use of aBSI in mCSPC treated with Ra-223. This tool may improve analysis of response to bone metastases in the metastatic setting. It may reduce risk of reporter bias and can be used to systematically follow up patients with multiple therapeutic interventions in this patient cohort. Sequential whole-body MRI's are available for comparison and will be evaluated on completion of this novel clinical trial. The use of aBSI in conjunction with ALP and PSA may help prognosticate response in mCSPC.

Funding Agency

royal embassy of saudi arabia cultural bureau

Email Address

a.alila.a@hotmail.com

Presentation Type

Poster

Primary author: Mr ALSHEHRI, Ali (Queen's University Belfast)

Co-authors: Mr SANDRA, Biggart (Northern Ireland Cancer Centre- Belfast Health and Social Care Trust, Nuclear Medicine Department, Belfast, United Kingdom.); Mr CAOIMHGHIN, Campfield (Northern Ireland Cancer Centre- Belfast Health and Social Care Trust, Nuclear Medicine Department, Belfast, United Kingdom.); Mr CHRISTOS, Chatzigiannis (Northern Ireland Cancer Centre- Belfast Health and Social Care Trust, Nuclear Medicine Department, Belfast, United Kingdom.); Dr AIDAN, Cole (Northern Ireland Cancer Centre- Belfast Health and Social Care Trust, Oncology, Belfast, United Kingdom.); Dr SUNEIL, Jain (Northern Ireland Cancer Centre- Belfast Health and Social Care Trust, Oncology, Belfast, United Kingdom.); Prof. JOE, O'Sullivan (Northern Ireland Cancer Centre- Belfast Health and Social Care Trust, Oncology, Belfast, United Kingdom.); Prof. KEVIN, Prise (Centre for Cancer Research and Cell Biology- Queen's University Belfast, Cancer Research and Cell Biology, Belfast, United Kingdom.); Dr PHILIP, Turner (Northern Ireland Cancer Centre- Belfast Health and Social Care Trust, Oncology, Belfast, United Kingdom.)

Presenter: Mr ALSHEHRI, Ali (Queen's University Belfast)

Contribution ID: **88** Type: **not specified**

Alpha DaRT: Revolutionary Alpha-Emitters Brachytherapy

Diffusing Alpha-emitters Radiation Therapy ('Alpha DaRT') is a revolutionary new cancer-treatment modality, which enables –for the first time - the treatment of solid tumors by alpha particles. The basic idea is to insert into the tumor an array of implantable seeds, whose surface is embedded with a low activity of radium 224. Each seed continuously emits into the tumor, by recoil, a chain of short-lived alpha emitting atoms (progeny of radium) which spread by diffusion and convection over several mm around it, creating a continuous "kill region"of high alpha-particle dose. After many years of basic work on the technology and associated physics, as well as an extensive campaign of preclinical studies in mice, Alpha DaRT has recently entered clinical trials, in the framework of a new company, Alpha TAU Medical Ltd.

The first trial, in Rabin Medical Center (Israel), focuses on recurrent skin and oral cavity squamous cell carcinoma, and tumor size < 5 centimeters in the longest diameter. So far, 15 of the enrolled patients have completed follow-up. Tumor locations included the chin, ear, tongue, lip, nose, forehead, scalp and parotid skin areas. Treatment was delivered based on a CT-simulation pre-treatment plan. DaRT seeds were inserted under local anesthesia using a specially designed applicator. The seeds (1 cm long and 0.7 mm in diameter) each carrying an activity of 2 μCi 224Ra were placed 5-6 millimeters from each other, based on a DaRT-specific dosimetry model. The total 224Ra activity administered was ~5 μCi per gram of tumor. Two to four weeks after implantation the seeds were removed, and six weeks after treatment CT was performed to assess the effect of treatment. Blood tests and urinalysis were performed during the treatment. The number of DaRT seeds inserted into the tumor was in the range of 7-169 seeds, and treatment duration was 14 to 26 days.

Initial efficacy results for a single application of DaRT seeds, for 15 subjects who have reached the study endpoint, are highly promising: eleven subjects (11/15, 73%) had a Complete Response to the treatment and four (4/15, 27%) had Partial Response (substantial reduction in tumor volume). The treatment was shown to be safe for both the patient and medical staff. Local side effects of the treatment were minimal, amounting to erythema, swelling and mild to moderate pain in the insertion area, which resolved either by the time the seeds were removed or shortly after. Radioactivity measurements of 212Pb in the blood were consistent with a biokinetic model of DaRT, which predicts negligible dose levels to distant organs. No clinically significant abnormal blood or urine lab results, or clinically significant changes in vital signs were observed.

Based on the successful outcomes of the first clinical trial, clinical protocols are in preparation for various indications with leading research centers worldwide, including cutaneous and mucosal neoplasia, neoadjuvant and recurrent rectal cancer, recurrent prostate cancer, inoperable breast cancer, recurrent gynecological cancer, sarcoma and pancreatic cancer.

Email Address

larazi@bgu.ac.il

Presentation Type

Contributed Oral

Primary author: Dr ARAZI, Lior (Nuclear Engineering Unit, Faculty of Engineering Sciences, Ben-Gurion University, Beer-Sheva Israel)

Co-authors: Prof. POPOVTZER, Aron (Rabin Medical Center, Petah Tikva, Israel); Prof. MIZRACHI, Aviram (Rabin Medical Center, Petah Tikva, Israel); Dr ROSENFELD, Eli (Rabin Medical Center, Petah Tikva, Israel); Prof. KELSON, Itzhak (School of Physics and Astronomy, Raymond and Beverly Sackler Faculty of Exact Sciences, Tel Aviv University, Tel Aviv, Israel); Dr SCHMIDT, Michael (Alpha TAU Medical Ltd., Tel Aviv, Israel); Mr BEN-HUR, Ran (Rabin Medical Center, Petah Tikva, Israel); Dr COOKS, Tomer (Department of Immunology and Microbiology, Faculty of Health Sciences, Ben-Gurion University, Beer-Sheva Israel); Prof. KEISARI, Yona (Department of Human Microbiology & Immunology, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel)

Presenter: Dr ARAZI, Lior (Nuclear Engineering Unit, Faculty of Engineering Sciences, Ben-Gurion University, Beer-Sheva Israel)

Contribution ID: **89** Type: **not specified**

The response of human papillomavirus associated head and neck squamous cell carcinoma cell lines on standard therapy and treatment with an experimental alpha-particle emitter immunoconjugate targeting EGFR (Bi-213-Cetuximab)

Introduction

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer worldwide. Despite considerable improvements in surgery, radio- and chemotherapy over the last decades, the five-year overall survival has not changed significantly. Radio resistance is a frequent issue that impedes success in therapy. Tumor hypoxia often is causing this resistance, hence targeted therapy with oxygenation-independent alpha-emitters could be a effective strategy for therapy of HNSCC. Another emerging factor for treatment response is infection with human papillomavirus (HPV). HPV associated HNSCC is known to have a better prognosis and therefore is described as distinct entity within HNSCC. Still there are contrary experimental studies on response to therapy and the underlying molecular mechanisms.

Objectives

Characterizing the relevance of HPV status of HNSCC cell lines for response to standard and experimental therapy with alpha-particle emitter immunoconjugate targeting EGFR (^{213}Bi-Cetuximab).

Materials & Methods

We analyzed proliferation, colony forming capability, cell cycle and DNA double strand brakes (yH2AX) in six HNSCC cell lines (3 HPV pos./3 HPV neg.) after treatment with chemotherapeutics, alpha-particle emitter ^{213}Bi-Cetuximab (9.25-111 kBq/mL) and irradiation by X-Rays (0.5-14 Gy). We also performed Western blot analysis and determined the impact of knockdown of DNA repair factors (RAD51, LIG4 or XRCC1) on proliferation.

Results

HPV-positivity was significantly associated with a more pronounced antiproliferative response to treatment with various chemotherapeutics, ^{213}Bi-Cetuximab as well as X-Ray irradiation with single or fractionated doses. Colony forming capability of the cells after treatment was also significantly correlated with HPV status. After treatment with ^{213}Bi-Cetuximab cells accumulated in the G2-Phase. After X-Ray therapy this effect could be seen in the HPV-positive cell lines only. Treatment with ^{213}Bi-Cetuximab (37 kBq/mL) resulted in a delayed, stronger and more persistent peak level of the DNA double strand break marker yH2AX compared to X-Ray therapy (2 Gy). HPV-positive cell lines showed slightly stronger yH2AX intensity changes with both treatments. Cleavage of PARP and phosphorylation of Erk1/2 after irradiation correlated with HPV-positivity. Rad51 protein level was HPV-independently upregulated, most notably with ^{213}Bi-Cetuximab treatment. Knockdown of RAD51 had an antiproliferative effect on the cells - especially in HPV-positive cells –whereas knockdown of LIG4 or XRCC1 did not affect proliferation. Irradiation-induced antiproliferative effects could be enhanced by knockdown of these DNA-repair factors, noticing the strongest effect with knockdown of RAD51.

Conclusion

HPV associated HNSCC showed a better response to all forms of therapy tested. Our results are suggesting a more pronounced G2-arrest to be responsible for this observation. Compared to X-Rays, the experimental therapy with the alpha-particle emitter ^{213}Bi-Cetuximab is a remarkably more effective approach to attenuate the proliferation potential of HNSCC. Since this superior response is also true for more radioresistant HPV-negative cell lines, targeted ^{213}Bi-Cetuximab treatment of HNSCC is a promising option and should be further developed.

Email Address

michael.siegl@tum.de

Presentation Type

Contributed Oral

Primary author: Mr SIEGL, Michael (Department of Otolaryngology Head and Neck Surgery, Technical University of Munich, Munich, Germany)

Co-authors: Dr MORGENSTERN, Alfred (European Commission, JRC, Directorate for Nuclear Safety and Security, Karlsruhe, Germany); Dr PICKHARD, Anja (Department of Otolaryngology Head and Neck Surgery, Technical University of Munich, Munich, Germany); Dr SEIDL, Christof (Department of Nuclear Medicine, Technical University of Munich, Munich, Germany); Dr BRUCHERTSEIFER, Frank (European Commission, JRC, Directorate for Nuclear Safety and Security, Karlsruhe, Germany); Prof. MULTHOFF, Gabriele (Center for Translational Cancer Research (TranslaTUM), Technical University of Munich, Munich, Germany); Mr PIONTEK, Guido (Department of Otolaryngology Head and Neck Surgery, Technical University of Munich, Munich, Germany); Prof. WEBER, Wolfgang (Department of Nuclear Medicine, Technical University of Munich, Munich, Germany)

Presenter: Mr SIEGL, Michael (Department of Otolaryngology Head and Neck Surgery, Technical University of Munich, Munich, Germany)

Track Classification: Preclinical

Contribution ID: **90** Type: **not specified**

LANTHANIDE-BASED NANOPARTICLES FOR MULTIMODAL MOLECULAR IMAGING AND TARGETED ALPHA THERAPY

Purpose: To assess the in vitro retention of therapeutically relevant radionuclides such as in vivo α-generators Ra-223, Ac-225, and Th-227 in lanthanide phosphate (LnPO4) and lanthanide vanadate (LnVO4) core-shell nanoparticles (NPs) towards their promising application as multifunctional platforms in nanomedicine.
Method and Materials: LnPO4 and LnVO4 core-shell NPs doped with either Eu-156, a radionuclide "cocktail"of Sr-85, Sr-89, Eu-156, or in vivo α-generators Ra-223, Ac-225, and Th-227 were synthesized in aqueous media. In vitro retention of radionuclides was assessed by dialyzing the radioactive NPs suspensions against deionized water and quantifying the activity in dialysate aliquots over time using a high purity germanium detector. The crystal structure, morphology, colloidal stability, luminescence and magnetic properties of LnPO4 and LnVO4 core-shell NPs were evaluated.
Results: Partial retention of Eu-156 (~70–95%) and Sr-85 (>80%) was evidenced in LnPO4 core NPs, while Th-227 and decay daughters were retained quantitatively (>99%) in LaPO4 core-shell NPs. Gd0.8Eu0.2VO¬4 and GdVO4 core-shell NPs showed partial retention of Ra-223 (~75 %), Ac-225 (75–95%), and Th-227 (>96%). Retention of decay daughters in LnVO4 NPs was enhanced after deposition of nonradioactive shells. Adjusting the lanthanide concentration provided luminescence and magnetic properties for fluorescence and magnetic resonance imaging. Emission intensities were higher for LnVO4 NPs with respect to LnPO4, whereas no significant difference was observed in the magnetic susceptibility. GdVO4 core NPs displayed enhancement of the signal intensity of T1-weighted images.
Conclusion: This work evidences the potential application of LnPO4 and LnVO4 core-shell NPs as platforms for multimodality molecular imaging and targeted alpha therapy. Partial retention of radionuclides may enhance the efficacy of treatment while minimizing the dose delivered to healthy organs. Radionuclide retention was influenced by the lanthanide concentration, the crystal structure, and the number of shells added.

Acknowledgments
This work was financed by the Virginia Commonwealth University (VCU) with the support of the Mechanical and Nuclear Engineering Department and NRC-HQ-84-14-FOA-002, Faculty Development Program in Radiation Detection and Health Physics at VCU. Work at ORNL was supported in part by (i) the U.S. Department of Energy Isotope Program within the Office of Nuclear Physics and (ii) an appointment to the Oak Ridge National Laboratory Nuclear Engineering Science Laboratory Synthesis Program, sponsored by the US Department of Energy and administered by the Oak Ridge Institute for Science and Education. We would like to thank the staff of Nuclear and Radiochemistry Group at ORNL for their help with radiochemistry and radioactivity measurements. The authors also wish to thank Dr. Joseph Turner from the Instrumentation Laboratory in the Department of Chemistry at VCU and the staff at the Nanomaterials Core Characterization Facility in the VCU College of Engineering.

Email Address

torogonzalezm@vcu.edu

Presentation Type

Contributed Oral

Primary author: Mr TORO-GONZALEZ, Miguel (Virginia Commonwealth University)

Co-authors: Dr ROJAS, Jessika V. (Assistant Professor, Virginia Commonwealth University); Dr MIRZADEH, Saed (Nuclear Security and Isotope Technology Division, Oak Ridge National Laboratory)

Presenter: Mr TORO-GONZALEZ, Miguel (Virginia Commonwealth University)

Track Classification: Targeting

Contribution ID: **91** Type: **not specified**

New Bifunctional Chelators for 225Ac and 227Th Radioimmunotherapy

The short particle range of alpha particles offers advantages for localized cancer treatment, sparing neighboring healthy tissue. Particularly interesting alpha-emitting radioisotopes include long-lived 225Ac (t1/2=9.92d) and 227Th (t1/2=18.7d), while the former also generates four net alpha particles through the short-lived progeny, rendering it highly potent. The key is to securely deliver the radioactive isotope to the cancerous tissue through stable complexation with a bifunctional chelator. For radioimmunotherapy, an acyclic chelator that allows quantitative radiolabeling in high stability at room temperature is strongly preferred. Therefore, the foci in this work is to compare the chelation chemistry of 225Ac and 227Th with three recently developed chelators from our group–H4octapa(N4O4), H4pypa(N5O4) and H4py4pa(N7O4), which cover potential coordination numbers from 8 to 11 with combinations of hard donor atoms, N and O, that possess strong affinity for actinides. While at least one bifunctional analog has been developed for each chelator, herein conjugates of monoclonal antibody, trastuzumab along with the non-bifunctional chelators are the foci. Synthesis and characterization of the ligands will be discussed, together with the radiolabeling and serum stability studies.
All synthesized chelators were characterized by NMR spectrometry, high-resolution mass spectrometry and elemental analysis. For the studies with 225Ac, despite the difference in chemical properties and covalency, non-radioactive Lanthanum(La) was chosen as an adequate analog due to the absence of stable actinides, and the complexation with H4pypa and H4py4pa was investigated by NMR spectrometry, showing a vast difference in complex geometry, where [La(pypa)]- appeared as an asymmetric complex while [La(py4pa)]- was highly symmetric. pM values of [La(octapa)]- and [La(pypa)]- were determined to be 19.7 and 19.9, respectively, by potentiometric titration and UV-vis spectrophotometry, while that of [La(py4pa)]- is in progress. Radiolabeling of [225Ac][Ac(L)]- (L=octapa, pypa, py4pa) was performed at room temperature in 30 minutes and the radiochemical yield percentages(RCY %) were analyzed by iTLC-salicylic acid impregnated, showing H4py4pa and H4octapa being the most promising (98%, 10-6M) while H4pypa required 10-fold higher concentration for 93% RCY, which was still significantly better than DOTA. The stabilities in human serum are being determined, in parallel with the experiments for the trastuzumab-conjugates. Besides 225Ac, H4py4pa also exhibited encouraging RCY in 2 hours at room temperature with 227Th and the complex was stable over at least 2 days. More studies with the bifunctional analog are in progress.
To summarize, three reported chelators have demonstrated promising radiolabeling results with 225Ac, while H4py4pa also has potential for 227Th. More studies are in progress.

Acknowledgements:

We thank NSERC CREATE IsoSiM (TRIUMF) for funding a PhD research stipend (LL), and both NSERC and CIHR for financial support via a Collaborative Health Research Project (CHRP to FB, CO and PS). TRIUMF receives additional funding via a contribution agreement with the National Research Council of Canada. The Th-227 labeling studies were supported by the US Department of Energy (DE-SC0015220).

Funding Agency

NSERC CREATE IsoSiM, NSERC, CIHR, National Research Council of Canada, US Department of Energy

Email Address

lilyli@chem.ubc.ca

Presentation Type

Contributed Oral

Primary author: Ms LI, LILY (Medicinal Inorganic Chemistry Group, Department of Chemistry, University of British Columbia, Vancouver BC, V6T 1Z1, Canada; Life Sciences Division, TRIUMF, 4004 Wesbrook Mall, Vancouver BC, V6T 2A3, Canada)

Co-authors: Mr ROBERTSON, Andrew (Life Sciences Division, TRIUMF, 4004 Wesbrook Mall, Vancouver BC, V6T 2A3, Canada); Prof. ORVIG, Chris (Medicinal Inorganic Chemistry Group, Department of Chemistry, University of British Columbia, Vancouver BC, V6T 1Z1, Canada); Dr WILBUR, D. Scott (Department of Radiation Oncology, University of Washington, Seattle WA, 98105, USA); Mr HAMLIN, Donald (Department of Radiation Oncology, University of Washington, Seattle WA, 98105, USA); Dr BÉNARD, François (Department of Molecular Oncology, BC Cancer Agency, Vancouver BC, V5Z 1L3, Canada); Ms ROUSSEAU, Julie (Department of Molecular Oncology, BC Cancer Agency, Vancouver BC, V5Z 1L3, Canada); Dr PELAEZ, Maria Guadalupe Jaraquemada (Medicinal Inorganic Chemistry Group, Department of Chemistry, University of British Columbia, Vancouver BC, V6T 1Z1, Canada); Ms SARDEN, Nicole (Medicinal Inorganic Chemistry Group, Department of Chemistry, University of British Columbia, Vancouver BC, V6T 1Z1, Canada); Dr SCHAFFER, Paul (Life Sciences Division, TRIUMF, 4004 Wesbrook Mall, Vancouver BC, V6T 2A3, Canada); Dr RADCHENKO, Valery (Medicinal Inorganic Chemistry Group, Department of Chemistry, University of British Columbia, Vancouver BC, V6T 1Z1, Canada; Life Sciences Division, TRIUMF, 4004 Wesbrook Mall, Vancouver BC, V6T 2A3, Canada); Dr LI, Yawen (Department of Radiation Oncology, University of Washington, Seattle WA, 98105, USA)

Presenter: Ms LI, LILY (Medicinal Inorganic Chemistry Group, Department of Chemistry, University of British Columbia, Vancouver BC, V6T 1Z1, Canada; Life Sciences Division, TRIUMF, 4004 Wesbrook Mall, Vancouver BC, V6T 2A3, Canada)

Track Classification: Radiochemistry

Contribution ID: **92** Type: **not specified**

Biparatopic targeting of epidermal growth factor receptor positive breast cancer cells using domain I/II and domain III specific antibody conjugates

Biparatopic targeting of epidermal growth factor receptor positive breast cancer cells using domain I/II and domain III specific antibody conjugates
Ayaz Ahmed KB1, Causey P2, Solomon VR1, Bernhard W3, Barreto K3, Wilson JJ4, Geyer CR3,Fonge H1,5.
1Department of Medical Imaging, University of Saskatchewan
2Canadian Nuclear Lab. Chalk River, ON
3Department of Pathology and Laboratory Medicine, University of Saskatchewan
4Department of Chemistry & Chemical Biology, Cornell University
5Department of Medical Imaging, Royal University Hospital Saskatoon

Background: Epidermal growth factor receptor (EGFR) is overexpressed in > 50% of breast cancer. EGFR consists of an extracellular or ligand binding domain which consists of four binding epitopes (domains I, II, III, IV). Anti-EGFR therapeutic antibodies such as nimotuzumab and cetuximab bind to domain III of EGFR. For the first time we have developed an antibody that binds to epitope I & II of EGFR called FabH. Our hypothesis is that simultaneous targeting of domains I/II and III using immunoconjugates that are specific to these epitopes can lead to enhanced therapeutic outcome in EGFR positive cancers. To accomplish this we aimed to deliver potent alpha particle to domain I/II using 225Ac-FABH (radioimmunotherapy) and potent cytotoxic agent (PEGylated maytansine using nimotuzumab-PEG6-DM1 antibody drug conjugate (an ADC) to domain III.
Methods: FABH was conjugated to an eight-membered macrocyclic chelator SCN-macropa, and then radiolabeled with 225Ac. The radiochemical yield of 225Ac-FABH was >90%. We investigated the cytotoxicity of this biparatopic approach in EGFR-positive breast cancer cells. 225Ac-FABH and nimotuzumab-PEG6-DM1 were developed and characterized by flow cytometry, bioanalyzer, HPLC and internalization rate (live-cell imaging). In vitro cytotoxicity was studied in MDA-MB-468, MDA-MB-231 and TrR1 EGFR-positive triple negative breast cancer cells. In vitro cytotoxicity using the biparatopic approach (225Ac-FABH + nimotuzumab-PEG6-DM1) was compared with 225Ac-FABH, + nimotuzumab-PEG6-DM1 or control non-specific immunoconjugates.
Results: Bioanalyzer showed the purity and size of FabH, nimotuzumab, nimotuzumab-PEG6-DM1, and their respective macropa conjugated immunoconjugates. Flow cytometry showed nearly > 90% binding to the cells. In all three cell lines, in vitro studies showed enhanced cytotoxicity of 225Ac-FABH + nimotuzumab-PEG6-DM1 compared with the single agents FABH, nimotuzumab, nimotuzumab-PEG6-DM1, 225Ac-FABH or non-specific (radio)immunoconjugates which was evident from low IC50 values ranging from 12nM«<47nM«65nM«105nM«125nM respectively.
Conclusions: The delivery of multiple cytotoxic agents to EGFR using this biparatopic approach is very promising in vitro. In vivo studies using mouse xenografts are planned.

Email Address

bak388@usask.ca

Presentation Type

Poster

Primary author: Dr KHAN, BEHLOL (UNIVERSITY OFSASKATCHEWAN)

Presenter: Dr KHAN, BEHLOL (UNIVERSITY OFSASKATCHEWAN)

Contribution ID: **93** Type: **not specified**

Pharmacokinetic variability of in vivo generated 213Bi and vector labeled 225Ac in murine cancer models

Since the approval of Xofigo® against metastatic castrated resistant prostate cancer there has been a growing interest in α-particle emitting radiopharmaceutical therapy. Actinium-225 (T1/2=10days) is one α-particle emitter of interest with a total emission of four α-particles in its decay chain (221Fr: T1/2=4.9min; 217At: T1/2=32.3ms; 213Bi: T1/2=45.6min; 213Po: T1/2=4.2μs). Using a chelator makes it possible to label 225Ac with different vectors, which can be used against different cancers. The bond between the chelator and the 225Ac atom is relatively weak (~10eV) and is broken when the α-particle is emitted from the 225Ac atom due to the high recoil energy (~100keV). Consequently the 225Ac decay daughters are not bound to the vector and are free to relocate. Depending on the vector's pharmacokinetics there will be different normal tissue uptake of vector labeled 225Ac. This suggests that depending on vector type the unbound decay daughters are present in different tissues at different concentrations, able to redistribute within the *in vivo* system.

In this study we investigated vector labeled 225Ac and unbound 213Bi, which has the longest half-life of the 225Ac decay daughters and is known to relocate and accumulate in the kidneys. We compared the pharmacokinetics of *in vivo* generated 213Bi and vector labeled 225Ac for three different vectors in murine cancer models (7.16.4 antibodies against breast cancer; anti-VLA-4 antibodies against melanoma; PSMA-targeted small molecule against castrate resistant prostate cancer). The mice were injected i.v. by the tail vein with the 225Ac labeled vectors and sacrificed at specific times after administration. The organs and tissues of interest were blood, liver, kidneys and spleen, which were harvested and directly measured in a gamma well counter in 1 minute intervals for up to 5 hours. The measured data was fitted with a bi-exponential function to determine the amount of unbound 213Bi and vector labeled 225Ac present in the different tissues.

All murine models showed accumulation of unbound 213Bi in the kidneys, accounting for ~60% of the mean absorbed dose to the kidneys. The main supplier of the unbound 213Bi to the kidneys for the small molecule and the anti-VLA-4 was the liver, and for the 7.16.4 the blood. In addition, vector labeled 225Ac has shown to be uniformly distributed for 7.16.4, and non-uniform for anti-VLA-4, PSMA-targeting small molecule and unbound 213Bi within the kidneys, suggesting the need for small scale dosimetry for an accurate absorbed dose calculation.

This study shows that the delivery of 225Ac using different vectors changes the pharmacokinetics and supply of unbound 213Bi to the kidneys. This is important for translation to clinical studies as in vivo imaging of 225Ac does not distinguish between the vector labeled 225Ac and unbound 213Bi, resulting in an possible overestimation of the absorbed dose to the kidneys and underestimation of the supplying tissues.

Email Address

ajosefs1@jhmi.edu

Presentation Type

Contributed Oral

Primary author: Dr JOSEFSSON, Anders (Johns Hopkins University, School of Medicine)

Co-authors: Dr MORGENSTERN, Alfred (European Commission DG Joint Research Centre - JRC); Dr BRUCHERTSEIFER, Frank (European Commission DG Joint Research Centre - JRC); Dr SGOUROS, George (Johns Hopkins University, School of Medicine); Dr NEDROW, Jessie (Johns Hopkins University, School of Medicine); Dr POMPER, Martin G. (Johns Hopkins University, School of Medicine); Dr HOBBS, Robert F. (Johns Hopkins University, School of Medicine); Dr RAY, Sangeeta (Johns Hopkins University, School of Medicine)

Presenter: Dr JOSEFSSON, Anders (Johns Hopkins University, School of Medicine)

Contribution ID: **94** Type: **not specified**

Advances in the radiolabeling of antibodies with astatine-211: toward simplified procedures and improved radiochemical yields

Background and Objectives: Current protein astatination protocols most often rely on reactions that were developed several decades ago. Yet these methods are generally suboptimal. However, given the quite low availability of the alpha emitter 211At, there is a need for new methodologies to limit the loss of radioactive material in each step. This can be achieved by improving reactions radiochemical yields (RCY) and/or purification processes. In this context, our aim was to improve these two critical steps of the astatination of an antibody, namely the prosthetic group radiolabeling step and the bioconjugation step.

Methods: Regarding the astatinated prosthetic group synthesis, we explored the potential of nucleophilic astatination of aryliodonium precursors instead of the conventional electrophilic demetallation of arylstannane compounds.2 We then payed attention to the bioconjugation step, which usually consist in the conjugation of the 211At-prosthetic group to lysines of proteins via an activated ester. Such approach cannot provide quantitative coupling yields since the activated ester degrades in the required conditions for bioconjugation. To solve this issue, we turned our attention to bio-orthogonal approaches that are known to be highly compatible with biological media.

Results and discussions: We observed that aryliodonium salts were highly reactive with astatine, more than expected from extrapolation of other halogens reactivity,1 and that the purification was simplified resulting in more than a doubling of the RCY for the astatination of the antibody (an anti-CD138 mAb for targeting multiple myeloma) in comparison with arylstannane chemistry. To solve the bioconjugation issue, we synthesized clickable astatinated prosthetic groups based on azide or tetrazine functionalities for ligation by 5 different modalities to pre-modified antibodies with the complementary bio-orthogonal handles. By this approach, the bioconjugation step yield was nearly quantitative, and in the best case (the tetrazine/trans-cyclooctene ligation) the coupling time was reduced from 30 min to few seconds which contributed significantly to improving the overall process RCY and duration.3 Additionally, the lower antibody concentration required in this approached allowed the increase of the specific activity of the resulting radioimmunoconjugate. In vitro evaluation showed that it preserved its binding ability, similar to the conventional approach.

In conclusion, the application of recent chemical technologies allowed us to improve the production efficiency of astatinated antibodies in terms of RCY and robustness. Further in vivo studies should confirm the usefulness of these approaches. Overall, these results should facilitate the development of astatinated radiopharmaceuticals and accelerate their transfer to the clinic.

References:
1 Guérard et al, Chem. Eur. J. 2016, 22, 12332.
2 Guérard et al, Bioorg. Med. Chem. 2017, 25, 5975.
3 Navarro et al, Bioorg. Med. Chem. In revision.

Funding Agency

IRON Labex no. ANR-11-LABX-0018-01, ANR-11-EQPX-0004, INCa-DGOS-Inserm_12558.

Email Address

jfgestin@nantes.inserm.fr

Presentation Type

Contributed Oral

Primary author: Dr GUÉRARD, François (CRCINA, Inserm, CNRS, Université d'Angers, Université de Nantes, Nantes, France)

Co-authors: Dr HADDAD, Ferid (GIP Arronax); Dr GESTIN, Jean-François (CRCINA, Inserm, CNRS, Université d'Angers, Université de Nantes, Nantes, France); Mr NAVARRO, Laurent (CRCINA, Inserm, CNRS, Université d'Angers, Université de Nantes, Nantes, France); Ms BERDAL, Marion (CRCINA, Inserm, CNRS, Université d'Angers, Université de Nantes, Nantes, France); Prof. CHÉREL, Michel (CRCINA, Inserm, CNRS, Université d'Angers, Université de Nantes, Nantes, France)

Presenter: Dr GESTIN, Jean-François (CRCINA, Inserm, CNRS, Université d'Angers, Université de Nantes, Nantes, France)

Contribution ID: **95** Type: **not specified**

PARP-1 targeted alpha-emitting radiotherapeutics: an examination of potential toxicity

Introduction: Radiolabeling poly-ADP ribose polymerase 1 (PARP-1) inhibitors potentially enables targeted delivery of alpha-emitting isotopes directly to cancer cells overexpressing PARP-1. However, there is concern for bone marrow toxicity due to its intrinsically high PARP-1 expression. Therefore, we examined bone marrow toxicity at therapeutically relevant doses of an astatine-211 labeled PARP-1 inhibitor, [211At]MM4.

Methods: Male and female C57BL6 mice received 0, 12, 24, and 36 MBq/kg of [211At]MM4 and then were sacrificed after 24 hours, 2 weeks, and 4 weeks. The red marrow-containing femur was harvested and was analyzed with colony formation assay, immunofluorescent (IF) microscopy, histopathology, and immunohistochemistry (IHC). Peripheral blood samples were analyzed for complete blood count (CBC). Additionally, we performed [211At]MM4 biodistribution assay on another set of 20 C57BL6 mice at post-injection time points of 5, 30, 60, 180, and 360 minutes. With the biodistribution data, OLINDA/EXM v1.1 was used for radiation dosimetry calculations in reference to human pediatric models.

Results: The CBC revealed significant lymphopenia only in the 2-week group treated with 24 MBq/kg. A slight decrease in lymphocyte percentage was observed in the 24 MBq/kg mice at 2 weeks and the 36 MBq/kg at 2 and 4 weeks. Significant neutrophilia was observed in all 2-week groups, as well as the 4-week group treated at 36 MBq/kg. Colony formation assay revealed no reduction, but rather significant increase in granulocyte, macrophage, and burst forming unit-erythroid colonies. Histopathology revealed maintained bone marrow cellularity across the treatment groups. IF and IHC demonstrated heterogeneous PARP-1 expression in the bone marrow. The biodistribution and subsequent dosimetry calculations found significantly higher, but non-lethal organ radiation dose per injected activity levels in the red bone marrow, spleen, and thyroid in both 1 and 5-year-old human models.

Conclusion: Overall, the results suggest that doses up to 36 MBq/kg of [211At]MM4 can be administered to C57BL6 mouse models without producing significant systemic or bone marrow toxicity. These results provide promising developments for understanding toxicity associated with the alpha-emitting compound [211At]MM4 *in vivo*. Future studies using fractionated dosing regimens in pre-clinical tumor models will evaluate therapeutic efficacy and further evaluate associated toxicities.

Email Address

adamamansfield@gmail.com

Presentation Type

Contributed Oral

Primary author: MANSFIELD, Adam (Division of Nuclear Medicine and Clinical Molecular Imaging, Department of Radiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA 19104, USA.)

Co-authors: Dr PAWEL, Bruce R. (Department of Pathology, Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA.); HOU, Catherine (Division of Nuclear Medicine and Clinical Molecular Imaging, Department of Radiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA 19104, USA.); Dr PRYMA, Daniel A. (Division of Nuclear Medicine and Clinical Molecular Imaging, Department of Radiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA 19104, USA.); Dr MARTINEZ, Daniel (Department of Pathology, Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA.); Dr LEE, Hwan (Division of Nuclear Medicine and Clinical Molecular Imaging, Department of Radiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA 19104, USA.); VERDONE, James (Division of Nuclear Medicine and Clinical Molecular Imaging, Department of Radiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA 19104, USA.); Dr MARIS, John M. (Division of Oncology and Center for Childhood Cancer Research, Children's Hospital of Philadelphia, Colket Translational Research Building, 3501 Civic Center Boulevard, Philadelphia, PA 19104, USA; Department of Pediatrics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA 19104, USA.); RATHI, Komal S. (Division of Oncology and Center for Childhood Cancer Research, Children's Hospital of Philadelphia, Colket Translational Research Building, 3501 Civic Center Boulevard, Philadelphia, PA 19104, USA; Department of Biomedical and Health Informatics and Center for Data-Driven Discovery in Biomedicine, Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA.); Dr MAKVANDI, Mehran (Division of Nuclear Medicine and Clinical Molecular Imaging, Department of Radiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA 19104, USA.); Dr SAMANTA, Minu (Division of Oncology and Center for Childhood Cancer Research, Children's Hospital of Philadelphia, Colket Translational Research Building, 3501 Civic Center Boulevard, Philadelphia, PA 19104, USA; Department of Pediatrics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA 19104, USA.); BURRELL, Paige E. (Division of Nuclear Medicine and Clinical Molecular Imaging, Department of Radiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA 19104, USA.); Dr RAMAN, Pichai (Division of Oncology and Center for Childhood Cancer Research, Children's Hospital of Philadelphia, Colket Translational Research Building, 3501 Civic Center Boulevard, Philadelphia, PA 19104, USA; Department of Biomedical and Health Informatics and Center for Data-Driven Discovery in Biomedicine, Children's Hospital of Philadelphia, Philadelphia, PA 19104, USA.); Dr MACH, Robert H. (Division of Nuclear Medicine and Clinical Molecular Imaging, Department of Radiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA 19104, USA.); Dr CARLIN, Sean D. (Division of Nuclear Medicine and Clinical Molecular Imaging, Department of Radiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA 19104, USA.)

Presenter: MANSFIELD, Adam (Division of Nuclear Medicine and Clinical Molecular Imaging, Department of Radiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA 19104, USA.)

Contribution ID: **96** Type: **not specified**

225Ac-PSMA-617 in chemotherapy-naive patients with advanced prostate cancer

Purpose: 225Ac- Prostate-specific membrane antigen (PSMA)-617 is a highly promising novel compound for therapy of prostate cancer. A remarkable therapeutic efficacy has been demonstrated in heavily pre-treated metastatic castration-resistant prostate cancer (mCRPC) patients, with xerostomia as the main side effect. A promising strategy for minimization of side effects is based on optimization of the dosing regime while maintaining sufficient therapeutic efficacy for several cohorts of patients, including chemotherapy-naïve patients.

Subjects & Methods: Fifty-seven patients with progressive advanced prostate cancer that had exploited established first-line or second line therapies available in South Africa or that were not eligible or refused certain established therapies were selected for treatment with 225Ac-PSMA-617 on the basis of compassionate use. Therapy was performed in 2 months intervals, with initial dose of 8 MBq (or 10 MBq in case of very advanced disease, superscan), then de-escalation to 6 or 4 MBq in case of good response. The patients were divided into two groups: A: patients that have undergone standard therapy (surgery, radiation therapy and androgen deprivation) and some second line therapies (N=17). B: patients that have undergone only standard therapy or only parts (N=40), while some patients were completely treatment naïve (n=10). Prostate-specific antigen (PSA) and blood cell count were measured every 4 weeks. Monitoring and follow-up included Eastern Cooperative Oncology Group score, pain symptoms, treatment-related toxicity, PSA-response and ALP-response. 68Ga-PSMA-PET/CT was used for baseline staging and imaging follow-up every 8weeks.

Results: Good antitumor activity by means of objective radiologic response or tumor marker decline was observed in 71% of patients in group A while a remarkable 92% response rate was observed in group B. Chemotherapy-naïve patients exhibited significantly increased rate of response, and of complete response. Both groups presented with significant palliation of bone pain and reduced toxicity to salivary glands due to de-escalation. These interim results also show a favourable hematological and renal toxicity profile and quality of life improvements.

Conclusion: The remarkable therapeutic efficacy of 225Ac-PSMA617 reported earlier is confirmed with even better clinical outcomes in chemotherapy-naive advanced prostate cancer patients treated. Reduced toxicity to salivary glands due to de-escalation should be further explored for informing clinical practice and clinical trial design.

Email Address

mike.sathekge@up.ac.za

Presentation Type

Contributed Oral

Primary author: Prof. SATHEKGE, Mike (University of Pretoria)

Co-authors: Prof. MORGERNSTERN, Alfred (EC, JRC, University of Pretoria); Dr REYNEKE, Florette (University of Pretoria); Dr BRUCHERTSEIFER, Frank (EC, JRC); Dr LAWAL, Ismaheel (University of Pretoria); Dr MOKOALA, Kgomotso (University of Pretoria); Prof. VORSTER, Mariza (Univer-

sity of Pretoria); Dr KNOESEN, Otto (NTP); Dr BOSHOMANE, Tebatso (University of Pretoria); Dr LENGANA, Thabo (University of Pretoria)

Presenter: Prof. SATHEKGE, Mike (University of Pretoria)

Contribution ID: **97** Type: **not specified**

HOPE FOR PATIENTS WITH PROSTATE CANCER WITH BONE METASTASES

In Oncology Regional Hospital Ternopil in 2015 -2017

Supervisors:

ABSTRACT: The process of treatment of patients with metastatic castrate-resistant prostate cancer (mCRPC) is pushing the boundaries of oncological treatments. The Ukrainian Society of Nuclear Medicine under the European Commission, Joint Research Centre has agreed on radium-223 chloride ((223) RaCl2) for the treatment of mCRPC patients whose metastases are limited to the bones. Radium 223 is a mildly radioactive form of the metal radium. It used to be called Alpharadin and now has the brand name Xofigo and accumulates in the bone.
BACKGROUND:
The concept of targeted alpha-therapy (TAT) is that Alpha-particle-emitting radionuclides are a subject of importance for investigation in cancer treatment. The reality of these models is that it is possible to sterilize individual cancer cells solely from self-irradiation with alpha-particle emitters, a result that is not possible to obtain with beta-particle emitters given dose-deposition characteristics, achievable radiopharmaceutical specific activity, tumor-cell antigen expression levels and the need to avoid prohibitive toxicity

METHOD
The aim was to see if there were better results in asymptomatic patients at baseline compared to symptomatic patients for early treatment with radium-223.Three men with ages 69, 72 and 53 diagnosed with metastatic castrate-resistant prostate cancer (mCRPC). Two approaches of targeting were used to in the treatment, The Mab J591, against the external domain of prostate-specific membrane antigen (PSMA) and PAI-2, a natural protein inhibitor of urokinase plasminogen (uPA) activator that binds to uPA bounds to surface receptor uPAR on prostate cancer cells. Each targeting molecule requires a bifunctional chelator that reacts both with the carrier molecule and the radioisotope.
RESULTS:
Among the three patients that had previously not responded to available standard treatments, including surgery, external radiation, hormonal and chemotherapy, have received 225Actinium-PSMA-617 as treatment. Several months into the therapy, PSA values have dropped below the detection limit (0.1 ng/ml) from values initially surpassing 3000 ng/ml, 647 ng/ml and 419 ng/ml respectively. To date, 9 months, 17 months and 12 months after their respective treatments, all patients have very satisfactory health status. Prior to the treatment, their life expectancy was of 2-4 months. The therapeutic responses observed in the majority of patients to date indicate that TAT with 225Actinium-PSMA-617 has the potential to change the future treatment of metastatic prostate cancer. It can be confirmed that a dose of 100 kBq/kg body weight is safe and effective with the only side effect being xerostomia. The survival rate is TAT is higher than other methods and also 82% had their tumor shrunk and had lower PSA.
CONCLUSION
In this abstract, we highlight the recent developments in α-particle therapy that have enabled me and my supervisors over the years to exploit this highly potent form of therapy by targeting tumor-restricted molecular biomarkers.
Keywords: 223Ra, α-particle therapy, molecular radiotherapy, nuclear medicine, radioimmunotherapy

Funding Agency

I do not require Travel Bursaries. I will be sponsored by my parents, who always sponsor my travels

Email Address

emmanuelnappiah@gmail.com

Presentation Type

Contributed Oral

Primary author: Mr APPIAH, EMMANUEL NYARKO (TERNOPIL STATE MEDICAL UNIVERSITY)

Co-author: Prof. I.Y.GALAYCHUK, IGOR (TERNOPIL STATE MEDICAL UNIVERSITY (Head of Department Oncology, Radiodiagnosis, Radiation Medicine))

Presenter: Mr APPIAH, EMMANUEL NYARKO (TERNOPIL STATE MEDICAL UNIVERSITY)

Contribution ID: **98** Type: **not specified**

Alternative Options to Produce 225Ac for Nuclear Medicine

The 225Ac radiopharmaceuticals are at the final phases of clinical trials to treat various cancers. Hence, there is a relevant issue of establishing its scaled-up production. The easiest way to produce 225Ac is generating from 229Th extracted from 233U. However, the quantity of produced 225Ac is limited by the availability of stored 233U. For example, from 1 kg 233U aged for 35 years up to 32 mCi 229Th can be produced, which makes possible to accumulate up to 20 mCi 225Ac every two weeks.

An alternative way to produce 229Th is irradiation of 226Ra in the high neutron flux. JSC "SSC RIAR"has performed a series of experiments to irradiate trial radium targets, and experimental yields of radium activation products have been determined. Calculation based on these data demonstrated that the maximum yield of 229Th is ~21 mCi/g 226Ra after 6 months irradiation in the neutron trap of the SM high-flux reactor. The produced 229Th contains 228Th with the activity being 4500 times higher than that of 229Th. While there are no actinium isotopes in the 228Th decay chain, high activity of 228Th and its daughter decay products would cause a number of serious problems. Firstly, high alpha activity determines high heat and gas rates during irradiation, shipment and storage of radium targets, thus limiting the maximum mass of 226Ra per target. Secondly, continuous cooling is required when storing the purified isotope mixture between the 225Ac generation cycles. Finally, it is hard to use traditional methods of 225Ac extraction due to intense radiolysis of the reagents.

The content of 228Th in 229Th can be reduced if using a two-stage irradiation process. The first stage involves irradiation of radium up to the maximum yield of 227Ac (33 mg/g 226Ra). At the same time, a mixture of thorium isotopes is generated with the 228Th:229Th activity ratio of ~25000:1 that can be used to produce 224Ra and 212Pb. At the second stage, when irradiating 227Ac extracted from several radium targets, the maximum yield of 229Th is achieved on the 60th day of irradiation (72 mCi/g 227Ac). The ratio of 228Th and 229Th activities at this point is almost the same as that resulted from single irradiation. However, due to complete burnout of 227Ac, further irradiation would lead to a fast decrease in the 228Th:229Th activity ratio. In the course of irradiation during 5-6 months, the 228Th:229Th activity ratio would make up 1500:1, but the yield of 229Th would decrease to 35 mCi/g 227Ac.

Another way to produce 225Ac is irradiation of natural thorium in particle accelerators. The produced 225Ac contains an impurity of 227Ac and is not suitable for radiopharmaceutical synthesis. However, it can be used in 213Bi generators. To implement this option, it is necessary to cooperate with a partner company that has a proton accelerator with the beam energy of at least 100 MeV. Currently JSC "SSC RIAR"considers all three production options for 225Ac.

Email Address

orip@niiar.ru

Presentation Type

Poster

Primary author: Mr BUTKALIUK, Pavel (JSC “SSC RIAR”)

Co-authors: Mr KUPRIYANOV, Alexander (JSC “SSC RIAR”); Mr KUPRIYANOV, Alexey (JSC “SSC RIAR”); Dr ROMANOV, Evgeny (JSC “SSC RIAR”); Mrs BUTKALIUK, Irina (JSC “SSC RIAR”); Mr ANDREEV, Oleg (JSC “SSC RIAR”); Dr KUZNETSOV, Rostislav (MEPhI’s Branch, Dimitrovgrad); Mr TARASOV, Valery (JSC “SSC RIAR”)

Presenter: Mr BUTKALIUK, Pavel (JSC “SSC RIAR”)

Contribution ID: **99** Type: **not specified**

Production and Quality Control of 223RaCl2 and 224RaCl2

Among all radium isotopes, at least two are used in nuclear medicine. Bayer-manufactured 223RaCl2 (trade name Xofigo) is applied for palliative care of bone metastasis. Microsources containing 224Ra are under clinical trials to treat malignant tumors of skin and mucous membrane using diffusing α-emitter radiation therapy (DaRT) that involves controlled migration of 220Rn.
These two radium isotopes have one common feature –they can be produced from radionuclide generators containing long-lived parent radionuclides 227Ac and 228Th. The essential quality control parameter is the content of the long-lived parent radionuclide in the final product. However, the direct measurement using alpha, beta or gamma spectrometry does not ensure the required detection limit. In alpha spectra the lines corresponding to 227Ac and 228Th are on the low-energy tail of alpha peaks for 223Ra, 224Ra and their daughter products. As for 227Ac, the situation gets more complicated due to low alpha-particle emission probabilities (1.38%) causing the detection limit of ~1% with the acquired statistics being 1 million counts in the alpha spectrum. The detection limit for 228Th in 224Ra under similar conditions is ~0.1%. Conversion electrons and beta radiation of 223Ra decay products (211Pb and 211Bi) are hurdles in measuring the activity of 227Ac by beta radiation. Compton scattering of gamma radiation from 212Pb and 208Tl becomes an obstacle in measuring the activity of 228Th with the use of gamma spectrometry. Decay 227Ac is not accompanied by emission of characteristic gamma radiation.
There are two basic approaches to determine long-lived parent radionuclides in 223Ra and 224Ra. One approach is that the left-off preparation sample is stored for a long time for 223Ra/224Ra to decay, and alpha/gamma spectra are measured. Another approach is based on the chemical extraction of 227Ac and 228Th traces from a preparation aliquot and further measurement of their activity.
JSC "SSC RIAR"performs experiments to generate trial samples of 223RaCl2 and 224RaCl2. For the purpose of long-lived impurities quantification, an aliquot with the activity ranging from 10 to 100 MBq is taken from every batch. The impurities are extracted chemically by sorption of radium isotopes on BioRAD AG-50x8 strong acid cation-exchange resin with EDTA in ammonium acetate buffer solution with a pH from 4.5 to 6.0. In these conditions actinium and thorium form stable complexes, and they are not sorbed on the cation-exchange resin. It has been found that the presence of EDTA, acetic acid and ammonium acetate in the solution does not affect the quality of obtained alpha spectra and impurity detection limits. Therefore, the analysis can be done without pre-desalting or diluting the obtained solutions. The achieved detection limits for long-lived impurities are ~10^{-5}% of the activity of radium isotopes, which is enough for their application in nuclear medicine.

Email Address

orip@niiar.ru

Presentation Type

Poster

Primary author: Mr BUTKALIUK, Pavel (JSC “SSC RIAR”)

Co-authors: Mr KUPRIYANOV, Alexander (JSC “SSC RIAR”); Mrs BUTKALIUK, Irina (JSC “SSC RIAR”)

Presenter: Mr BUTKALIUK, Pavel (JSC “SSC RIAR”)

Track Classification: Quality & Regulatory Assurance

Contribution ID: **100** Type: **not specified**

Radiolabeling of DOTA-conjugated Lintuzumab with 225Ac: Comparison of Th-229-produced and High-Energy Proton Accelerator-produced 225Ac

Lintuzumab is a humanized monoclonal antibody (mAb) against CD33, an antigen widely expressed on myeloid stem cells and leukemic blast cells in patients with Acute Myeloid Leukemia (AML). Actinium Pharmaceuticals is advancing several targeted radio-immunotherapy programs utilizing Lintuzumab conjugated with the potent alpha emitting radionuclide Actinium-225 (225Ac) to treat cancer patients. Currently, the supply of 225Ac for clinical manufacturing is produced by a generator system from the decay of Thorium-229 (229Th); however, the capacity of 229Th generators to supply Ac-225 is limited (< 2 Ci/year). A highly promising source of Ac-225 supply is via high-energy linear proton accelerator (Linac) where 225Ac is produced via irradiation of Thorium-232. Linac-produced 225Ac, however, contains minor quantities (0.1-0.7% activity) of low energy 227Ac which has a half-life of 21.8 years. 225Ac has a half-life of 10 days. Because of the large differences in decay rates of these two isotopes, even at very low activity levels, the 227Ac molecule is present in high quantities in the mixture. For example, at 0.3% activity, the molar ratio of 227Ac to 225Ac is approximately 2.3. At this level, the 227Ac in linac preparations of 225Ac may have a negative impact on labeling efficiency, stability and potency.

In order to assess the potential impact of the 227Ac impurity on antibody labeling efficiency and other parameters, we conducted experimental studies where lintuzumab-DOTA conjugates were comparatively labeled with 225Ac produced by both 229Th generator and linac. In these studies, we compared radiolabeling efficiency and critical quality attributes of the radiolabeled finished drug product. Previously, in vivo mouse studies of linac-produced 225Ac, free or DOTA-chelated, demonstrated similar biodistribution/dosimetry/toxicity profiles to 229Th generated 225Ac [1]. In our experimental scheme, a preparation of lintuzumab-DOTA conjugate was first prepared using a qualified manufacturing process. The lintuzumab-DOTA conjugate was then divided into two parts, and one part was radiolabeled with 229Th generated 225Ac and the second part with Linac-generated 225Ac. Both 225Ac radioisotope lots were supplied by the Department of Energy (DOE). Post-labeling, the radiolabeled lintuzumab-DOTA-Ac-225 preparations were passed through separate size exclusion chromatography columns to remove unlabeled 225Ac from the preparation. The eluents were analyzed for radiochemical purity and immunoreactivity. Further, radiolabeling efficiency was determined for both 225Ac radionuclide preparations. For verification of results, the study was repeated a second time with new lots of 225Ac from each source. Our results demonstrated that, radiolabeling of lintuzumab-DOTA with 225Ac generated by high energy proton accelerator exhibited similar characteristics in terms of radiolabeling efficiency, immunoreactivity and radiochemical purity to 229Th generated 225Ac, suggesting that the elevated molar concentration of low energy 227Ac in linac preparations does not have a significant negative impact on the labeling of monoclonal antibodies for the generation of radioimmunoconjugates.

Email Address

dludwig@actiniumpharma.com

Presentation Type

Poster

Primary author: Dr LUDWIG, Dale (Actinium Pharmaceuticals)

Co-authors: Dr RAY, Nitya (Actinium Pharmaceuticals); Dr PATEL, Vimal (Actinium Pharmaceuticals)

Presenter: Dr LUDWIG, Dale (Actinium Pharmaceuticals)

Contribution ID: **101** Type: **not specified**

Capabilities of JSC “SSC RIAR”in Producing 227ThCl4

227Th is considered to be one of the promising radionuclides for target radionuclide therapy of cancer. Its advantages are chemical properties which are good for the synthesis of the complexes with chelating agents and emission of five alpha particles with complete decay of one 227Th nucleus. The apparent disadvantage is the presence of 223Ra among daughter products the chemical properties of which are fundamentally different from thorium that can cause its redistribution in the human body. A rather big half-life of 227Th (18.7 days), on the one hand, is good for the preparation production and shipment, and on the other hand, it specifies high-level requirements to the preparation stability in the human body.

In addition to using 227Th for radiopharmaceutical synthesis, it can be applied in manufacturing 223Ra generators. While such generators have a rather small period of use, they have a number of advantages over 227Ac/223Ra generators. In particular, there is no need to check every batch for the 227Ac content, and there are no long-lived radioactive wastes.

JSC “SSC RIAR”performs experiments to produce trial samples of 227Th by generating from long-lived parent radionuclide 227Ac extracted from the 226Ra targets irradiated during 20-25 days in the SM reactor neutron trap. To separate 227Th and 227Ac, thorium is sorbed on BioRad AG 1x8 (NO3-) strongly basic anion-exchange resin from 8M HNO3 with further elution using 0.1-0.5 M HNO3 or HCl. To produce the preparation of desired radionuclide purity, the purification process must be carried out at least twice. The key challenge in producing 227Th is determination of the 227Ac content. It is not possible to directly determine 227Ac by its own alpha radiation at its activity of less than 1% of the 227Th activity. The yield of alpha radiation in 227Ac decay is only 1.38 %, and its peak in the spectrum is on the low-energy tail of 227Th and its daughter products. 227Th conversion electrons and beta radiation of the daughter products, namely 211Pb and 211Bi, are obstacles in measuring the 227Ac activity by beta radiation. The presentation discusses possible methods to check the content of 227Ac with its preliminary chemical extraction from a preparation aliquot and gives the characteristics of 227Th experimental samples.

Email Address

orip@niiar.ru

Presentation Type

Contributed Oral

Primary author: Mr BUTKALIUK, Pavel (JSC “SSC RIAR”)

Co-authors: Mr KUPRIYANOV, Alexander (JSC “SSC RIAR”); Mrs BUTKALIUK, Irina (JSC “SSC RIAR”); Dr KUZNETSOV, Rostislav (MEPhI’s Branch, Dimitrovgrad)

Presenter: Mr BUTKALIUK, Pavel (JSC “SSC RIAR”)

Contribution ID: **102** Type: **not specified**

A Versatile Immune-Stimulatory Actinium-225 Complex for Combination Radiotherapy and Antibody Recruiting Therapy

Antibody recruiting small molecules (ARMs) are a unique class of immune-stimulatory agents that contain two key regions: the antibody-binding terminus (ABT), which recruits endogenous antibodies, and the target-binding terminus (TBT), which interacts with the site of interest.(1,2) When bound to a cell, the endogenous antibodies can promote antibody-dependent cellular cytotoxicity (ADCC) resulting in clearance of the antibody-labelled cells. There is an opportunity to enhance the immune response caused by ARMs through the addition of a radionuclide that delivers cytotoxic radiation directly to the site of interest.(3) Evidence suggests that for cancerous lesions combination therapy of immune stimulation and cytotoxic radiation can lead to regression of not only primary tumours, but also simultaneous regression and control of distant metastases.(3)
Rather than develop a specific targeted radiolabelled ARM for each biomarker, a platform was established with three functional regions, a tetrazine, a DOTA chelate and a 2,4-dinitrophenyl moiety. The tetrazine was introduced in place of the TBT, permitting a bioorthogonal reaction with a trans-cyclooctene (TCO)-labelled ligand to be employed for targeting a choice tumour marker. The chelate, DOTA, was chosen due to the wide range of radiometals it can bind, including alpha emitters such as actinium-225. The target trifunctional ligand was synthesized and radiolabelled with lutetium-177 and actinium-225 in high yield and both compounds were found to be stable in formulation over 24 hours. A proof of concept study has been performed by reacting the lutetium-177 ligand with TCO functionalized bovine serum albumin (BSA) aggregates, which act as a protein "anchor". The radiolabelled aggregates were injected intratumourally in a 4T1 breast cancer model which showed high retention over 24 hours. As a result of the high tumour retention, we will proceed with a therapy study comparing the individual monotherapies, targeted alpha and antibody recruiting, to the combination therapy to determine if this platform can generate an antitumour response.

1. Chirkin, E. et al. Angew Chem. Int. Ed. 2017; 56:13036-13040.
2. McEnaney, P. J. et al. ACS Chem. Biol. 2012; 7:1139-1151.
3. Yasuda, K. et al. Cancer Sci. 2011; 102:1257-1263.

Funding Agency

NSERC, Canadian Cancer Society, Canadian Institutes for Health Research

Email Address

rathmasm@mcmaster.ca

Presentation Type

Contributed Oral

Primary author: Ms RATHMANN, Stephanie (McMaster University)

Co-authors: Prof. VALLIANT, John (McMaster University); Mrs JANZEN, Nancy (McMaster University)

Presenter: Ms RATHMANN, Stephanie (McMaster University)

Contribution ID: **103** Type: **not specified**

Targeted alpha particle therapy of EGFR-positive breast cancer using site-specifically labeled 225Ac–dN-SpyCatcher-SpyTag-nimotuzumab

Introduction: Targeted alpha-particle therapy is a promising approach for breast cancer treatment. Anti-EGFR antibodies e.g. cetuximab, panitumumab, and nimotuzumab are used to treat different EGFR positive cancers. Especially, nimotuzumab is better tolerated and has low skin toxicities, because it's "affinity optimized"binding characteristic ensures low transient binding to low EGFR-expressing healthy tissues such as the skin. In this study, we have radiolabeled an anti-EGFR antibody nimotuzumab with 225Ac at the Fc domain using SpyCatcher/SpyTag protein ligase system. We have evaluated the 225Ac-dN-SpyCatcher-SpyTag-nimotuzumab in EGFR-positive MDA-MB468 cells and mouse xenograft.
Methods: Nimotuzumab was site-specifically labeled by a two-step process. Firstly, dN-SpyCatcher was reduced using TCEP, which was followed by desferoxamine (DFO-maleimide conjugation to yield a reactive DFO-dN-SpyCatcher. The DFO-dN-SpyCatcher was reacted with SpyTag-nimotuzumab to obtain stable dN-SpyCatcher-SpyTag-nimotuzumab. Radiolabeling was performed with 89Zr, and the conjugate was used for imaging in vivo. Similarly, dN-SpyCatcher was conjugated to an eight-membered macrocyclic chelator SCN-macropa, and used to radiolabel the SpyTag-nimotuzumab with Actinum-225. All constructs were characterized using biolayer interferometry, flow cytometry, radioligand binding assays, HPLC and bioanalyzer. The in vitro cytotoxicity of 225Ac-dN-SpyCatcher-nimotuzumab-SpyTag was evaluated in EGFR-positive MDA-MB-468 and EGFR-negative MDA-MB-435 cells using live-cell imaging and the in vivo efficacy was studied in mice bearing MDA-MB-468 xenografts. When tumors had reached 50 −100 mm3, mice were treated with two 450 nCi doses of 25Ac-dN-SpyCatcher-SpyTag-nimotuzumab 14 days apart. Non-specific binding antibody construct was used as control.
Results: In vitro binding in MDA-MB-468 cells was specific. Radiochemical yield for 89Zr and 225Ac radioimmunoconjugates was >90 % with a purity >95 % of both tracer agents. MicroPET/CT imaging showed good tumor uptake of 89Zr-dN-SpyCatcher-SpyTag-nimotuzumab with the highest % injected activity per gram of 6 % at 48 h post injection. The IC50 of 225Ac-dN-SpyCatcher-SpyTag-nimotuzumab and 225Ac-Control-IgG against MDA-MB468 cells was 0.13 ± 0.09 and 0.43 ± 0.16 nCi/mL, respectively. 225Ac-dN-SpyCatcher-nimo significantly prolonged the survival of MDA-MB468 mice (60 days) compared to 225Ac-control IgG (33.5 days) or PBS treated mice (30 days). Further evaluation in other EGFR positive xenografts is ongoing.
Conclusion: The results showed that the conjugation and labeling by dN-SpyCatcher system to nimotuzumab did not significantly alter the receptor binding and internalization nimotuzumab compared to non-specific conjugation approach. 225Ac-dN-SpyCatcher-SpyTag-nimotuzumab was effective in vitro and showed to be promising in a breast cancer xenograft.

Email Address

rav137@mail.usask.ca

Presentation Type

Poster

Primary author: Dr VISWAS, Raja Solomon (University of Saskatchewan)

Co-author: Dr FONGE, humphrey (University of Saskatchewan)

Presenter: Dr VISWAS, Raja Solomon (University of Saskatchewan)

Contribution ID: **104** Type: **not specified**

Small Scale Modeling and Dosimetry for the Salivary Gland: Application to 177Lu- and 225Ac-PSMA Therapy

Objectives: Salivary gland toxicity is a quality of life concern in radioiodine treatment of thyroid cancer and more recently has become a concern for radiolabeled-PSMA therapy of prostate cancer. Clinically observed toxicity is inconsistent with absorbed doses (AD) to the salivary glands calculated by absorbed fraction methods, even considering the alpha-particle RBE. Small scale anatomical modeling and activity apportionment, the macro-to-micro methodology, has been proven to reconcile discrepancies between whole organ AD values and clinically or pre-clinically observed toxicities for alpha-particle renal toxicity.

Methods: Uptake in the salivary glands has been shown to be primarily confined to the epithelial striated ducts where PSMA is expressed. Dimensions of typical striated duct cells were obtained from the literature. Based on the fraction of occupancy of these cells within the salivary glands (5.1 %), striated cells were placed randomly in gridded spheres of increasing size representing the salivary glands and was used to simulate decay of activity in these cells. The GEANT4 Monte Carlo was used to simulate decays for both 177Lu and 225Ac in the striated ducts. The absorbed dose .was calculated to both striated cells and acinar cells, which make up 60 % of the salivary glands. Dose volume histograms of these two cell types were obtained as a function of salivary gland size as was the ratio of average striated duct AD and acinar cell AD to whole organ AD.

Results: The grid-based Monte Carlo results showed a ductal cell AD to salivary whole organ AD ratio of 5.1 −5.3 for 177Lu and 13.4 −13.8 for 225Ac dependent on salivary gland size (5 - 25 ml). This suggests an average salivary gland dose threshold of ~ 0.45 Gy for 225Ac, assuming an RBE of 5, and a threshold of ~5.8 Gy for 177Lu.

Conclusions: This is a significant step in quantifying the discrepancy between clinically observed toxicity and predicted toxicity based on whole organ AD values using small scale dosimetry, which has been shown to explain similar discrepancies in different cases, particularly alpha-particle dosimetry. This study shows that while the salivary glands may be considered as parallel organs for external beam radiation, the physiology for activity uptake means that for radiopharmaceutical therapy, they have a more complex structure.

Funding Agency

NIH

Email Address

rhobbs3@jhmi.edu

Presentation Type

Contributed Oral

Primary author: Dr HOBBS, Robert (Johns Hopkins)

Co-authors: Dr PLYKU, Donika (Johns Hopkins); Dr SGOUROS, George (Johns Hopkins)

Presenter: Dr HOBBS, Robert (Johns Hopkins)

Contribution ID: **105** Type: **not specified**

Development and Validation of Methods for Quantitative In Vivo SPECT of Pb-212

Pb-212 (T1/2 = 10.6h) has gained considerable interest in targeted alpha-therapy (TAT) since it serves as an in vivo generator for Bi-212 (T1/2 = 61 m), producing both α- and β-particles. Accurate dosimetry requires estimates of organ activity at multiple time points. Imaging Pb-212 is challenging because of the relatively low administered activities, complicated decay scheme in including multiple daughters, and wide range of energies emitted. The objective of this study is to develop and validate a Pb-212 quantitative SPECT (QSPECT) imaging method that includes compensations for all physical image degrading effects.

Experimental projection data were obtained using a NEMA IEC Body Phantom with one off-center hot sphere (3.7cm diameter) imaged by a Siemens Symbia system. A medium energy collimator was used with energy windows of 67-91 keV and 220-257 keV. The energy windows were selected by optimizing a signal-to-noise ratio that considered geometrically collimated photons as signal and all other photons as adding only noise. Measured, simulated, and model-based projector generated projections were compared quantitatively. Simulated anthropomorphic-phantom data were also generated using the SIMIND Monte Carlo code. We investigated the qualitative image quality and precision of activity estimates at 1, 24, and 48 hours post-administration of a 2.1 mCi injected activity.

Good agreement was achieved between measured phantom projection, simulation, and mode-based projector. For the simulated patient data, we studied the convergence properties of the iterative reconstruction by looking at the reconstructed counts in the organs as a function of iteration. These tended to converge at about five iterations. The coefficients of variation (COVs), a measure of precision, for organs other than the marrow at five iterations ranged from 1.0-2.6% at 1 hr, 2.2 to 9.4% at 24 hours, and 7.5-23% at 48 hours. The COVs for a marrow compartment were substantially higher, ranging from 16% at 1 hour to 43% at 48 hours.

The results indicate that quantitative imaging pf Pb-212 is feasible. The improved quantitative accuracy from QSPECT methods has the potential for providing more accurate patient specific dosimetry in TAT.

Email Address

binhe77@gmail.com

Presentation Type

Contributed Oral

Primary author: HE, Bin (Radiopharmaceuticals Imaging and Dosimetry)

Co-authors: DELPASSAND, Ebrahim (RADIOMEDIX, Inc.); FREY, Eric (Radiopharmaceuticals Imaging and Dosimetry); SGOUROS, George (Radiopharmaceuticals Imaging and Dosimetry); TWOROWSKA, Izabela (RADIOMEDIX, Inc.); GHALY, Michael (Radiopharmaceuticals Imaging and Dosimetry)

Presenter: HE, Bin (Radiopharmaceuticals Imaging and Dosimetry)

Contribution ID: **106** Type: **not specified**

Automated Production of Alpha-Emitting Therapeutic Radionuclides

Alpha particle therapy is predicated on high energy emissions (MeV) with path lengths of only several cell diameters (μm). It has generated tremendous interests since the approval of the first in class alpha particle emitting radionuclide, Xofigo or 223Ra-dichloride. This agent is utilized for the treatment of castrate resistant prostate cancer, with successful outcomes with patient end-of-life quality improvements and overall survival extension of 4 months. Consequently, attempts to further expand 223Ra-dichloride applications are ongoing. Many trials for expanded alpha particle emitter work are underway, particularly in the combination therapy space, however few if any have been evaluated preclinically. There is little scientific rationale for many of these proposed trials. A central issue is the lack of access to Radium-223 for preclinical testing. To address this issue, we are developing automated production tools capable of supplying 223Ra and 227Th dedicated for preclinical research. Our solution is a permanent automated production unit of ready-to-inject 223Ra-Dichloride and ready to label 227Th with low isotopic parent breakthrough, high throughput and complete parent recovery post-production for regeneration. The long lived Actinium-227 source is immobilized on a cationic polymeric resin cartridge followed by a separation and elution of each isotope in high radiopurity. The chromatographic radionuclide separator consists of an automated fluidic device allowing for a fast, low-dose exposure and reduced loss system. To this end, a modularly concentrated solution of high radioactive content is generated formulated as a ready-made drug: 223Ra solvated in sodium citrate 0.03M and saline 0.9%; as prepared for patient dose. Similarly, 227Th-Nitrates can be isolated and utilized for further radiolabeling procedures. Live monitoring of radioactive elution is conducted utilizing a gamma-detector looped to the automated separator. Further quality control is executed using High Purity Germanium detector to define the radiochemical purity of produced 223Ra or 227Th and the recovery of isotopic parents 227Ac and/or 227Th. Finally, through acidic wash the isotopic parents are recollected off the resin for recycling into a fresh cartridge for the next production cycle. To the best of our knowledge, this is the first automated synthetic unit proposed for simultaneous production of 223Ra and 227Th for preclinical production. . This approach offers a fast, low exposure and high recovery strategy to producing alpha-emitting material for research use while recollecting the isotopic parents for repeated production. In a time when restricted access makes alpha particle therapy research cost-prohibitive, having a high quality on-site production may open commercial opportunities to supply nationwide needs for preclinical testing of Radium-223 and Thorium-227.

Funding Agency

Mallinckrodt Institute of Radiology

Email Address

dabou@wustl.edu

Presentation Type

Contributed Oral

Primary author: Dr ABOU, Diane (Washington University School of Medicine)

Co-authors: Dr THOREK, Daniel (Washington University School of Medicine); Mr GAEHLE, Gregory (Washington University School of Medicine); Mr LAWRENCE, Luke (Washington University School of Medicine); Dr WOODARD, Pamela (Washington University School of Medicine); Mr ZERKEL, Patrick (Washington University School of Medicine)

Presenter: Dr ABOU, Diane (Washington University School of Medicine)

Contribution ID: **107** Type: **not specified**

Comparison of Reactor Production of 229Th vs. Accelerator Production of 229Th at Oak Ridge National Laboratory

Comparison of Reactor Production of 229Th vs. Accelerator Production of 229Th at Oak Ridge National Laboratory

J. R. Griswold, R. Copping, D. W. Stracener, R. Howard, R. Boll, C. U. Jost, S. H. Bruffey, D. Denton, L. Heilbronn, and S. Mirzadeh

Actinium-225 (t1/2 = 10.0 ± 0.1 d) is one of the more effective radioisotopes used in alpha radioimmunotherapy. It has been used to treat many forms of cancer including glioblastoma, acute myeloid leukemia, prostate cancer, and breast cancer. Actinium-225 can be directly applied in vivo or used as a generator of the short-lived daughter product 213Bi (t1/2 = 45.59 ± 0.06 minutes). Actinium-225 can be produced directly via cyclotron through the 226Ra(p,2n)225Ac reaction or by high energy proton spallation (Ep > 90 MeV) of thorium targets. However, because of its ten-day half-life, it is more efficient to create its precursor, 229Th (t1/2 = 7932 ± 28 years). Current supplies of 229Th originate from the decay of 233U [t1/2 = (1.592 ± 0.002) x 105 y], but that supply is insufficient to support the demand for 225Ac and access to 233U is limited. In order to close the gap between supply and demand of 225Ac, work has been initiated at Oak Ridge National Lab to produce 229Th through the irradiation of 226Ra targets in the High Flux Isotope Reactor. This method to produce 229Th will be presented and compared to previous studies performed at ORNL to produce 229Th through the low energy proton bombardment (Ep < 40 MeV) of 232Th at the Holifield Radioactive Ion Beam Facilities Tandem Accelerator.

Funding Agency

DOE Isotope Program, managed by the Office of Nuclear Physics in the Office of Science

Email Address

griswoldjr@ornl.gov

Presentation Type

Poster

Primary author: Dr GRISWOLD, Justin (Oak Ridge National Laboratory)

Co-authors: Dr COPPING, Roy (Oak Ridge National Laboratory); Dr BOLL, rose (ORNL)

Presenter: Dr GRISWOLD, Justin (Oak Ridge National Laboratory)

Track Classification: Nuclide Production Supply

Contribution ID: **108** Type: **not specified**

Pre-Clinical Evaluation of 225Ac-DOTATOC Pharmacokinetics, Dosimetry, and Histopathology to Enable Phase-1 Clinical Trial in Patients with Neuroendocrine Tumors

Objectives: Evaluate pharmacokinetics of 225Ac-DOTATOC with and without kidney protection (KP); to compare 225AcNO3 or "free"225Ac derived from accelerator production versus stockpile extraction; to estimate predicted radiation absorbed dose (RAD) to humans receiving 225Ac-DOTATOC; and to evaluate histopathology 90 days post-administration.
Methods: 225AcNO3-accelerator, 225AcNO3-stockpile, or 225Ac-DOTATOC prepared using 225AcNO3-stockpile, with and without KP, was administered IV to male Sprague Dawley rats, n= 5 per cohort per time point. At 1-hour to 90-days post-administration, rats were euthanized. Blood was collected for CBC and metabolic testing. Organs were collected, weighed, evaluated for radioactivity using a gamma counter and processed for histopathological examination. Cumulative organ radioactivity was used as the input function to estimate mean radiation absorbed tissue dose in humans (OLINDA 1.0). Mean Residence Times (Mbq-h/Mbq) were determined to allow estimation of RAD in mSv/MBq.
Results: 225Ac-DOTATOC (10uCi +KP, 3uCi +KP, 10uCi, 3uCi), 225AcNO3-accelerator, and 225AcNO3-stockpile RAD to kidneys were (1.09E+02, 7.39E+01, 1.39E+02, 1.37E+02, 1.83E+02, 1.29+E02, respectively). KP decreased RAD 22% and 46% following 10uCi and 3uCi 225Ac-DOTATOC, respectively. 225Ac-DOTATOC treated animals showed similar CBC to controls. Untargeted 225AcNO3 from either accelerator or stockpile significantly decreased white and red blood cells, and overall survival. Three rats that received 225AcNO3- stockpile and two rats that received 225AcNO3-accelerator did not survive 90 days. The 225AcNO3 stockpile and accelerator groups each had a single rat found dead which was not necropsied. Over the entire study, vehicle control rats continuously gained weight, while the groups receiving either 225AcNO3 stockpile or accelerator gained weight slower, with body weights remaining almost unchanged. There was no bone marrow hypoplasia in vehicle control, DOTATOC control, or 3 μCi-KP DOTATOC rats. Rats receiving 3 μCi+KP DOTATOC, 10 μCi+KP DOTATOC, and 10 μCi-KP DOTATOC developed mild to moderate bone marrow hypoplasia. All DOTATOC groups showed normal pattern of fat replacement in bone marrow consistent with normal aging. Bone marrow hypoplasia was marked to very marked in rats receiving 225AcNO3-accelerator and was slightly less severe in 225AcNO3-stockpile. All treatment groups showed evidence of previous or ongoing renal tubular nephrosis. All treatment groups except 3 μCi-KP DOTATOC group showed evidence of renal glomerulopathy; lesions were most severe in 225AcNO3 stockpile and accelerator groups. Cardiac lesions of myofiber and epicardial mineralization were seen only in 225AcNO3- accelerator group. The histological impact in control and 225Ac-DOTATOC groups was negligible at all timepoints.
Conclusion: The estimated radiation absorbed dose from 225Ac-DOTATOC was low in all critical organs. Accelerator produced 225Ac contains 227Ac (t½ ~ 21yrs) as a trace impurity, resulting in increased radiation dose when compared to stockpile-derived 225AcNO3. The histopathological results show moderate impact from untargeted 225AcNO3. The clinical impact is believed to be insignificant, since patients will receive targeted 225Ac-DOTATOC which showed negligible toxicity at all timepoints.

Funding Agency

US Department of Energy #4000145752; UNM Comprehensive Cancer Center, Internal Pilot Award

Email Address

jnorenberg@salud.unm.edu

Presentation Type

Poster

Primary author: Prof. NORENBERG, Jeffrey (Radiopharmaceutical Sciences Program, UNM HSC)

Co-authors: Ms GOFF, Chelsea (Radiopharmaceutical Sciences Program, UNM HSC); Dr KUSEWITT, Donna (UNM Comprehensive Cancer Center); Dr HESTERMAN, Jacob (inviCRO); Dr FAIR, Joanna (UNM Comprehensive Cancer Center); Dr ORCUTT, Kelly (inviCRO); Dr JOHN, Kevin (Los Alamos National Laboratory); Ms NYSUS, Monique (Radiopharmaceutical Sciences Program, UNM HSC); Dr RIXE, Olivier (UNM Comprehensive Cancer Center); Mrs JACQUEZ, Quiteria (Radiopharmaceutical Sciences Program, UNM HSC); Dr HELOISA, Soares (UNM Comprehensive Cancer Center); Mrs DANIELS, Tamara (Radiopharmaceutical Sciences Program, UNM HSC)

Presenter: Prof. NORENBERG, Jeffrey (Radiopharmaceutical Sciences Program, UNM HSC)

Contribution ID: **109** Type: **not specified**

Targeted alpha-emitter therapy of neuroendocrine tumors using 212Pb-octreotate (AlphaMedix TM)

Objectives:

The high potency of alpha-emitters combined with high affinity of the somatostatin analogs provides the fundamental strength and rationale for using Targeted Alpha-emitter Therapy (TAT) in neuroendocrine cancers (NETs). The 212Pb-octreotate analog, (AlphaMedix™) will be the next generation of peptide receptor radionuclide therapy for the metastatic NETs patients. RadioMedix and Orano Med initiated the Phase I, non-randomized, open-label, dose escalation study of AlphaMedix™ to determine the safety, bio-distribution, and preliminary effectiveness of this drug in adult subjects with somatostatin receptor expressing NETs. The Investigational New Drug application was approved by U.S. FDA (IND# 135150) and BRANY IRB of New York. The clinical trial site is the Excel Diagnostics and Nuclear Oncology Center in Houston.

Methods:

Subjects with histologically confirmed NETs and prior positive somatostatin analog scans, with no prior history 177Lu/90Y/111In peptide receptor radionuclide therapy (PRRT), were enrolled in this study. Each subject underwent a screening visit within 14 days prior to receiving the investigational agent. Vital signs, laboratory tests, and ECG were measured before and at multiple time points after the drug administration. These assessments were repeated through the follow-up phase of the study. For the efficacy assessment, the imaging studies including CT/MRI, 18F-FDG-PET/CT, and other known imaging modalities were used to monitor any change in the size and function of the tumor. The quality of life (QOL) were also monitored using ECOG performance status and the EORTC-QLQ-C30 QOL questionnaire. The treatment regimen started with single intravenous (IV) administration of ascending doses of AlphaMedix™. Each cohort consisted of 3 subjects meeting the inclusion and exclusion criteria of the protocol. There was an incremental 30% increase of the dose between each cohort. Dosing was continued until the tumor response or DLT is observed. The Single Ascending Dose (SAD) regimen has been converted to a Multiple Ascending Dose (MAD) regimen which consists of 3 IV injections of selected doses of drug administrated at 8 (+/-1) week intervals.

Results:

As of November 2018, we have enrolled nine patients (6 females and 3 males) with SSTR expressing metastatic NETs. All subjects well-tolerated treatments with single ascending or the first multi-ascending doses of AlphaMedix™. Few mild adverse events were reported during the follow-up visits (nausea and mild hair loss in 2/9 patients; the abdominal pain and diarrhea in 3/9 patients, the fatigue in 2/9 patients). There was no dose-limiting toxicity.

Conclusion:

The AlphaMedix™ treatment has shown a favorable safety profile at the currently tested doses. The efficacy and the safety study are still ongoing. The favorable properties of 212Pb causing irreversible damage to the double stranded DNA of tumor cells can potentially translate into longer progression-free survival of the patients with metastatic SSTR (+) NETs.

Funding Agency

NCI SBIR Phase II Contract 2018 (PIID:HHSN261201800048C UPIID:75N91018C00048)

Email Address

itworowska@radiomedix.com

Presentation Type

Contributed Oral

Primary authors: Dr DELPASSAND, Ebrahim S. (RadioMedix Inc; Excel Diagnostics and Nuclear Oncology Center); Dr TWOROWSKA, Izabela (RadioMedix Inc)

Co-authors: Dr MUZAMMIL, Ali (Excel Diagnostics and Nuclear Oncology Center); Dr SAIDI, Amal (Orano Med LLC); Dr HE, Bin (Rapid LLC); Dr FREY, Eric (Rapid LLC); Dr SHANOON, Farah (Excel Diagnostics and Nuclear Oncology Center); Dr SGOUROS, George (Rapid LLC); Dr TORGUE, Julien (Orano Med LLC); Dr BOLEK, Luke (Excel Diagnostics and Nuclear Oncology Center); Dr GHALY, Michael (Rapid LLC); Dr STALLONS, Tania (Orano Med LLC)

Presenter: Dr DELPASSAND, Ebrahim S. (RadioMedix Inc; Excel Diagnostics and Nuclear Oncology Center)

Contribution ID: **110** Type: **not specified**

Application of a trabecular and cellular model of bone marrow dosimetry for targeted 223Ra therapy

Objectives: There is growing awareness in the radiopharmaceutical therapy community that dosimetry-based treatment planning is a highly desirable objective, potentially leading to greater efficacy and safety for patients. Ra-223, a bone-seeking radionuclide, has been used extensively as a therapeutic for bone metastases of prostate cancer. However, dosage follows a strict regimen based on mass and attempts to understand the dosimetry of Ra-223 have had limited success, in part due to the low count rate of emissions, the disseminated and dynamic natures of the disease and organ at risk, the multiplicity of radioactive daughters as well as the short range and high LET of the alpha-particles, making it the most difficult dosimetry of any radiopharmaceutical to date. We propose to take the next step in Ra-223 bone marrow dosimetry by combining (a) small scale geometrical trabecular and cellular model, (b) detailed alpha-particle absorbed fractions from human cadaver studies, (c) high resolution autoradiography of resected mouse femurs and (d) clinical pharmacokinetics.

Methods: Human pharmacokinetics, time-integrated activity (TIA) and whole organ absorbed dose values, including blood and bone were taken from the literature for patients treated with 100 kBq/kg. The time integrated activity (number of decays) in the bone was apportioned to the bone matrix, endosteal layer and marrows cavities based on murine imaging data obtained using high resolution storage phosphor autoradiography as well as alpha-Camera images of resected mouse femurs sectioned on a cryostat. These TIAs were converted to absorbed dose to the endosteal layer, the bone matrix and the marrow as a function of marrow distance from bone surface different depths using absorbed fractions obtained from human cadaver data from a previous publication. The trabecular and cellular model was used to obtain cell dose histograms.

Results: The activity and therefore TIA was primarily concentrated in the endosteal layer. Consequently, due to the short range of the emitters, the absorbed dose was predominantly deposited near the bone surface, either in the endosteal layer or the shallow marrow. The dose cell histograms results were used to plot the percentage of marrow cells that received less than a potentially toxic dose (2 or 4 Gy) as a function of the average absorbed dose. The results show a heterogeneous distribution of cellular absorbed dose, strongly dependent on the position of the cell within the marrow cavity, such that increasing the average marrow cavity absorbed dose, or equivalently, increasing the administered activity results in only a small increase in number of marrow cell with cytotoxic dose.

Conclusion: Small scale modeling has been successful at interpreting localized dose in other organs, such as the kidneys and salivary glands. The dynamic and systemic nature of the bone marrow make it a more complex organ at risk, yet the use of small scale modeling offers insight into the lack of expected bone marrow toxicity as calculated from average absorbed dose and is a significant step towards reconciling dosimetry and toxicity.

Funding Agency

NIH

Email Address

rhobbs3@jhmi.edu

Presentation Type

Contributed Oral

Primary author: Dr HOBBS, Robert (Johns Hopkins)

Co-authors: Dr JOSEFSSON, Anders (Johns Hopkins University, School of Medicine); Dr THOREK, Daniel (Washington University School of Medicine); Dr ABOU, Diane (Washington University School of Medicine); Dr SGOUROS, George (Johns Hopkins); Dr BOLCH, Wesley (University of Florida)

Presenter: Dr HOBBS, Robert (Johns Hopkins)

Contribution ID: **111** Type: **not specified**

Bioconjugation of actinides using a peptoid scaffold

The targeted delivery of alpha-generating radionuclides such as actinium-225
and thorium-227 is emerging as a promising treatment approach for a range of cancers. Advances in protein engineering are driving new developments in targeted drug delivery through increased availability of monoclonal antibodies and similar delivery vehicles. This work utilizes a modular, solid-phase synthetic method to generate biopolymers suitable for chelating f-block elements. The peptoid platform, polymeric chains of N-substituted glycines, can incorporate essentially any functional group bearing a pendant primary amine, allowing us prepare a tetramer of 1,2-hydroxypyridinone (HOPO) moieties optimized for actinide chelation. Further inclusion of a range of suitable functionalities enables bioconjugation via maleimide-Cys, succinate ester-Lys, or azide-alkyne coupling chemistry. Antibody-peptoid conjugates provide a versatile platform for antigen-specific delivery of therapeutic alpha generators, as well as other radionuclides such as zirconium-89, a positron emitter ideally suited for PET imaging.

Funding Agency

United States Department of Energy

Email Address

jarees@lbl.gov

Presentation Type

Poster

Primary author: Dr REES, Julian (Lawrence Berkeley National Lab)

Co-author: Prof. ABERGEL, Rebecca (University of California, Berkeley)

Presenter: Dr REES, Julian (Lawrence Berkeley National Lab)

Contribution ID: **112** Type: **not specified**

225Ac-NM600 targeted alpha therapy extends survival in a model of triple negative breast cancer.

Triple negative breast cancer (TNBC) remains the most lethal breast cancer histology. Currently, approved targeted therapies for TNBC do not exist, and novel tumor-targeted interventions to complement/supplant the current standard of care using chemotherapy are urgently needed [1]. Our research group has developed a series of tumor-avid alkyphosphocholine analogs (APC) that can carry a radiolabel for both imaging and targeted radionuclide therapy of breast cancer. In this study we investigated the potential of NM600, our lead APC analog, radiolabeled with the alpha emitter ²²⁵Ac, for targeted alpha therapy (TAT) in a mouse model of TNBC. Radiolabeling yields were nearly quantitative (>95%) with a specific activity of 3.4 GBq/μmol. Excipient and serum stability of ²²⁵Ac-NM600 at 8 days was 90% and 95%, respectively. Longitudinal ex vivo biodistribution studies were performed in Balb/C mice bearing mammary adenocarcinoma 4T1 tumor grafts injected with 20 kBq ²²⁵Ac-NM600 at 4, 24, 48, 96, and 216 h post injection (p.i.). Elevated radioactivity was observed in the blood (15.2 ± 1.2 %ID/g) at 4 h p.i. and gradually declined overtime with a 23.1 ± 1.9 h biological half live (n = 3). Due to the hepatobiliary excretion of ²²⁵Ac-NM600, distribution in normal tissue was most prominent in the liver, peaking at 28.1 ± 3.6 %ID/g at 96 h p.i. ²²⁵Ac-NM600 uptake in 4T1 tumors progressively increased from 6.7 ± 3.0 %ID/g at 4 h to 26.1 ±15.6 %ID/g (n = 3) at the final timepoint, 216 h p.i.. Biodistribution did not change when ²²⁵Ac-NM600 was administered with a 50-fold lower specific activity. In therapy studies, three groups of mice bearing 4T1 tumors (~150 mm3, n = 5) were administered either excipient (control), 20 kBq, or 40 kBq ²²⁵Ac-NM600, and tumor progression and animal survival were monitored for 60 days. Significant tumor regression (P < 0.001) was observed in both treatment arms compared to control within a week following treatment; however, a survival benefit was only achieved in the 20 kBq group, in which all mice showed controlled disease and no signs of acute toxicity. The administration of 40 kBq was acutely radiotoxic. These preliminary results demonstrate the potential of TAT using NM600 for the treatment of TNBC and warrant further treatment optimization and the exploration of potential long-term toxicities.

1. Bianchini, G., et al., Triple-negative breast cancer: challenges and opportunities of a heterogeneous disease. Nat Rev Clin Oncol, 2016. 13(11): p. 674-690.

Email Address

hernandez6@wisc.edu

Presentation Type

Contributed Oral

Primary author: Dr HERNANDEZ, Reinier (University of Wisconsin-Madison)

Co-authors: Ms BITTON, Ariana (UW-Madison); Mr MASSEY, Christopher (UW-Madison); Dr ALUICIO-SARDUY, Eduardo (UW-Madison); Prof. WEICHERT, Jamey (UW-Madison); Prof. ENGLE, Jonathan (UW-Madison); Dr GRUDZINSKI, Joseph (UW-Madison)

Presenter: Dr HERNANDEZ, Reinier (University of Wisconsin-Madison)

Track Classification: Preclinical

Contribution ID: **113** Type: **not specified**

Development of 211At production via continuous extraction of 211Rn

Critically needed radionuclides for cancer therapy include the alpha-emitter 211At [1] and therapeutically useful Auger-electron emitters. The ATLAS (Argonne Tandem Linac Accelerator System) superconducting linac at Argonne National Laboratory is suitable for production of these radionuclides. Our work is initially focusing on demonstrating production capabilities for 211At (7.2 h half-life) using the 209Bi(7Li,5n)211Rn reaction. Cross sections for these reactions peak at 600 mbarn [2,3] making production of 10's of mCi per batch feasible using only a very small percentage of the accelerator beam time. Presently, in the U.S. 211At is primarily produced at 3 university facilities using the 209Bi(α,2n)211At reaction at in-house cyclotrons. Hence, clinical use of 211At nation-wide is limited due to its short half-life. By using the lithium induced reaction, the 211At daughter is extracted from the parent 211Rn, which has a half-life of 14 h, significantly extending the time-frame for effective distribution and use of this important radionuclide. ATLAS is an appropriate and flexible accelerator for production of medical isotopes because it can provide beams of any ion including protons, helium, lithium, and heavier ions with energies adjustable over a wide range. An upgrade of the accelerator to produce more intense lithium beams and the construction of improved neutron shielding is in progress. Following the completion of this work, currents of lithium beams of 1-10 particle microamps will be available to support the development of a 211Rn/211At generator. These combined upgrades will enable yields of ~100 mCi of 211Rn per batch. As part of this development, an option for the continuous collection of 211Rn from a bismuth oxide target followed by separation of the 211At daughter product is being investigated. Porous bismuth oxide targets have been developed by Innosense, LLC under a DOE Small Business Grant. [4] In two test runs to date, 211Rn released from the targets was collected in charcoal traps. In the first run a metallic bismuth target was used and in the second the recently developed bismuth oxide target was used. In both runs only a low fraction of the 211Rn was released and collected on line. The first case was limited by the melting point of the metal target, and the second was limited by the target being heated only to 60 oC. The release and capture were quantified by off-line gamma counting of the long lived 207Bi daughter remaining in the production target and in the charcoal. In upcoming test runs target heating up to 600 oC will be implemented to increase release and collection efficiency.

1. Vaidyanathan. G. and Zalutsky, M.R., Curr Radiopharm. 2011 October ; 4(4): 283–294.
2. Meyer, G.J., Lambrecht, R.M., Inter. J. of App. Rad. and Isotopes, 31(1980)351-355.
3. Washiyama, K., et al., 16th International Workshop on Targetry and Target Chemistry, Santa Fe, NM, 2016
4. Sampathkumaran, U. and Winter, R., Innosense, LLC, Torrance, CA, U.S. DOE SBIR project

Funding Agency

This work was supported by the DOE Office of Nuclear Physics, Contract No. DE-AC02-06CH11357.

Email Address

Nolen@ANL.gov

Presentation Type

Contributed Oral

Primary author: Dr NOLEN, Jerry (Argonne National Laboratory)

Co-authors: Dr MUSTAPHA, Brahim (Argonne National Laboratory); Prof. CHEN, Chin-Tu (University of Chicago); Dr ROTSCH, David (Argonne National Laboratory); Dr SONG, Jeongseog (Argonne National Laboratory); Mr GREENE, John (Argonne National Laboratory); Prof. WASHIYAMA, Kohshin (Fukushima Medical University); Dr BROWN, M. Alex (Argonne National Laboratory); Dr GOTT, Matthew (Argonne National Laboratory); Mr GAMPA, Ravi (Argonne National Laboratory); Mr WINTER, Raymond (Innosense, LLC); Dr DE KRUIJFF, Robin (Argonne National Laboratory); Dr ZHU, Shaofei (Argonne National Laboratory); Dr SAMPATHKUMARAN, Uma (Innosense, LLC)

Presenter: Dr NOLEN, Jerry (Argonne National Laboratory)

Contribution ID: **114** Type: **not specified**

Tuning of the Radium biodistribution by dietary supplements in a CD1 mice model.

Although ²²³RaCl₂ has been approved for the treatment of bone metastases originating from mCRPC (EMA, FDA and others), further data on ²²³Ra biodistribution and possible metabolism tuning are needed particularly after the discovery of increased risk of death and fractures due to the interactions of ²²³Ra with abiraterone, prednisone/prednisolone treatment.
Thus we report here the results of biodistribution study with ²²³RaCl₂ applied intravenously to a healthy female CD1 mice fed with various dietary supplements - vitamin D and CaCl₂ or with co-treatment with zoledronic acid. Ex vivo biodistributions were determined in major organs in 24 and 96 h. p.i.
Our results indicate that the vitamin D and CaCl₂ supplements and co-treatment with zoledronic acid have direct impact on Radium biodistribution and elimination kinetics.
We speculate that under optimized conditions the treatment of bone metastases may become more efficient and safer compared to application of ²²³RaCl₂ only.

Funding Agency

Technology Agency of the Czech Republic, grant No.: TA03010027.

Email Address

jan.kozempel@fjfi.cvut.cz

Presentation Type

Contributed Oral

Primary author: Dr KOZEMPEL, Ján (CTU in Prague)

Co-authors: Ms KUKLEVA, Ekaterina (CTU in Prague); Ms MERHAUTOVÁ, Jana (UJV Rež); Ms FICENZOVÁ, Karolína (UJV Řež); Ms JANDOVÁ, Ludmila (UJV Řež); Dr VLK, Martin (CTU in Prague); Ms SUCHÁNKOVÁ, Petra (CTU in Prague)

Presenter: Dr KOZEMPEL, Ján (CTU in Prague)

Track Classification: Preclinical

Contribution ID: **115** Type: **not specified**

Evaluation of specific activity and stable impurities in 225Ac derived from ISAC and 229Th decay.

Introduction

Targeted Alpha Therapy (TAT) is a promising method for the treatment of cancer, due to the high Linear Energy Transfer (LET) of alpha particles resulting in a short range and dense ionization tracks in tissue. 225Ac (half-life 9.92 d) in particular was identified as one of the most favorable candidates for TAT due to its half-life, multiple alpha decays and favourable chelation chemistry. [1,2] To validate its potential, various studies have demonstrated the effectiveness of 225Ac treatments of metastatic and late-stage cancers. [1-3] The current supply of 225Ac for clinical studies has mainly come from 229Th generators obtained from 233U. The available supply from these sources, however, is not enough to support large-scale clinical studies, limiting the development of 225Ac-based radiopharmaceuticals.

Methods

The Life Sciences group at TRIUMF works in collaboration with Canadian Nuclear Laboratories (CNL) to establish and test various methods of production of 225Ac. This includes production using the ISAC facility, spallation reaction on thorium, and decay of 229Th (provided by CNL). A comparison study was performed using ISAC-produced and CNL-produced 225Ac to compare the specific activity and presence of stable contaminants that may affect radiolabeling with chosen chelators. The aim of this study was to establish the quality and applicability of 229Th-generated 225Ra/225Ac from CNL to enable future use of material in important chelation studies with novel ligands. If high purity and high specific activity 225Ac can be readily available through the collaboration with CNL, TRIUMF has the opportunity to make significant contributions to the chelation chemistry and in vivo use of 225Ac.

Experimental

The comparison study was designed to replicate a concentration dependence experiment, where the radiolabeling of 2-[4,7,10-tris(carboxymethyl)-1,4,7,10-tetrazacyclododec-1-yl]acetic acid (DOTA) and N,N'-bis[(6-carboxy-2-pyridil)methyl]-4,13-diaza-18-crown-6 (macropa) with various sources of 225Ac (ISAC and CNL) were tested. [4] Results of this study lead to changes in the separation procedure of 225Ra/225Ac from 229Th at CNL. The collaboration continues to work to optimize the purification process and work toward using the obtained 225Ac with higher specific activity for chelation studies that will translate to further in vitro and in vivo testing.

Acknowledgements

TRIUMF receives funding via a contribution agreement with the National Research Council of Canada.

References

1. Apostolidis, C., et al. "Production of Ac-225 from Th-229 for targeted α therapy." Analytical chemistry 77.19 (2005): 6288-6291.

2. A Scheinberg, David, and Michael R McDevitt. "Actinium-225 in targeted alpha-particle therapeutic applications." Current radiopharmaceuticals 4.4 (2011): 306-320.

3. Kratochwil, Clemens, et al. "225Ac-PSMA-617 for PSMA-targeted a-radiation therapy of metastatic castration-resistant prostate cancer." J Nucl Med 57.12 (2016): 1941-1944.

4. Thiele, Nikki A., et al. "An eighteen-membered macrocyclic ligand for actinium-225 targeted alpha therapy." Angewandte Chemie International Edition 56.46 (2017): 14712-14717.

Funding Agency

TRIUMF, Canadian Nuclear Laboratories, National Research Council of Canada

Email Address

mynericj@mcmaster.ca

Presentation Type

Contributed Oral

Primary author: Ms MYNERICH, Jenasee (TRIUMF)

Co-authors: Mr ROBERTSON, Andrew (TRIUMF); Dr RAMOGIDA, Caterina (TRIUMF); Mr SAEKHEIE, Meelad (TRIUMF); Dr CAUSEY, Patrick (Canadian Nuclear Laboratories); Dr SCHAFFER, Paul (TRIUMF); Dr PERRON, Randy (Canadian Nuclear Laboratories); Dr RADCHENKO, Valery (TRIUMF); Ms BROWN, Victoria (TRIUMF)

Presenter: Ms MYNERICH, Jenasee (TRIUMF)

Contribution ID: **116** Type: **not specified**

Quantified cell binding of astatinated immunoconjugates on ovarian cancer cell spheroids by alpha camera imaging

Purpose. Optimization of patient dosing for intraperitoneal α-radioimmunotherapy of microtumours can be performed with the help of a biokinetic model. The goal of this study was to investigate whether simulations of mathematical models can be confirmed by in vitro models. We used the α- camera micro-imaging technology to quantify cell binding of 211At-radiolabelled monoclonal antibodies to small ovarian cancer cell clusters.
Materials and methods. Various sized spheroids (NIH:OVCAR-3) were treated with 211At-MX35 and 211At-Farletuzumab (170kBq/mL) for different time periods. Cell clusters were stained and evaluated as a whole or by serial sectioning using the α-camera device and the γ-counter as reference method. Alpha camera images were frame-parsed to determine the activity uptake and distribution. Cell numbers were estimated by area evaluation of conventional α-camera images in case of whole spheroids or, in case of cross-sections, by manual counting of adjacent haematoxylin and eosin stained cryosections. Kinetic binding curves were derived using the total number of bound antibodies per cell and compared to model simulations.
Results. Quant imaging with the α-camera provides an accurate and precise method for activity quantification. In contrast to 211At-Farletuzumab, binding kinetics of 211At-MX35 were considerably different from the model simulation predictions. Experimental data showed equilibrium binding within 4 hours after treatment followed by a decline in activity due to cell death. The in vitro model did confirm that lower levels of activity uptake per cell were reached for larger spheroids, especially near the core. For this particular cell line, the antibody binding characteristics of MX35 led to higher activity levels.
Conclusion. This study demonstrated that antibody binding characteristics play an important role in intraperitoneal α-radioimmunotherapy. Our observations indicate that radiation effects may occur already shortly after treatment initialization and thus elucidating a parameter that needs to be added in the models used for treatment planning.
Key words: astatine-211, radioimmunotherapy, alpha-particle therapy, quantification, biokinetic model

Email Address

tom.back@radfys.gu.se

Presentation Type

Contributed Oral

Primary author: Dr BACK, Tom (University of Gothenburg)

Co-authors: Dr ANEHEIM, Emma (University of Gothenburg, Sweden); Dr JENSEN, Holger (PET and Cyclotron unit, Copenhagen University Hospital); Ms VERHOEVEN, Marjolein (University of Gothenburg); Dr ALBERTSSON, Per (Sahlgrenska Academy, University of Gothenburg); PALM, Stig

(University of Gothenburg); Dr LINDEGREN, Sture (Departemnt of Radiation Physics, Institute of clinical Sciences Sahlgrenska Academy at Gotehnburg University)

Presenters: Ms VERHOEVEN, Marjolein (University of Gothenburg); Dr BACK, Tom (University of Gothenburg)

Contribution ID: **117** Type: **not specified**

Has the dream come true? A retrospective look at the development of alpha therapy and its promise for the future.

Shortly after the discovery of alpha particle emission by Rutherford, scientist began to explore the possibility of using these alpha emitting radionuclides in experiments for treating disease. However it was approximately 100 years before clinical trials using such radionuclides began in spite of numerous animal studies demonstrating efficacy over the ensuing years.

This talk will explore this history and discuss the remaining challenges to overcome in order to make targeted alpha therapy a routine approach to treating disease.

Email Address

truth@triumf.ca

Presentation Type

Contributed Oral

Primary author: Dr RUTH, Thomas (TRIUMF)

Presenter: Dr RUTH, Thomas (TRIUMF)

Contribution ID: **118** Type: **not specified**

A Novel Reaction for “Click”-based 211At-Astatination

Purpose & Introduction

The α-emitter 211At is a highly promising radionuclide for targeted alpha therapy (TAT). High linear energy transfer renders alpha particles highly radio-toxic to adjacent cells, making TAT a efficient treatment option for cancer.[1]

211At is the only alpha emitter used in therapy that allows for covalent labeling, thus preventing the use of chelating ligands. In general, astatinations are carried out utilizing stannyl-precursors and oxidative conditions. Due to the low abundance of this element, the chemistry of astatine is rather unexplored. The availability of other straight forward radio-astatination procedures would extend the variety of accessible 211At-TAT agents, leading to more options in clinical research and the treatment of malignant disease.

Methods & Results

Within this contribution a novel methodology for introduction of 211At into small molecules is presented. In this multi-component labeling reaction, an azide-moiety (A), an alkyne-moiety (B), and 211At are combined using base and metal catalysis. The product formed consists of a 1,2,3-triazole (T) bearing both structural motifs (A and B) with the astatine located at the formed triazole system (A-T(211At)-B). The reaction, which has shown to be unaffected by high starting activities, was optimized towards reaction time and radiochemical yield (RCY), finally providing >70% RCY within 10 min.
The reaction is highly tolerant considering the structural motifs A and B, as shown in a related study applying 125I as radioisotope.[2] This allows a high degree of structural variation, enabling straight-forward tuning of pharmacokinetic properties. We chose to use a biotin-azide as A and a tetrazine-alkyne as B, giving rise to a 211At agent that is suitable for biotin/streptavidin or tetrazine/trans-cyclooctene (TCO) based labeling and pre-targeting studies. The structure of the product was verified by binding experiments to TCO and streptavidin modified beads. Stability of the formed astatine-triazole bond was investigated by incubation of formed 211At-Beads in plasma for 300 min, showing 88% intact substance. Stability was further increased to 99% by click-assembly of a PEG-corona to the bead, using the tetrazine moiety of this multifunctional agent.

Discussion & Conclusion

To the best of our knowledge we have developed a new, high yielding, fast and versatile labeling system for astatine-211. Applying this chemistry we were able to prepare the first 211At-labeled 1,2,4,5-tetrazine that furthermore bears a biotin functional motif. This agent is capable of binding to TCO and/or streptavidin in a highly efficient manner, thus providing a tool for pre-targeted alpha radiotherapy (pTAT) and macromolecule labeling. We are convinced that this new astatination-strategy is a step forward towards broader application of TAT by expanding the variety of 211At based therapeutic agents.

[1]Elgqvist et al, Front Oncol. 2013.
[2]Yan et al J. Am. Chem. Soc., 2013

Email Address

christoph.denk@tuwien.ac.at

Presentation Type

Contributed Oral

Primary author: Dr DENK, Christoph (Vienna University of Technology)

Co-authors: Dr ANEHEIM, Emma (University of Gothenburg, Sweden); Dr WILKOVITSCH, Martin (Vienna University of Technology); Dr HERTH, Matthias (Rigshospitalet, Copenhagen, DENMARK, University of Copenhagen, DENMARK); Dr LINDEGREN, Sture (Departemnt of Radiation Physics, Institute of clinical Sciences Sahlgrenska Academy at Gotehnburg University)

Presenter: Dr DENK, Christoph (Vienna University of Technology)

Contribution ID: **119** Type: **not specified**

A Phase 2 Study of Actinium-225 (225Ac)-lintuzumab in Older Patients with Untreated Acute Myeloid Leukemia (AML)

Background: Older patients with AML unfit for intense induction chemotherapy have a poor prognosis with 5-year survival of <10%. 225Ac-lintuzumab is composed of 225Ac linked to a humanized anti-CD33 monoclonal antibody. Data were previously presented on the initial 13 patients who received 2.0μCi/kg/dose (ASH 2017, Abstract 616). Although that dose resulted in a high response rate of 69%, it was associated with a 46% incidence of Grade 4 thrombocytopenia lasting >6 weeks. Therefore, the dose was reduced to 1.5μCi/kg/dose for further evaluation.

This study enrolled older patients with untreated AML who were considered to be unfit for standard induction chemotherapy. Patients 60-74 years were required to have significant comorbidities, while all patients ≥75 years were eligible. Antecedent hematologic disorders (AHDs) were allowed. Other eligibility criteria included ECOG PS 0-2 and CD33 expression on >25% of blasts. 225Ac-lintuzumab was administered on Days 1 and 8.

Results: 40 patients were treated (13 at 2.0μCi/kg and 27 at 1.5μCi/kg). The median age was 75 years and median ECOG PS was 1. 23 patients had prior AHDs. Of the patients with known cytogenetics, 3 had favorable-risk, 17 had intermediate-risk, and 10 had adverse-risk AML. The median baseline BM blast percentage was 31% (range, 20-66%) with median CD33 expression 63% (range, 14-100%) of AML cells.

Objective responses were seen in 9 patients (69%, 2.0μCi/kg) and 6 patients (22%, 1.5μCi/kg). Overall, there were 1 complete remission, 5 complete remissions with incomplete platelet count recovery (CRp) and 9 complete remissions with incomplete hematologic recovery (CRi).

Myelosuppression was seen in all patients including Grade 4 thrombocytopenia with marrow aplasia for >6 weeks after the first dose in 46% (2.0μCi/kg) and 30% (1.5μCi/kg) with data at 6 weeks. One patient with prior MDS had pancytopenia for >4 months.

Conclusions: Preliminary data from this analysis of 225Ac-lintuzumab monotherapy in older AML patients unfit for intensive therapy indicate a lower rate of myelosuppression at 1.5μCi/kg/dose but also a lower response rate than was seen at 2.0μCi/kg/dose. Although the study met the prespecified response criteria for continuing enrollment, it was closed to further accrual since targeted radiation, like other AML therapies, will likely have the best outcomes when used in combination or in settings where myelosuppression is expected. An extensive development program in MDS, AML, and multiple myeloma is planned. In MDS, Lin-Ac225 will be used as targeted conditioning prior to hematopoietic stem cell transplant in patients with Poor/Very Poor Cytogenetics. In AML, Lin-Ac225 will be used in combination with venetoclax, with venetoclax and HMAs, with CLAG-M salvage chemotherapy, and as a single-agent for post-remission therapy. Lin-Ac225 will also be used as a single-agent for CD33-expressing relapsed multiple myeloma.

Email Address

mberger@actiniumpharma.com

Presentation Type

Contributed Oral

Primary authors: Dr ATALLAH, Ehab (Medical College of Wisconsin); Dr JURCIC, Joseph (Columbia University Medical center); Dr BERGER, Mark (Actinium Pharmaceuticals)

Co-authors: Dr PERL, Alexander (University of Pennsylvania); Dr RIZZIERI, David (Duke University); Dr ROBOZ, Gail (Weill Medical College of Cornell University); Dr PARK, Jae (Memorial Sloan Kettering Cancer Center); Dr OROZCO, Johnnie (Fred Hutchinson Cancer Research Center); Dr BEGNA, Kebede (Mayo Clinic); Dr FINN, Laura (Ochsner Medical Center); Dr CRAIG, Michael (West Virginia University); Dr LEVY, Moshe Yair (Baylor University Medical Center); Dr MAWAD, Raya (Swedish Cancer Institute); Dr KHAN, Sharif (Saint Francis Cancer Center); Dr TSE, William (University of Louisville)

Presenter: Dr BERGER, Mark (Actinium Pharmaceuticals)

Contribution ID: **120** Type: **not specified**

Improved tumor control and absence of late neurotoxicity using alpha (213Bi) as compared to beta (90Y) labelled-DOTA-Substance P for the treatment of low grade gliomas

Low-grade gliomas (LGG) of astrocytic, oligodendrocytic or mixed phenotype represent an unmet medical need as orphan disease. Due to relatively long median survival time of 8-15 years, prospective clinical studies are rarely conducted. Recommended therapeutic regimens range from an observational strategy to extensive resection with awake craniotomy in order to diminish the risk of transformation into a higher grade glioma. We have conducted an observational study in 8 low grade gliomas using the radiopeptidic targeting vector [213Bi]/[90Y]-DOTA-substance over a period of 18 years (4-18 years, median). Besides therapeutic efficacy, we assessed long-term effects, especially late neurotoxicity of beta- and alpha-therapy following local injection. Since biodistribution of the small peptidic vector (1.8 KD) extends over large parts of the ipsi- and possibly contralateral CNS, late toxicity is of principal concern although no NK-1 receptors are expressed in the normal supratentorial brain. The alpha particles releases their decay energy within an ultrashort range that represents the diameter of 1-2 tumor cells (virtual single cell radiotherapy) while beta-therapy targets many more cells (cross-fire effect). We are comparing long-term side effects following alpha-therapy (Bi-213, range 0.1mm) with those of beta-therapy (Y-90: range 5mm, 2.3 MeV). So far, no recurrence or late toxicity has been observed in newly alpha-treated LGG over a period of 18 (OGII), 11 (AII), 10 (AII), 7 (OGII), 4 (OGII) and 3 (AII) years. Injection of [213Bi]-DOTA-substance into an LGG infiltrating the motor cortex was well tolerated with only transient neurological deficits. In contrast, all Y-90 treated LGG cases either developed signs of late radiotoxicity or recurrence after an observation interval of 8-10 years. Two of these beta-cases were subsequently treated with one cycle of alpha-therapy. One of them showed a slight worsening of pre-existing aphasia, presumably due to previous application of high-dose beta irradiation. In conclusion, local alpha therapy appears to be superior to beta-therapy regarding long-term tumor control and late toxicity.

Email Address

adrian.merlo@bluewin.ch

Presentation Type

Contributed Oral

Primary author: Prof. MERLO, Adrian (University of Basel)

Co-authors: Dr MORGENSTERN, Alfred (European Commission, Joint Research Centre, Directorate for Nuclear Safety and Security, Karlsruhe, Germany); Dr CORDIER, Dominik (University of Basel); Dr BRUCHERTSEIFER, Frank (European Commission, Joint Research Centre, Directorate for Nuclear Safety and Security, Karlsruhe, Germany); Prof. KROLICKI, Leszek (University of Warsaw Medical Center)

Presenter: Prof. MERLO, Adrian (University of Basel)

Contribution ID: **121** Type: **not specified**

Dosimetric Impact of Ac-227 in Accelerator-Produced Ac-225

Actinium-225 (225Ac) has a 10-day half-life and a decay scheme that yields four alpha-particle emissions. This radionuclide is produced by a generator system from the decay of thorium-229. Accelerator-produced 225Ac via thorium-232 irradiation (denoted 225/7Ac) contains a low percentage (0.1-0.3%) 227Ac; (21.77 year half-life) at end of bombardment. The biological consequences of this contamination have been recently examined [1]. We examine the contribution of 227Ac and its daughters to tissue absorbed doses when the level of contamination is 0.7% (by radioactivity) at time of injection. The dosimetric analysis was performed for antibody-conjugated 225/7Ac administered intravenously to treat patients with hematological cancers.

Published pharmacokinetic models are used to obtain the distribution of 225/7Ac -labeled antibody and also the distribution of either free or antibody-conjugated 227Th. Since 227Th is obtained from the beta decay branch (99% yield) of 227Ac rather than a more energetically disruptive alpha-emitter decay, it is possible that a significant fraction of the 227Th generated remains antibody-conjugated. A pharmacokinetic model representing the distribution of radiolabeled antibody in patients with hematologically distributed cancer is adapted from reference [2] to obtain the pharmacokinetics for 225/7Ac and 227Th-labeled-antibody. A model representing the pharmacokinetics of free 227Th is used to model the distribution of unconjugated 227Th [3]. Under both circumstances, 223Ra generated by 227Th decay is simulated using a pharmacokinetic model that is relevant to free 223Ra [4]. The 1% of 227Ac that decays to francium-223 (223Fr, T ½ = 22 min) is considered to have a negligible impact on tissue absorbed dose relative to that from 227Th which is already expected to be very low because of the low initial amount of 227Ac in 225/7Ac. The tissue absorbed dose from 227Ac is negligible in the context of therapy; less than1.4 mGy/MBq for the top 5 highest absorbed tissues and < 0.007 mGy/MBq for all other tissues. Compared to that from 225Ac, the absorbed dose from 227Ac makes up a very small component (<0.4%) of the total absorbed dose delivered to the 5 highest dose tissues: red (active) marrow, spleen, endosteal cells, liver and kidneys when accelerator produced 225/7Ac-conjugated anti-CD33 antibody would be used to treat leukemia patients. For all tissues, the dominant contributor to the absorbed dose arising from the 227Ac is 227Th, the first daughter of 227Ac which has the potential to deliver absorbed dose both while it is antibody-bound and while it is free. The results suggest that the dose arising from 227Ac to normal organs is negligible for 225/7Ac-labeled antibody that targets hematological cancer.

Email Address

gsgouros@jhmi.edu

Presentation Type

Contributed Oral

Primary author: Prof. SGOUROS, George (Johns Hopkins Medical Institute)

Co-authors: Dr HE, Bin (Radiopharmaceutical Imaging and Dosimetry, LLC); Mr LUDWIG, Dale (Actinium Pharmaceuticals, Inc.); Prof. FREY, Eric (Johns Hopkins University, School of Medicine); Mr RAY, Nitya (Actinium Pharmaceuticals, Inc.)

Presenter: Prof. SGOUROS, George (Johns Hopkins Medical Institute)

Contribution ID: **122** Type: **not specified**

Impact of Target Cell Number on Target cell and Tissue Dose for Antibody-Mediated delivery of Alpha-Emitters

225Ac-Lintuzumab- is an alpha-particle emitter labeled anti-CD33 antibody that is in clinical trial evaluation for the treatment of patients with leukemia and myelodysplastic syndrome (MDS). It is also being developed as a targeted conditioning regimen to irradiate and ablate the bone marrow as part of a marrow transplant treatment regimen. We examine the influence of target cell number on the absorbed dose to organs considered critical from the perspective of acute toxicity or late stage or stochastic effects

A previously published pharmacokinetic (PK) model [1] is used to obtain the distribution of 225Ac -labeled antibody for 109 up to 1012 antigen-positive cells corresponding approximately to a range of 1 to 1000 g cells. The PK output was integrated to provide time integrated activity (TIA) input for dosimetry. Absorbed dose calculations were performed using the MIRD Committee S-value based method as described in pamphlet 21 [2]. The International Commission on Radiological Protection (ICRP) recently released absorbed fractions for a new series of phantoms that include far more tissues than were previously available [3]. These were used to perform the dosimetry calculations provided in this report. Decay schemes and half-lives for 225Ac were obtained from ICRP publication 107 [4]. A detailed comparison of the results obtained using OLINDA and the new set of ICRP data has been published [5].

The results for different numbers of antigen positive cells are shown below.

Absorbed dose (mGy/MBq)

Ag+ cells marrow kidneys liver lungs

109 402 2939 468 416

1010 1150 2385 431 337

1011 2444 869 333 123

1012 2708 157 289 22

The results obtained are derived from model-based simulations of anti-CD33 antibody pharmacokinetics in patients with leukemia. The model makes it possible to project the impact of different antigen-positive numbers of cells (e.g., tumor burdens) on pharmacokinetics and dosimetry. The low red marrow and high kidney dose under the condition of 109 antigen-positive cells reflects the low retention of 225Ac-Ab in the marrow when there are very few targets in the marrow. The high kidney dose occurs because low target cell number reduces the capture of free 213Bi by internalization. The model assumes that 50% of free 213Bi in circulation will decay in the kidneys.

The model suggests that organ absorbed doses will vary based on the number of antigen positive cells.

Email Address

gsgouros@jhmi.edu

Presentation Type

Contributed Oral

Primary author: Prof. SGOUROS, George (Johns Hopkins Medical Institute)

Co-authors: Mr HE, Bin (Radiopharmaceutical Imaging and Dosimetry (Rapid), LLC); Dr LUDWIG, Dale (Actinium Pharmaceuticals); Prof. FREY, Eric (Johns Hopkins University, School of Medicine); Mr BERGER, Mark (Actinitum Pharmaceuticals, Inc)

Presenter: Prof. SGOUROS, George (Johns Hopkins Medical Institute)

Contribution ID: **123** Type: **not specified**

Synthesis and Functionalization of Radium-doped Barium Sulfate Nanoparticles

Objectives

The radionuclides radium-223 and radium-224 are two alpha-emitting radionuclides with suitable properties for the TAT. To this date, radium-223 in form of [223Ra]radium chloride (Xofigo) is the only EMA and FDA approved alpha-emitting radiopharmaceutical. Due to its calcimimetic behavior, the radium ion is a bone-seeking therapeutic. To extend the radiopharmaceutical potential of both radionuclides, novel carrier systems have to be developed. Therefore, it is appropriate to investigate different kinds of nanoparticles for their ability to transport radium. Especially, a barium sulfate matrix seems to be sufficient since the principle of co-precipitating the sulfates of radium and barium allows an easy and fast synthesis of radium-doped nanoparticles. Beyond the incorporation of alpha-emitting radionuclides like radium-223 and radium-224, the homologue radionuclide barium-131 can be incorporated as well. Barium-131 decays by electron capture and provides suitable properties for diagnostic applications in nuclear medicine. Radium-223/-224 and barium-131 form a matched pair for new theragnostic approaches. In our research group, we are developing simple methods for the synthesis of small radiolabeled radium/barium sulfate nanoparticles. Furthermore, we are investigating suitable surface functionalizations to attach biological targeting moieties.

Methods

Nanoparticles were synthesized by simple precipitation. Three different methods have been investigated: microemulsion systems, water/THF mixtures, and water/ethanol reaction systems. The reactions were performed under a variety of different parameters. Particle size distributions were determined initially by dynamic light scattering (DLS) and transmission electron microscopy (TEM), respectively. Using a one-pot method, the synthesis of alendronate-coated nanoparticles was achieved. The radiolabeling of the nanoparticles was performed using the water/ethanol reaction method. [224Ra]radium nitrate was separated from a Thorium-228 source by ion exchange chromatography. [133Ba]barium chloride was commercially obtained and used for test labeling instead of barium-131.

Results

The smallest nanoparticle sizes of around 150 nm (measured by DLS) were obtained by using the water/ethanol barium sulfate precipitation method. The functionalization with alendronate derivative was proven by infrared spectroscopy and the further reactivity of the alendronate functionalities was verified by active ester coupling with a dye and the performance of fluorescence spectroscopy measurements, respectively. The radiolabeling of the nanoparticles was successfully tested via co-precipitation of radium/barium sulfate by substituting equivalent amounts of non-radioactive Ba2+ by [133Ba]Ba2+ and [224Ra]Ra2+, respectively. TEM measurements showed that the actual average particle size is comparable to the DLS results.

Conclusions

The successful co-precipitation method can be a starting point for future therapeutic applications. The functionalization and reactivity showed that it is in principle possible to attach any targeting unit. Next steps will deal with the optimization of the particle size, the design of targeting moieties and the performance of first biological studies.

Email Address

d.bauer@hzdr.de

Presentation Type

Poster

Primary author: Mr REISSIG, Falco (Helmholtz-Zentrum Dresden-Rossendorf, Institute of Radiopharmaceutical Cancer Research)

Co-authors: Dr MAMAT, Constantin (Helmholtz-Zentrum Dresden-Rossendorf, Institute of Radiopharmaceutical Cancer Research); Mr BAUER, David (Helmholtz-Zentrum Dresden-Rossendorf, Institute of Radiopharmaceutical Cancer Research); Dr PIETZSCH, Hans-Jürgen (Helmholtz-Zentrum Dresden-Rossendorf, Institute of Radiopharmaceutical Cancer Research); Prof. STEINBACH, Jörg (Helmholtz-Zentrum Dresden-Rossendorf, Institute of Radiopharmaceutical Cancer Research)

Presenter: Mr BAUER, David (Helmholtz-Zentrum Dresden-Rossendorf, Institute of Radiopharmaceutical Cancer Research)

Contribution ID: **124** Type: **not specified**

Calixarene based ligands for Radium and Barium

Objectives

Due to their high biological effectiveness and suitable half-lives, there is increased interest in using the radionuclides radium-223 and radium-224 for radiopharmaceutical applications [1]. Xofigo ([223Ra]radium chloride) is a bone-seeking, alpha-emitting radiopharmaceutical with EMA and FDA approval. It is used to treat bone metastasis of castrate-resistant prostate cancer. To expand the possible applications for these promising radionuclides, it is necessary to stably bind the radionuclide within a chelator. Therefore, calixarene-based ligands have been synthesized, which show encouraging affinities to radium ions. In our recent studies, we have already presented the high potential of these ligands [2,3]. Since radium and barium have similar chemistry, and therefore comparable affinities to our ligands, it is possible to create a matched pair for theragnostic approaches. The radionuclide barium-131 has a suitable physical half-life for therapeutic applications and the potential of being a SPECT nuclide.

Methods

A series of ten calixarene derivatives, functionalized with a crown ether bridge, has been synthesized. To form a neutral complex, two deprotonable moieties have been attached to the calixarene backbone, consisting of perfluorinated sulfone amides. A variety of different sulfone amides has been compared to investigate their influence on the stability of the formed metal-complex. The complexation behavior of these ligands was studied with non-radioactive barium via UV/Vis and NMR spectroscopy. Radiolabeling was performed with barium-133 (for test labeling instead of barium-131, due to its longer half-life) and radium-224 in a simple chloroform/water-two-phase extraction for one hour at room temperature. The ion extraction potential and logK values were determined from the radioactivity distribution equilibrium. In a second step, re-extraction experiments were performed to determine the radiometal release in presence of competing metal ions like Ca2+.

Results

All synthesized calixarene derivatives showed strong interactions with barium ions in initial UV/Vis and NMR measurements. Stability constants in a range of logK=5 7 were obtained for the complexation of [133Ba]Ba2+ and [224Ra]Ra2+ via the radioactivity distribution equilibrium. Depending on the functionalization of the ligand, different amounts of radioactivity release (5-30%) were obtained in the competitive extraction studies. The complexation of radioactive [133Ba]Ba2+ ions was verified by HPLC as well.

Conclusions

Calixarene derivatives, modified with perfluorinated sulfone amides, are suitable ligands for the complexation of heavy alkaline earth metal ions. Ongoing research is concentrating on the functionalization of these ligands, regarding their water solubility and biocompatibility. Furthermore, a biological targeting unit will be attached and first biological studies will be performed.

References:

[1] M. Gott et al., *The Radiochemical and Radiopharmaceutical Applications of Radium*, Open Chem. 2016, **14**, 118-129.
[2] Steinberg, J., et al., *Modified Calix[4]crowns as Molecular Receptors for Barium.* ChemistryOpen, 2018, **7**, 432.
[3] Bauer, D., et al., *Chelation of heavy group 2 (radio)metals by p-tert-butylcalix[4]arene-1,3-crown-6 and logK determination via NMR.* Spectrochim Acta A Mol Biomol Spectrosc, 2018, **199**, 50.

Email Address

d.bauer@hzdr.de

Presentation Type

Poster

Primary author: Mr BAUER, David (Dresden)

Co-authors: Dr MAMAT, Constantin (Helmholtz-Zentrum Dresden-Rossendorf, Institute of Radiopharmaceutical Cancer Research); Mr REISSIG, Falco (Helmholtz-Zentrum Dresden-Rossendorf, Institute of Radiopharmaceutical Cancer Research); Dr PIETZSCH, Hans-Jürgen (Helmholtz-Zentrum Dresden-Rossendorf, Institute of Radiopharmaceutical Cancer Research); Prof. STEINBACH, Jörg (Helmholtz-Zentrum Dresden-Rossendorf, Institute of Radiopharmaceutical Cancer Research)

Presenter: Mr BAUER, David (Dresden)

Contribution ID: **125** Type: **not specified**

Challenges of actinium coordination chemistry for nuclear medicine

Actinium-225 (225Ac) holds remarkable potential as radionuclide for targeted alpha-particle therapy (TAT) due to its advantageous properties, i.e. 10-day half-life and radioactive decay by emission of 4 alpha particles. To create a targeted alpha therapeutic comprising this radiometal, one must assemble two additional parts: a targeting moiety and a chelating ligand. Developing rationally designed 225Ac chelators for TAT applications is an ongoing challenge of primary importance. The chelating molecules must display fast kinetics of coordination under mild conditions and guarantee thermodynamic stability in vivo of the resulting complex. Part of this challenging task is the lack of fundamental knowledge of the coordination chemistry of actinium. In an effort to unravel the bonding interactions that govern actinium chemistry, we have prepared a set of macrocyclic ligands bearing pendant 1,2-hydroxypyridinone (HOPO) and catecholamide (CAM) moieties. To understand the suitability towards Ac chelation, we have performed spectroscopic experiments taking advantage of lanthanides as non-radioactive surrogates.

Email Address

LArnedoSanchez@lbl.gov

Presentation Type

Poster

Primary authors: Dr ARNEDO-SANCHEZ, Leticia (Lawrence Berkeley National Laboratory); Prof. ABERGEL, Rebecca (University of California, Berkeley)

Presenter: Dr ARNEDO-SANCHEZ, Leticia (Lawrence Berkeley National Laboratory)

Contribution ID: **126** Type: **not specified**

Use of bone health agents (BHAs) in patients with metastatic castration-resistant prostate cancer (mCRPC) treated with radium-223 after abiraterone: An interim review of REASSURE

Background

When the radium-223 Phase III clinical trial (ALSYMPCA) was conducted, abiraterone was an investigational agent that was only available through clinical trials. REASSURE is a prospective, observational clinical study of radium-223 in patients with mCRPC with a 7-year follow-up (NCT02141438). Patients could have had anti-hormonal agents, such as abiraterone, prior to receiving radium-223. The objective of this interim review was to evaluate the fractures and symptomatic skeletal events (SSEs) based on prior abiraterone use and the use of BHAs, denosumab and bisphosphonates.

Methods

Descriptive statistics were generated for baseline characteristics, fractures, SSEs, and overall survival (OS) by BHA use in patients who had completed abiraterone treatment prior to receiving radium-223 (prior abiraterone) or who had no prior abiraterone (abiraterone-naïve). SSEs consisted of events reported as "musculoskeletal"adverse events (fracture, spinal cord compression, radiotherapy to bone, surgery, and SSE documented as a type of progression).

Results

As of November 2017, 1439 patients were enrolled, with a median follow-up time of 9.1 months. 720 (50%) patients had received BHAs prior to, concomitantly with, or after radium-223. 431 (30%) patients received prior abiraterone; 675 (47%) patients were considered abiraterone-naïve. For the prior-abiraterone group, median time of exposure to abiraterone was 11 months. The median time from diagnosis of CRPC to initiation of radium-223 was 9 months in abiraterone-naïve patients and 23 months in prior-abiraterone patients. In the prior-abiraterone group, SSEs occurred in 18% and 25% of patients with and without BHAs, respectively. In the abiraterone-naïve group, 19% of patients with BHAs and 20% of those without BHAs had SSEs. Fractures were reported in 10/431 patients (2%) in the prior-abiraterone group. In the abiraterone-naïve group, fractures were reported in 5/302 (2%) and 11/373 (3%) patients with and without BHAs, respectively. OS from the initiation of radium-223 initiation was 15.5 months in the abiraterone-naïve group and 11.3 months in the prior-abiraterone group.

Conclusion

Similar rates of fractures were observed in abiraterone-naïve patients and those who received abiraterone prior to radium-223. Patients with prior abiraterone treatment had a shorter OS, and these patients received radium-223 at a later time during their disease course, as reflected by a longer time from CRPC to radium-223 initiation.

Funding Agency

Bayer

Email Address

joe.osullivan@qub.ac.uk

Presentation Type

Poster

Primary author: Dr O'SULLIVAN, Joe M. (Center for Cancer Research and Cell Biology, Queen's University Belfast, Northern Ireland Cancer Center, Belfast City Hospital, Belfast, Northern Ireland)

Co-authors: Dr TOMBAL, Bertrand (Cliniques Universitaires Saint-Luc, Brussels, Belgium); Dr HIGANO, Celestia (University of Washington, Seattle, WA, USA); Dr LOGOTHETIS, Christopher (MD Anderson Cancer Center, Houston, TX, USA); Dr STERNBERG, Cora N. (Englander Institute for Precision Medicine, Weill Cornell, New York, New York, USA); Dr BOTTOMLEY, David (St. James's University Hospital, Leeds, UK); Dr SAAD, Fred (University of Montreal Hospital Center, Montreal, Quebec, Canada); Dr BAYH, Inga (Bayer AG, Wuppertal, Germany); Dr KALINOVSKY, Jan (Bayer Consumer Care AG, Basel, Switzerland); Dr BELLMUNT, Joaquim (Dana-Farber Cancer Institute, Boston, MA, USA); Dr LOGUE, John (The Christie NHS Foundation Trust, Manchester, UK); Dr SADE, Juan P. (Instituto Alexander Fleming, Buenos Aires, Argentina); Dr MILLER, Kurt (Charité Berlin, Berlin, Germany); Dr HARSHMAN, Lauren (Dana-Farber Cancer Institute, Boston, MA, USA); Dr SCHOSTAK, Martin (Department of Urology, University of Magdeburg, Magdeburg, Germany); Dr SARTOR, Oliver (Tulane University School of Medicine, New Orleans, LA, USA); Dr DIZDAREVIC, Sabina (Brighton & Sussex University Hospitals NHS Trust, Brighton, UK); BALDARI, Sergio (Nuclear Medicine Unit, University of Messina, Messina, Italy); RICHARDSON, Timothy (Wichita Urology, Wichita, KS, USA)

Presenter: Dr O'SULLIVAN, Joe M. (Center for Cancer Research and Cell Biology, Queen's University Belfast, Northern Ireland Cancer Center, Belfast City Hospital, Belfast, Northern Ireland)

Contribution ID: **127** Type: **not specified**

Activities of the Consortium for Medicine, Chemistry, and Physics at Osaka University

In the fall of 2015, the Graduate School of Science, Osaka University's Graduate School of Science, the Graduate School of Medicine, and the Center for Nuclear Physics cooperated to establish the project "Formation of an International Medical Center for Advanced Cancer Therapy by Medical Collaboration"as an estimate request project. Currently, one-third of cancer patients in Japan have so-called "advanced cancer,"which has invaded neighboring organs or undergone distant metastasis at the time of initial consultation. Its 5-year survival rate is less than 15%; therefore, new treatment methods need to be developed. In this context, radiopharmaceuticals are beginning to attract the limelight. A radiopharmaceutical is a medicine using a radionuclide (RI), and since it uses a beta-ray nuclide which is frequent from RI, there has been a problem of side effects being generated due to the influence on surrounding normal tissues. It appeared in nuclear medicine treatment using alpha-ray nuclides. Since α-rays have a range of about one cell in the body, they can be used to minimize radiation damage to normal organs and can be easily shielded against, eliminating the need for a special treatment room and enabling the use of treatment in regular hospitals. In 2016, in Japan, radium 233 (233RaCl, product name Zofigo) adapted to bone-metastasized prostate cancer was approved for the first time as a nuclear medicine remedy using alpha rays. This medicine is a radiopharmaceutical that can be administered on an outpatient basis.At Osaka University in Japan, the several medical collaboration project is being promoted to realize various advanced cancer treatments with drugs using α-ray nuclides. The option currently focused on the most is astatine 211 (211At).

211At is a short-lived nuclide that releases only α-rays with a half-life of 7.2 h, and it can be introduced into pharmaceutical molecules by covalent bonding since it is a halogen element. To date, studies have been undertaken to confirm the dynamics of 211At in the body of rats, to combine 211At with antibody drugs and virus-like particles used for cancer treatment, and with target compounds of amino acid transporters.All of these considerations can be carried out within the Osaka University Suita Campus. At the nuclear physics research center (RCNP) in the university, one of the leading accelerators in Japan is installed, so 211At can be efficiently manufactured. It is planned to be remodeled soon to be administered to people. In addition, it is close to the RI Center, which is a facility where purification and complexation of 211At can be performed, along with cell and animal experiments, as well as hospitals that can carry out clinical trials. It is a nuclear medicine remedy that is compliant with GMP manufacturing quality management regulations. Production planning is ongoing. It is expected that new medical innovations generated from such matching of science and medicine will lead to the development of drugs for dreams.

Email Address

kaba@chem.sci.osaka-u.ac.jp

Presentation Type

Poster

Primary author: Dr KABAYAMA, Kazuya (Department of Chemistry, Graduate School of Science, Osaka University)

Co-authors: Dr SHIMOYAMA, Atsushi (Department of Chemistry, Graduate School of Science, Osaka University); Prof. SHINOHARA, Atsushi (Institute for Radiation Sciences, Osaka Univeresity); Prof. TOYOSHIMA, Atsushi (Institute for Radiation Sciences, Osaka Univeresity); Dr KANEDA, Kazuko (Institute for Radiation Sciences, Osaka Univeresity); Prof. FUKASE, Koichi (Department of Chemistry, Graduate School of Science, Osaka University); Dr WATABE, Tadashi (Department of Nuclear Medicine, Graduate School of Medicine, Osaka University); Prof. YOSHIMURA, Takashi (Radioisotope Research Cencer, Osaka University); Dr SHIRAKAMI, Yoshifumi (Department of Nuclear Medicine, Graduate School of Medicine, Osaka University); Dr MANABE, Yoshiyuki (Department of Chemistry, Graduate School of Science, Osaka University); Dr ZHANG, Zijian (MS-CORE, Project Research Center, Graduate School of Science, Osaka University)

Presenter: Dr KABAYAMA, Kazuya (Department of Chemistry, Graduate School of Science, Osaka University)

Contribution ID: **128** Type: **not specified**

Radium-223 (Ra-223) therapy after abiraterone: analysis of symptomatic skeletal events (SSEs) in an international early access program (iEAP) in patients with metastatic castration-resistant prostate cancer (mCRPC)

Background

The Ra-223 Phase III study (ALSYMPCA) was conducted before abiraterone became available. The Ra-223 iEAP study included abiraterone-treated patients. Here we assessed SSEs, overall survival (OS) and bone health agent (BHA) use in Ra-223–treated patients who received abiraterone as a prior treatment.

Methods

This open-label, single-arm trial enrolled patients with bone-predominant mCRPC (≥2 bone metastases). Patients who received prior anti-cancer therapies were included; use of BHAs (bisphosphonates and denosumab) was permitted before/during the study. Median follow-up was 7.5 months. Baseline characteristics, SSEs, (external beam radiation therapy, symptomatic pathological fractures, spinal cord compression or surgical intervention) and OS were analyzed descriptively for patients who completed prior abiraterone therapy and abiraterone-naïve patients.

Results

Of 708 mCRPC patients, 85% of prior-abiraterone and 36% of abiraterone-naïve patients had previously received docetaxel. During Ra-223 therapy, 14% and 17% of patients received concomitant bisphosphonates and 20% and 17% concomitant denosumab in the prior-abiraterone and abiraterone-naïve groups, respectively. Median time since diagnosis of bone metastasis and start of Ra-223 was 37 and 21 months in the prior-abiraterone and abiraterone-naïve groups, respectively. Median PSA at baseline in the prior-abiraterone group was 290 µg/l and 100 µg/l in the abiraterone-naïve group. Median OS was 15.9 months overall (11.2 months for prior-abiraterone and 17.1 months for abiraterone-naïve patients). More patients had SSEs in the prior-abiraterone group (26%) than the abiraterone-naïve group (14%); incidence of pathological bone fractures was similar in both groups (5% for both).

Conclusions

Patients in the prior-abiraterone group had a longer time from diagnosis of bone metastasis to Ra-223 initiation. These patients seem to have more-advanced disease, as reflected by higher median baseline PSA and more patients with prior docetaxel therapy. Similar rates of pathological and non-pathological fractures were reported in Ra-223–treated patients regardless of prior use of abiraterone.

Acknowledgments
This study was funded by Bayer.

Funding Agency

Bayer Pharmaceuticals

Email Address

joe.osullivan@qub.ac.uk

Presentation Type

Poster

Primary author: Dr O'SULLIVAN, Joe M. (Centre for Cancer Research & Cell Biology, Queen's University Belfast, Belfast, Northern Ireland)

Co-authors: Dr HEIDENREICH, Axel (Urology, University Hospital Cologne, Cologne, Germany); Dr HEINRICH, Daniel (Oncology, Akershus University Hospital, Oslo, Norway); Dr SAAD, Fred (Urology, University of Montreal Hospital Center, Montreal, QC, Canada); KALINOVSKY, Jan (Medical Oncology, Bayer Consumer Care AG, Basel, Switzerland); Dr CARLES, Joan (Medical Oncology, Vall d'Hebron University Hospital, Barcelona, Spain); Dr MILLER, Kurt (Urology, Charité Berlin, Berlin, Germany); Dr WIRTH, Manfred (Urology, University Hospital Carl Gustav Carus, Dresden, Germany); Dr NILSSON, Sten (Oncology-Pathology, Karolinska University Hospital, Stockholm, Sweden)

Presenter: Dr O'SULLIVAN, Joe M. (Centre for Cancer Research & Cell Biology, Queen's University Belfast, Belfast, Northern Ireland)

Contribution ID: **129** Type: **not specified**

Development and non-clinical evaluation of an 111In/225Ac theranostic for triple negative breast cancer

Purpose: The purpose of this study was to develop an Indium-111/Actinium-225 based theragnostic utilizing the tMUC1 targeting humanized antibody, TAB004, and its evaluation in a tumor bearing rodent model.

Triple negative breast cancer (TNBC) is an aggressive phenotype that comprises only 15-20% of all new breast cancer cases but is responsible for a majority of related deaths. Chemotherapy is the current mainstay treatment for TNBC but side effects and drug-resistance remain an issue, so development of targeted therapies for TNBC is critical. Tumor associated Mucin 1 (tMUC1), an aberrantly glycosylated transmembrane glycoprotein, is overexpressed in >90% of TNBCs and as such is an attractive target. The humanized antibody hTAB004 shows high affinity and selectivity to tMUC1 and was thus used to develop a theranostic strategy for TNBC.

Method: hTAB004 was conjugated to DOTA-NHS, purified, formulated in a metal free buffer and radiolabeled with Indium-111 or Actinium-225 to produce 111In-DOTA-hTAB004 and 225Ac-DOTA-hTAB004, respectively. The radiolabeled molecule was evaluated for stability. Retention of affinity of cold-labeled molecules was validated.

In vivo and ex vivo biodistribution studies of 111In-DOTA-hTAB004 were performed in HCC70 orthotopic xenograft tumor-bearing female NSG mice (n=3) using SPECT/CT imaging over 120h. Dosimetry analysis was performed utilizing the in vivo data. Therapeutic efficacy of 225Ac-DOTA-hTAB004 was determined in HCC70 orthotopic xenograft tumor-bearing female nude mice (n=5/group) by monitoring bodyweights and tumor sizes over time.

Results: DOTA-hTAB004 was labeled successfully with both Indium-111 and Actinium-225. The radiolabeled molecules were found stable in both formulation and mouse serum and the non-radioactively labeled surrogates 115In-DOTA-hTAB004 and 139La-DOTA-hTAB004 retained their affinity to tMUC1.

In vivo biodistribution data revealed increased tumor accumulation of 111In-DOTA-hTAB004 over 120 h, reaching 65±15 percent of injected dose per gram (%ID/g). The next organs of significant uptake (Spleen 8.9±0.6 %ID/g and Liver 8.3±1 %ID/g) had a 7-fold lower uptake at 120 h. All mice treated with a single injection of 225Ac-DOTA-hTAB004 (500 nCi, 18 kBq) showed a complete response with tumor volumes shrinking by > 89% within 48 days. No therapy associated toxicities were seen in any of the mice outside of tail necrosis in one animal which may have been due to dose extravasation. All the control mice, which received the DOTA-hTAB004, showed continued tumor growth and had to be sacrificed by day 35.

Conclusions
111In-DOTA-hTAB004 biodistribution data indicates the excellent tumor targeting capabilities of hTAB004. 225Ac-DOTA-hTAB004 therapy data shows exceptional clinical benefit in mice bearing human tumors. Given this data, radiolabeled hTAB004 is a promising targeted treatment and imaging option for TNBC.

Email Address

oilovich@invicro.com

Presentation Type

Poster

Primary author: ILOVICH, Ohad (Invicro)

Co-authors: VIJAY, Gottumukkala (Invicro); MUKHERJEE, Pinku (OncoTab); Dr RAHUL, Puri (OncoTab); Dr COELHO, Rick (Invicro); Dr WU, Shu-ta (OncoTab); Dr KELLY, Vanessa (Invicro)

Presenter: ILOVICH, Ohad (Invicro)

Contribution ID: **130** Type: **not specified**

The strategic plans of SCK•CEN towards a routine production of 225Ac from 226Ra

With the steadily growing demand in alpha emitting radionuclides for cancer therapy, a project has been launched at the Belgian Nuclear Research Centre (SCK•CEN) aiming towards the routine production of 225Ac. In possession of a large stock of purified 226Ra from earlier activities (1), the goal of the project is to exploit the most efficient production route and implement it in the coming years on site. The envisaged nuclear reactions involve the direct 226Ra(p,2n)225Ac route using a cyclotron or the indirect reaction via 226Ra(γ,n)225Ra(β-)225Ac using Bremsstrahlung photons from an electron accelerator (2).

In order to be able to handle large activities of alpha emitters as well as the progeny of 226Ra, a sophisticated Rn trapping system will be implemented into an existing hot-cell, where Ci levels of 226Ra will be processed in the future. The radiochemical separation system has already been developed at tracer levels and tested for the separation of Ra/Ac and Ac/Pb, Bi and Po.

The handling of large quantities of radium in connection with the design of a suitable target for irradiation purposes are considered as the most demanding challenges of this project. We present a roadmap of the envisaged activities and give an overview on strategic partners involved in the 225Ac development program.

(1) Baetsle L.H., Dejonghe P., Demildt A.C.: Large scale production of 227Ac and development of an isotopic heat source fueled with 227Ac2O3, Proceedings of the 4th United Nations International Conference on the Peaceful Uses of Atomic Energy, Geneva (Switzerland), A/Conf.49/P/287, New York, 191-203 (1972).

(2) Pottier, J.: A new type of rf electron accelerator: the rhodotron, Nuclear Instruments and Methods in Physics Research Section B: Beam Interactions with Materials and Atoms 40-41, 943-945 (1989).

Email Address

stephan.heinitz@sckcen.be

Presentation Type

Contributed Oral

Primary author: HEINITZ, Stephan (Project leader)

Co-authors: ELEMA, Dennis (SCK-CEN); Mr MAERTENS, Dominic (SCK.CEN); MERMANS, Jasper (SCK-CEN); Prof. CARDINAELS, Thomas (SCK-CEN)

Presenter: HEINITZ, Stephan (Project leader)

Contribution ID: **131** Type: **not specified**

Ra-226/Ac-225 chemical separation R&D at SCK•CEN

The radiochemistry group of SCK•CEN possesses a purified Th-229 source since the beginning of 2017, routinely providing Ra-225, Ac-225, and Bi-213 tracers. This Th-229 had to be separated from long-lived Ac-227 and Ra-226 contaminants. The source originated from an Ac-227 production program in the 1970s, where highly radioactive Th-228 was co-produced by neutron capture of Ac-227 in the BR2 reactor when irradiating large Ra-226 targets. After 45 years in interim storage, the near-complete decay of Th-228 revealed the presence of useful quantities of Th-229, and Ra-226/Ac-227 impurities from the thorium separation process. SCK•CEN remained in possession of this large purified Ra-226 stock.

Easy access to significant quantities of Ac-225 and Ra-225 tracers had sparked interest and research in the field of Ra/Ac separation chemistry, mainly because cost-efficient large scale production of non-carrier added Ac-225 is conceivable using the strategic Ra-226 stock as the starting material. Protons, deuterons, neutrons, and photons can be used to produce Ac-225 using Ra-226 as a target material. Especially fast neutron and photon production pathways benefit from a large Ra-226 target mass.
Extraction chromatography experiments have been performed to identify a number of feasible separation and purification pathways to produce pure Ac-225 free from Ra-226 and its progeny (Pb, Bi, Po). Diglycolamide (DGA) and dialkylphosphoric acid (HDEHP) type solid phase extraction resins were tested as an approach to obtain high separation factors between Ra and Ac. Combining these two resin types was the key to efficient separation systems, as they work in the opposite acidity range. The choice of mineral acid (HNO3, HCl) influences the decontamination of Ac-225 from the progeny of Ra-226. The combination of a DGA or HDEHP resin with a U-TEVA and/or crown ether extraction resin was determined to be beneficial for removal of the progeny of Ra-226.

As a pre-purification step, precipitation in strong mineral acid (HNO3, HCl) can remove the vast majority of Ra-226 from the solution. Especially when large target masses are used, this process becomes advantageous. The choice of acid can be influenced by the irradiation target compound.

Ra-226 recycling throughout the process is necessary to avoid significant losses to the aqueous and solid waste. Decontamination of aqueous streams can be achieved by precipitation as RaSO4, or co-precipitation as Ba(Ra-226)SO4. RaSO4 can be converted to RaCO3, and re-dissolved in a mineral acid.
These separation experiments have offered a valuable insight into the Ra/Ac separation chemistry.

Email Address

dmaerten@sckcen.be

Presentation Type

Poster

Primary author: Mr MAERTENS, Dominic (SCK.CEN)

Co-authors: MERMANS, Jasper (SCKCEN); HEINITZ, Stephan (Project leader); Prof. CARDINAELS, Thomas (SCKCEN/KULeuven)

Presenter: HEINITZ, Stephan (Project leader)

Contribution ID: **132** Type: **not specified**

PRELIMINARY IN-VITRO STUDY OF 223Ra IMPACT ON SELECTED TISSUE AND TUMOR CELL LINES

Targeted alpha-particle therapy (TAT) is very rapidly evolving field of radionuclide therapy. Nevertheless, there are some severe issues that need to be addressed to enable TAT to be a leading modality in radionuclide therapy. The nuclear recoil effect that causes the daughter nuclei release from the original radiopharmaceuticals is critical for alpha emitters [1-2]. Moreover, targeting and proper dosimetry is still an issue [3]. Therefore, it is very important to understand the dosimetry both on cellular and subcellular level.

The first step of each dosimetric study is the determination of survival curves. For our preliminary study we used Ra-223 as a model alpha-emitting nuclide. Selected cell lines were V79 (Chinese hamster lung fibroblasts), DU145 (human adenocarcinoma cell line) and U87 (human primary glioblastoma cell line) obtained from American Type Culture Collection (ATCC). All cells were cultured in humidified atmosphere under standard conditions (37 ℃, 5 % CO2). Chines hamster cell line (V79) was cultured in Dulbecco's Modified Eagle's Medium (Sigma-Aldrich, Germany) supplemented with 10% of Fetal Bovine Serum South America Origin (Biosera, France) and 1% of Penicillin-Streptomycin (Biosera, France)). Human adenocarcinoma cell line (DU145) and human glioblastoma cell line (U87) were cultured in Eagle's minimum essential medium (Sigma-Aldrich, Germany) supplemented with 10% of Fetal Bovine Serum of South America Origin (Biosera, France), 1% of Penicillin-Streptomycin (Biosera, France)), 1 % of L-glutamine (Sigma-Aldrich, Germany), 1 % of Non-essential amino acids (Sigma-Aldrich, Germany) and 1 % of pyruvate (Sigma-Aldrich, Germany). All cell lines have been cultivated in the presence of Ra-223 for 24 hours after the monolayer of the cells was created. After the cultivation with Ra-223, the clonogenic survival test was performed and survival curves for all cell lines were constructed.

All obtained survival curves correspond to the linearly quadratic model. Sensitivity of both human carcinoma cell lines (adenocarcinoma and glioblastoma cell line) to Ra-223 treatment is higher than the sensitivity of Chinese hamster cell line. Preliminary results indicates higher radiosensitivity of DU145 and U87 against V79 cells. The achieved results enabled further progress in enhancing the dosimetric knowledge.

[1] Mokhodoeva, O.; Vlk, M.; Málková, E.; Kukleva, E.; Mičolová, P.; Štamberg, K.; Šlouf, M.; Dzhenloda, R.; Kozempel, J. Study of Ra-223 uptake mechanism by Fe3O4 nanoparticles: Towards new prospective theranostic SPIONs. Journal of Nanoparticle Research, 2016, 18(10), 301.

[2] Woodward, J.; Kennel, S.J.; Stuckey, A.; Osborne, D.; Wall, J.; Rondinone, A.J.; Standaert, R.F.; Mirzadeh, S. LaPO4 nanoparticles doped with actinium-225 that partially sequester daughter radionuclides. Bioconjugate chemistry, 2011, 22(4), 766-776.

[3] Kozempel, J.; Mokhodoeva, O.; Vlk, M. Progress in targeted alpha-particle therapy. What we learned about recoils release from in vivo generators. Molecules, 2018, 23(3), 581.

Funding Agency

Health Research Agency of the CR, No.: 16-30544A and Technological Agency of CR, No:TJ01000334.

Email Address

martin.vlk@fjfi.cvut.cz

Presentation Type

Poster

Primary author: Mr ONDRÁK, Lukas (Czech Technical University in Prague, Faculty of Nuclear Science and Physical Engineering, Department of Nuclear Chemistry, 115 19 Prague 1, Czech Republic)

Co-authors: Dr KOZEMPEL, Jan (Czech Technical University in Prague, Faculty of Nuclear Science and Physical Engineering, Department of Nuclear Chemistry, 115 19 Prague 1, Czech Republic); Ms VACHELOVA, Jana (Department of Radiation Dosimetry, Institute of Nuclear Physics of the CAS, 180 00 Prague 8, Czech Republic); Dr DAVIDKOVA, Marie (Department of Radiation Dosimetry, Institute of Nuclear Physics of the CAS, 180 00 Prague 8, Czech Republic); Dr VLK, Martin (Czech Technical University in Prague, Faculty of Nuclear Science and Physical Engineering, Department of Nuclear Chemistry, 115 19 Prague 1, Czech Republic)

Presenter: Dr VLK, Martin (Czech Technical University in Prague, Faculty of Nuclear Science and Physical Engineering, Department of Nuclear Chemistry, 115 19 Prague 1, Czech Republic)

Contribution ID: **133** Type: **not specified**

Production and Chemical Separation of No Carrier Added (nca) Lutetium-177.

Lutetium-177 dotatate gained FDA approval for use in certain neuroendocrine tumors, opening the door for research looking at other avenues of radiopharmaceutical use. With a half-life of 6.647 days and average \beta - particle range in soft tissue of ~670 μm, ^{177}Lu has promise for other therapy applications. Another benefit of ^{177}Lu is that it produces low energy gammas (113 keV, 208 keV), suitable for imaging purposes, allowing biodistribution and excretion kinetics to be monitored. Lutetium-177 can be produced as carrier added (ca) and no carrier added (nca) from enriched ^{177}Lu or ^{176}Yb, respectively by two production routes:
^{176}Lu(n,⊠)^{177}Lu,
^{176}Yb(n,⊠)^{177}Yb⟶β-^{177}Lu.
The later requires separation of Lu from the Yb target following irradiation. The ORNL High Flux Isotope Reactor (HFIR) with a max thermal neutron flux of 2.1x1015 n•cm-2 •s-1 (85 MW) is ideally suited to produce high specific activity ^{177}Lu. Separating nca ^{177}Lu is a complex process because it requires separating micro amounts of ^{177}Lu from macro amounts of ^{176}Yb and they are both part of the lanthanide series. The best method of separation will be tested from previous work to come up with a method that will cut down on waste, time, and improve the overall radio-purity of ^{177}Lu.

Funding Agency

Research sponsored by the U.S. Department of Energy, Office of Nuclear Physics, Isotope Program

Email Address

vbautista@tamu.edu

Presentation Type

Poster

Primary author: BAUTISTA, Victor (Texas A&M)

Co-authors: Dr DAME, Ashley (Oak Ridge National Labratory); Dr COPPING, Roy (Oak Ridge National Laboratory)

Presenter: BAUTISTA, Victor (Texas A&M)