The background features a complex, abstract graphic of molecular structures in shades of blue and teal. Several isotopes are highlighted with yellow wavy lines and labels:  $^{225}\text{Ac}$ ,  $^{89}\text{Zr}$ ,  $^{68}\text{Ga}$ ,  $^{177}\text{Lu}$ ,  $^{18}\text{F}$ , and  $^{99\text{m}}\text{Tc}$ .

# BOOK OF ABSTRACTS: INTERNATIONAL SYMPOSIUM ON TRENDS IN RADIOPHARMACEUTICALS

#ISTR2023

IAEA Headquarters  
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17 – 21 April 2023



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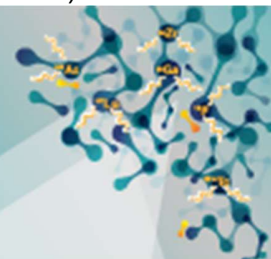
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# INTERNATIONAL SYMPOSIUM ON TRENDS IN RADIOPHARMACEUTICALS

#ISTR2023

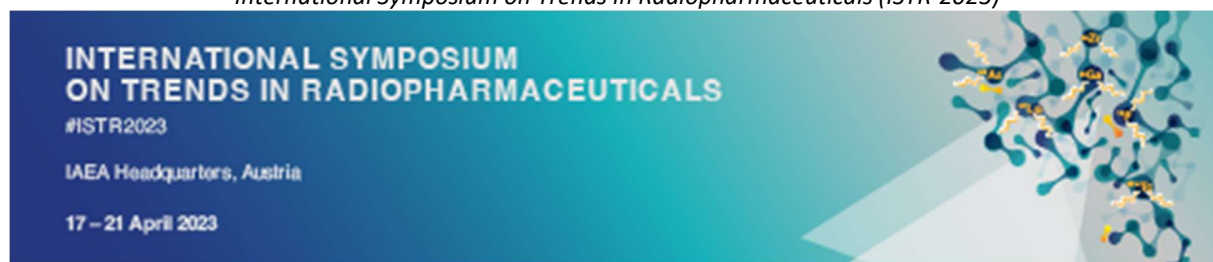
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*International Symposium on Trends in Radiopharmaceuticals (ISTR-2023)*



## **BOOK OF ABSTRACTS**

**IAEA-CN-310**

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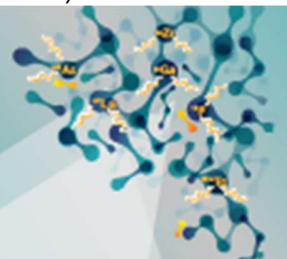
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INTERNATIONAL SYMPOSIUM  
ON TRENDS IN RADIOPHARMACEUTICALS

#ISTR2023

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IAEA-CN-310/2

## Development of [<sup>153</sup>Sm-DOTA-Bevacizumab for Radio Targeted Therapy in Rat Model (SW480 Cell Line)

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Combining beta particle effect with therapeutic properties of bevacizumab as a monoclonal antibody in colorectal cancer was the aim of this study.

The Avastin (Bevacizumab) was labeled with [<sup>153</sup>Sm]- Chloride after conjugation with DOTA. Conjugated bevacizumab obtained by the addition of 1 mL of bevacizumab pharmaceutical solution (5mg/mL in phosphate buffer, pH 7.1) to glass tube precoated with freshly prepared DOTA (0.01-0.1mg) at room temperature. <sup>153</sup>SmCl<sub>3</sub> was obtained using a thermal neutron flux ( $5 \times 10^{13} \text{ n.cm}^{-2} \cdot \text{s}^{-1}$ ) of an enriched <sup>153</sup>Sm<sub>2</sub>O<sub>3</sub> sample dissolved in acidic media. Radiolabeling was performed in one hour by the addition of DOTA conjugated Bevacizumab at room temperature.

Radiochemical purity of 97% (ITLC) and 98%(HPLC) were obtained for the final radiopharmaceutical (specific activity = 120 TBequerel/mmol). The final isotonic <sup>153</sup>Sm-Bevacizumab complex checked by gel electrophoresis for protein integrity retention. Biodistribution studies in normal and tumoral rats were performed to determine radioimmunoconjugate distribution up to 72 hours. Images were also obtained using gamma camera taking advantage of 103 KeV photon up to 36 hours.

The accumulation of the radiolabeled antibody in liver, spleen, kidney, bone, and other tissues demonstrates a similar pattern to the other radiolabeled anti-VEGF immunoconjugates. <sup>153</sup>Sm-DOTA-bevacizumab has potential for diagnosis and treatment studies and follow-up of VEGF expression in oncology.



**IAEA-CN-310/3**

**Critical Organ Dose Estimation from Tc-99m-MIBI in Nuclear Medicine Cardiology Based on Distribution Data in Rats**

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Calculating the organs dose in nuclear medicine scan is essential in order to identify critical organs. The radiation risk estimation and optimization of radiopharmaceutical injection and dose is necessary. In this study, the biological distribution of  $^{99}\text{Tc}$ -MIBI as the most common radiopharmaceutical in cardiac study in human organs based on animal samples was investigated.

After  $^{99}\text{Tc}$ -MIBI preparation, the complex was injected into 15 Rats intravenously. After killing the Rats, the organs uptake at 15, 30 and 45 minutes was measured using HPGE detector and the percentage of injected dose per gram of organs was calculated. Cumulative activity was calculated from the radiopharmaceutical decay diagram with time. absorption of radioactive complex in human organs based on animal data was calculated by applying a correction factor. Organs dose was calculated using S factor and the effective dose was calculated using tissue weight coefficients.

The effective dose mean per unit of activity was 0.0062 mSv/MBq and effective dose mean of total injected activity (27.5 mcg) was 6.3 mSv. In this study, blood uptake was 0.28, heart 2.92, lung 1.85, thyroid 24.82, liver 11.13, spleen 7.03, 20.95, stomach wall 1.11, muscle 4.97 and bone 22.22 mGy was calculated.

The effective dose of human organs based on the animal model was evaluated by injection of  $^{99}\text{Tc}$ -MIBI. The kidneys, salivary glands, thyroid and spleen were the most critical organs that should be considered in dose optimization studies. The effective dose limit was 28% lower than values reported in international references.





**IAEA-CN-310/4**

**Gamma-Ray Attenuation Characteristics of Some Essential Amino Acids for  $^{57}\text{Co}$ ,  $^{192}\text{Ir}$ ,  $^{18}\text{F}$  and  $^{116}\text{mIn}$  Sources**

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In different tissues of the body, proteins are important parts that are made up of building blocks called amino acids. Considering the wide applications of radioactive sources in industry and medicine, the need to study the attenuation characteristics of amino acids is determined.

To study the attenuation characteristics of the amino acids, linear and mass attenuation coefficients, half and tenth value layers, mean free path, effective atomic and electronic cross sections, effective atomic numbers and effective electron densities of five types of amino acids were calculated for  $^{57}\text{Co}$ ,  $^{192}\text{Ir}$ ,  $^{18}\text{F}$  and  $^{116}\text{mIn}$  sources using MCNPX Monte Carlo code and XMuDat program. In order to validate the theoretical results, the obtained values were compared with the available experimental data.

The difference between the theoretical and experimental results was less than 11%. The results showed that with increasing photon energy, the linear and mass attenuation coefficients and effective atomic and electronic cross sections decreased, while the half and tenth value layers and mean free path quantities increased. Furthermore, the linear attenuation coefficients, the effective atomic and electronic cross sections, as well as the effective atomic number values increased with increasing amino acid density, while the effective electron density behaves independently of the amino acid density.

The presented theoretical methods produced data similar to experimental results with fair accuracy, so by using this methods, attenuation properties of other amino acids can be obtained over a wide range of energies.



**IAEA-CN-310/5**

**Specific Activity Retrospective Analysis of Lu-177(C.A.) Locally Produced and Comparative Requirements for <sup>177</sup>Lu-DOTA-Peptides Preparation**

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Comision Nacional de Energia Atomica (CNEA), Centro Atomico Constituyentes (CAC), Av. Gral. Paz 1499 - B1650 Villa Maipú, Buenos Aires, Argentina

The aim of the present work were to do a retrospective analysis of Specific activity Lu-177 (c.a.) locally produced in the neutron trap of the RA-3 Research Reactor. Lu-177 (c.a.) specific activity (S.A.) theoretical calculations were made taking into account Lu-176 target burn up, thermal and epithermal neutron flux and the Lu-177 decay to Hf-177. After the analysis of 74 irradiated Lu-176 targets of 39.6, 82.2 and 86.8 % enrichment, at 3.16, and 3.54 days per irradiation cycle, an average neutron flux value was calculated for the irradiation position G4 of the RA-3. Based on the obtained theoretical neutron flux of  $2.39 \pm 0.35$  n/cm<sup>2</sup>\*s and even using a 74.5 % Lu-176 commercially available enriched target, it is possible to obtain a Lu-177 S.A. of 16.81 mCi/μg at End of Bombardment (EOB) after 2 irradiation cycles of 4.5 days per week. Iron impurities were determined by RX Fluorescence and were similar to commercial Lu-177 radiopharmaceutical precursor.

Reducing the fractionation and labelling time and iron contamination, it is possible to prepare <sup>177</sup>Lu-DOTA-peptides with approximately S.A. for clinical applications using Lu-177 (c.a.) locally produced after 2 irradiation cycles at 2.5 d post EOB.



**IAEA-CN-310/6**

### **Alpha-Beta-Targeted Therapy**

Luciana Magalhães Rebelo Alencar, Aline Oliveira da Silva de Barros, Martha Sahylí Ortega Pijeira, Ralph Santos-Oliveira

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Alpha and Beta particulate radiation are used to non-treated neoplasia due to their ability to reach and remain in tumor sites. Radium-223 ( $^{223}\text{Ra}$ ), an alpha emitter, promotes localized cytotoxic effects while radioactive gold ( $^{198}\text{Au}$ ), beta-type energy, reduces radiation in surrounding tissues. Nanotechnology, including several radioactive nanoparticles, can be safely and effectively used in cancer treatment. In this context, this study aims to analyze the antitumoral effects of [ $^{223}\text{Ra}$ ]Ranomicelles co-loaded with radioactive gold nanoparticles ([ $^{198}\text{Au}$ ]AuNPs). To this, we synthesize and characterize nanomicelles, analyzing some parameters such as particle size, radioactivity emission, dynamic light scattering, and microscopic atomic force. [ $^{223}\text{Ra}$ ]Ranomicelles co-loaded with [ $^{198}\text{Au}$ ]AuNPs, with simultaneous alpha and beta emission, showed no instability, mean particle size of 296 nm, and a PDI of 0.201 ( $\pm$  0.096). Furthermore, nanomicelles were tested in an in vitro cytotoxicity assay. We observed a significant increase in tumor cell death using combining alpha and beta therapy in the same formulation compared to these components used alone. Together, these results show, for the first time, an efficient association between alpha and beta therapies that could become a promising tool in the control of tumor progression.



**IAEA-CN-310/7**

## **Radiopharmaceutical Production in Hashemite Kingdom of Jordan**

Ala' Khwaj, Abdullah Abu orouq

Radioisotopes production in Hashemite Kingdom of Jordan, King Hussein Medical Centre, P.O.Box 830397, King Abdulla II street, Amman, Jordan

The production of radioisotopes in HKJ began in 2004 at JRMS1 in the Nuclear Medicine and Cyclotron Center/ in KHMC2 by producing  $^{18}\text{F}$ -FDG, using 11-Mev Eclipse cyclotron.

At that time, there was only one PET3 scan in Jordan which located in KHMC.

Then new Cyclotron center was then built in the private sector in 2013.

Nowadaysthere are 9 PETs working in Jordan, and some others under construction.

In 2010 HKJ decided to enter the nuclear world via establishing a nuclear reactor for research & training purposes.

Its main object was to build a man power that can operate the nuclear power plant for producing electricity, training the nuclear engineering students, researches, and Radioisotopes production for medical and industrial uses. For all these purposes the Jordan Research & Training Reactor (JRTR) was born.

The Jordan Research & Training Reactor (JRTR) is a part of the Jordanian nuclear program that has been realized as the first nuclear critical facility. It is located in the north of Hashemite Kingdom of Jordan (HKJ), in the campus of Jordan Science & Technology University (JUST), 70 km far north of the Jordan capital city Amman.

It was built in collaboration with Korean Atomic Energy & Research Institute (KAERI) and Daewoo Engineering (KDC) Consortium, as advanced model of open pool type reactor, and considered to be the safest research reactor model. The project construction started in 2010 and finished in 2016.

JRTR got the operation license from the Jordanian regulatory Authority; Energy & Minerals Regulatory Commission (EMRC), in 2017 to operate and produce ( $^{131}\text{I}$ ,  $^{99\text{m}}\text{Mo}$ , and  $^{192}\text{Ir}$ ).

In December 2018 we produced the first sample product of  $^{131}\text{I}$ , and distributed to all NM centers in Jordan after subjected to the all quality control tests according to the EuPh4.

In our future vision and plan for the radiopharmacy field, we look forward to produce more radioisotopes either in JRMS or in the JRTR, and to control all nuclear lab (hot lab) in Jordan, as an unique specialists in our country to control the usage of nuclear materials in medicine and to give this material the pharmaceutical status under the JFDA5 rules.



IAEA-CN-310/10

## **In-vivo Therapeutic Efficacy of Samarium-153 Oxide Loaded Polystyrene Microspheres in Liver Tumour-Bearing Rats**

Hun Yee Tan

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The therapeutic efficacy of samarium-153 oxide loaded polystyrene ( $[^{153}\text{Sm}]\text{Sm}_2\text{O}_3\text{-PS}$ ) microspheres, a nuclear research reactor produced radiopharmaceutical had been investigated on Sprague-Dawley (SD) rats, each bearing a liver tumour after intra-tumoural injection.

Twelve male SD rats (150 – 200 g) that implanted with N1-S1 hepatoma cell line orthotopically were divided into two groups (Group 1 – treatment group and Group 2 – control group) to monitor the tumour size after 60 days of treatment. Group 1 received an intra-tumoural injection of approximately 37 MBq  $[^{153}\text{Sm}]\text{Sm}_2\text{O}_3\text{-PS}$  microspheres, while Group 2 received an intra-tumoural injection of 0.1 mL saline solution. Group 3 is a healthy group comprised of 6 rats without liver tumour and any surgical procedures. The rats were subjected to static gamma imaging at Day 1, Day 2, Day 3, and Day 7 post-injection using a compact gamma camera to assess the diagnostic imaging capabilities of the radioactive microspheres. Clinical single photon emission computed tomography/computed tomography (SPECT/CT) system was used to scan the rats at Day 5 post-injection to obtain functional and anatomical images.

At Day 60, no tumour was observed on the ultrasound images of all rats in the treatment group. In contrast, the tumour sizes in the control group were 24-fold larger at the end of the study. Statistically significant difference was observed in the tumour sizes between the treatment and control groups ( $p < 0.05$ ). Static gamma images clearly showed the accumulation of  $^{153}\text{Sm}$  radioactivity in the liver tumour at Day 1 with no significant leakage of the microspheres up to Day 7 (nearly after 4 half-lives) post-injection. The SPECT/CT images similarly displayed a high uptake of  $^{153}\text{Sm}$  radioactivity in the liver tumour at Day 5 post-injection for treatment group. Additionally, the injection site of the  $[^{153}\text{Sm}]\text{Sm}_2\text{O}_3\text{-PS}$  microspheres was visible on the CT images and this has added to the benefit of  $^{153}\text{Sm}$  as a CT contrast agent.

Neutron-activated  $[^{153}\text{Sm}]\text{Sm}_2\text{O}_3\text{-PS}$  microspheres were effectively suppressed the growth of liver tumours in the SD rats and demonstrated excellent diagnostic imaging capabilities. The location of the microspheres in the liver tumour can be clearly visualized on SPECT and CT images, respectively.



**AEA-CN-310/11**

## **Radiopharmaceuticals and Their Applications: Role of Pharmacists as Community Educators**

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It is of great importance for pharmacy graduate to have good knowledge in the field of radiology and nuclear medicine. In the case of the absence of these topics in the basic curriculum, the design of suitable elective courses can close the knowledge gap. Teaching “Pharmaceutical Radioisotopes” for pharmacy students have two major outcomes. First outcome: directing pharmacy graduates to new research areas related to the production of radiopharmaceuticals making use of their strong chemistry background, in this case; new job opportunities will be available for pharmacy graduates. The second outcome is related to the role of the pharmacist as community health educator. Pharmacist with good background about radiation and radioisotopes can give advice and increase the awareness of patients and the public about the different applications of radiation and radioisotopes and more important, about the related safety precautions. This presentation will discuss mainly the second outcome.





**IAEA-CN-310/12**

## **Regulatory Harmonization Between Different Authorities Involved in the Radiopharmaceutical Production: Essential Action and a Challenge to Face**

Ramón Hernández Alvarez

Office for Environment and Safety Regulation, Nuclear Safety Division, Cuba.

Radiopharmaceuticals contains both: a drug and a radionuclide, and this distinctiveness can be very challenging from a regulatory point of view. As a consequence, the preparation of radiopharmaceuticals for injection implies compliance with the regulations on radiological protection, as well as the corresponding work standards in aseptic conditions (GMP). The production of radiopharmaceuticals encompasses several aspects that can be a great challenge for manufacturers. These include: the operation and maintenance of processing facilities, compliance with current codes of good manufacturing practice, the need to ensure effective quality assurance and control systems, compliance with radiological safety requirements, transportation of radioactive materials, obtaining the health registration from the corresponding health authorities, as well as regulatory control by the authorities involved. Generally, the regulatory authorities are more than one, which can lead to the appearance of certain problems in the regulatory framework, such as legal dispersion, ambiguity, overlaps, excessive bureaucratic burden for those regulated, among others. This paper presents an overview of the issues listed above and also aims to share key lessons learned on how to deal with them in order to obtain better harmonization between the regulatory authorities involved.



**IAEA-CN-310/13**

## **Regulatory Status for Radiopharmaceuticals in Ethiopia**

Seble Shambel Enyew, Yohannes Jorge LAGEBO

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According to the National Health Policy, Ethiopia's health sector is organized into three pillars: Service provider, Service purchaser and Health regulator. In addition, based on the mandate given by Proclamation no. 1112/2019 Food and Medicine Administration is mandated to regulate safety and quality of Food; safety, quality and performance of Medical Devices; safety, efficacy, quality and proper use of Medicines; competence and ethics of health professionals and standards of health institution. As part of medicines, regulation of radiopharmaceuticals is clearly stipulated in: National drug policy of 1993, Proclamation No. 1112/2019, Regulation No.299/2013 and Comprehensive Specialized Hospital National Minimum Standards (2013). Hence, Proclamation No. 1112/2019 [Art 2(13)] defines radiopharmaceuticals as "medicine which has one or more radionuclide substance used in the diagnosis and treatment of human disease and includes non-radioactive reagent kit used for a preparation of medicine and radionuclide generator". Moreover, on different articles of Proclamation No. 1112/2019 and Regulation No. 299/2013 enlightenment was given on manufacture, import, export, wholesale or store of radiopharmaceuticals, extemporaneous preparation of a radiopharmaceutical as well as market authorization of radiopharmaceuticals up on ensuring safety, efficacy and quality. Proclamation No 1112/2019 and Regulation no. 299/2013 also stated on the packaging, transportation, storage and distribution of radiopharmaceuticals shall be in such a manner that minimizes danger to the life of human being, animals and the environment. It was also highlighted that the safety, efficacy and quality of radiopharmaceuticals will be regulated by Medicine regulatory authority (Ethiopian Food and Drug Authority (EFDA) whereas, the radiation safety of the patient, workers and public and buildings & design for radiotherapy unit should be regulated by Ethiopian radiation protection authority (ERPA). Moreover, the Healthcare facility minimum national standards on different sections stated about Radiopharmacy and Nuclear medicine services: Oncology services [Section six: 6.3], Nuclear medicine services [Section six: 6.4], Radiopharmacy Services and Radiology services [Section six: 6.5]. Currently there are three nuclear medicine centers operating in Ethiopia with adequate facilities and appropriately trained personnel that provides radiopharmacy and nuclear medicine services. In addition, there are five new public facilities for nuclear medicine and radiopharmacy service which are in various stages of development and expansion. The national cancer centre at Black lion hospital is providing radiation therapy and chemotherapy treatment sessions for cancer patients. The safety standards of radiation are in accordance with International Atomic Energy Agency (IAEA) standards and buildings and rooming styles for radiotherapy is



accordance with Ethiopian radiation protection authority (ERPA) standards. Thus, following finalization of construction and renovation of radiopharmacy section, newer instruments such as SPECT/CTs, SPECT, Radio-HPLC, TLC-Scanner, handheld gamma camera system for intra-operative imaging, freeze dryers, Detection Device Gamma Supp II, dose calibrators, laminar air flow cabinets, radiochromatogram scanners, gamma spectrometer are being installed. In addition, various equipment for production and QC of radiopharmaceuticals such as fume hoods, modern dose calibrators, sterile Tc-99m generator and elution system, radiopharmaceuticals processing system(set-up) large lead shielded storage box and, SPECT/CT dedicated for breast imaging are available at radiopharmacy facilities The national nuclear medicine and Radiopharmacy expansion program is under the direct follow up of the central government which is chaired by the State minister of the Federal Ministry of Health (FMOH) and is under follow up of First Lady of Ethiopia. The regulation of nuclear medicine and radiopharmacy service is designed in the 4Ps (Practice, Premises, Professionals and Products). Although regulation of radiopharmaceuticals is stated in different legislations such as National drug policy, Proclamation No. 1112/2019, Regulation 299/2013, there are many challenges on its implementation to improve the quality of radiopharmacy and nuclear medicine services. The challenges are stated below:

- Radiopharmaceuticals are a unique kind of pharmaceutical products that need special expertise and training.
- Inadequate collaboration between medicine regulatory authorities and radiation protection authorities specially in developing countries.
- Inadequate regulatory legislation for radiopharmaceuticals in developing countries on: Dossier assessment, Good Manufacturing Practice (cGMP) and Quality specifications.
- Inadequate capacity of radiopharmaceutical regulators for: cGMP inspection, Dossiers Assessment, inspections and audits on radiopharmaceutical preparations.
- Most developing countries do not have radiopharmaceuticals manufacturer and products are imported from abroad.



**IAEA-CN-310/14**

### **A New Production Route of Zirconium-89 Radiopharmaceuticals for PET Imaging with Cyclone-30 Cyclotron**

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In this study, a simple and efficient method for producing Zirconium-89 ( $^{89}\text{Zr}$ ) with high radiochemical and radionuclide purity was developed. A novel procedure for producing a new targetry for Cyclone-30 cyclotron was introduced. The procedure was to include the preparation of a highly pure compressed yttrium oxide target material, design of a target made by copper for better heat transfer, electrodeposition of target with gold to prevent the entry of impurities, evaluation of the nuclear reaction cross sections for optimization of production with new target, irradiation of the target, and radiochemical purification of  $^{89}\text{Zr}$  from the target. The purified  $^{89}\text{Zr}$  in the form of  $[\text{}^{89}\text{Zr}] \text{Zr-Oxalate}$  had a high radionuclide purity (>99.9%) and a low chemical impurity concentration (<0.5 ppm).



**IAEA-CN-310/15**

## **Preparation and Biological Evaluation of $^{68}\text{Ga}$ -WSSF-DOTA-Bombesine Nanoparticle**

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By 2050, cancer incidence is expected to reach about 27 million worldwide. Cancer nanotechnology would play an important role in changing the current treatment systems by providing more efficient cancer diagnostics and therapeutics. Nowadays, nanocarriers already play a vital role in the early detection of cancer and delivering anticancer drugs. Engineered nano-constructs can serve as targeted drug delivery vehicles capable of delivering high radionuclide doses into cancer tissues while sparing normal tissues and reducing the side-effects. Emerging new methods improve the specific uptake of radionuclides in tumor cells while sparing the normal tissues. Several advanced strategies for radionuclides delivery have been studied extensively for the development of novel multimodality and multifunctional therapeutics. The presented research is designed to synthesize  $^{68}\text{Ga}$ -Water Soluble Silk Fibroin-DOTA-Bombesine ( $^{68}\text{Ga}$ -WSSF-DOTA-Bombesine) as a novel, smart drug delivery system with target-specific recognition, potentially useful in tumor imaging. Radiosynthesis of  $^{68}\text{Ga}$ -WSSF-DOTA-Bombesine: 0.1mg of WSSF-DOTA-Bombesin dissolved in 50 $\mu\text{l}$  H<sub>2</sub>O, 200 $\mu\text{l}$  of Ga-68 solution (0.05M HCl) = 700 $\mu\text{Ci}$ , 100 $\mu\text{l}$  of ammonium acetate 0.25M, PH=4.4, Allow to react for 30 min at 90°C, then TLC and HPLC analysis TLC system: Na Citrate with PH=8.5. HPLC system: HPLC analyses were carried out on semi-preparative Phenomenex C-18 (250 mm x 10 mm). Radiolabeled product was detected using the 0.065%TFA in 100%water (v/v) [C] and 0.05%TFA in 100% MeCN(v/v) [D] system at 2 ml/min, wavelength was 220nm, Pump system; was 0-15 min 0% [C], 100% [D], 15-30min 100% [C], 0% [D]. The biodistribution of  $^{68}\text{Ga}$ -WSSF-DOTA-Bombesine was investigated in 12 male mice (3 animals per group). The first group was the control group injected with saline (200  $\mu\text{l}$ ), the other three groups; each animal was injected with 100  $\mu\text{l}$  saline contains average of 70  $\mu\text{Ci}$  of  $^{68}\text{Ga}$ -WSSF-DOTA-Bombesine at the time of injection. The time points were 30 min, 60 min and 120 min.  $^{68}\text{Ga}$ -WSSF-DOTA-Bombesine is rapidly cleared from the circulation and its biodistribution changes very slowly (in most organs > 50% of the activity disappeared after 1 hour of injection). However, it looks like, clearance from the tissues can be considered as the physical decay of  $^{68}\text{Ga}$  (half-life = 68 min). Only in the liver and intestine where the activity accumulated during the first hour and no much accumulation in the brain is noted. Noticeably high uptake of  $^{68}\text{Ga}$ -WSSF-DOTA-Bombesine in blood, lung, kidney, intestine, heart, muscle and thyroid, especially on the 30 min time point. Only on the blood, lung and heart we see an accumulated uptake of  $^{68}\text{Ga}$ -WSSF-DOTA-Bombesine on the time point. >50% of the injected dose was cleared from the body after 1 hour and after 2 hours 92% were cleared. About 60% of the remaining activity on the one hour time point was concentrated in the liver, lung, kidney and intestine. This research succeeded to synthesize  $^{68}\text{Ga}$ -WSSF-DOTA-Bombesine Nanoparticle as a novel, smart drug delivery system with target-specific recognition, potentially useful in tumor imaging. Radiolabeling of WSSF-DOTA-Bombesin compound with Ga-68 was done then analysis by TLC and HPLC. The radiochemical purity was  $96 \pm 2\%$ , determined by ITLC.  $^{68}\text{Ga}$ -WSSF-DOTA-Bombesine NP was prepared as specific targeting and its biological evaluation in normal mice was successfully done. The authors would like to acknowledge Prof. Wanvimol Pasanphan, Kasetsart University, THAILAND, for supporting us WSSF-DOTA-Bombesine Nanoparticle and IAEA for funding this work under CRP "Nanosized delivery systems for radiopharmaceuticals".



IAEA-CN-310/17

### **Computational Study and Preclinical Evaluation of a Novel Radiosynthesized $^{47}\text{Sc}$ -Dipeptide Derivative as a Promising Cancer Theranostic Agent**

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During past decades, a great interest has been paid for the development of new radiopharmaceuticals which have high selectivity to tumor cells versus the healthy ones. Peptides are molecules of paramount importance in the fields of health care and nutrition. Several technologies for their production are now available, among which chemical and enzymatic synthesis are especially relevant. Scandium-47 labeled with a suitable ligand is a potential radiopharmaceutical. Thus, this study introduces an innovative synthesized acyclic dipeptide molecule radiolabeled with Sc-47 as a novel potential cancer theranostic agent. The experimental conditions, such as dipeptide amount, pH, time of reaction and temperature were optimized to achieve high complexation efficiency of 90% and in-vitro serum stability up to 48h. Computational tools were employed to predict the most stable structure of  $^{47}\text{Sc}$ -dipeptide complex based on the highest binding energy. This computational analysis followed by simulation the binding mode for the stable complexes with the target protein. Moreover, the  $^{47}\text{Sc}$ -dipeptide complex was investigated in tumor bearing mice and high tumor/tissue ratio was obtained. Our finding clearly suggests  $^{47}\text{Sc}$ -dipeptide complex as a potential agent, which can pave theranostics approach in personalized targeted radiotherapy to compensate different cancer types.





**IAEA-CN-310/18**

### **Sustainable Raw Material Supply Chains for Radiopharmaceutical Cancer Treatment by Extraction of Ra-226 from Phosphogypsum**

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Radium-226 (Ra-226) is among the most sought-after naturally occurring radioactive raw materials to produce radiopharmaceuticals utilized for medical diagnostic and therapeutic applications. Yet there is no conclusive raw material supply chain for Ra-226, resulting in about 50,000 current cancer patients going untreated in the USA alone.

The main challenge of the Ra-226 supply chain is the lack of suitable raw materials for radiopharmaceutical suppliers. Possible sources include electronic instruments, recovered bearing coatings, lightning rods, uranium mining tailings, and phosphogypsum (PG) tailings as waste material from phosphate fertilizer production. The known U.S. demand is currently about 10 Ci per annum. However, it is expected to multiply when including patients from outside the USA. Recent research (e.g. EIT RawMaterials-funded project raPHOSafe) showed that PG tailings in Serbia, Bulgaria, Morocco, and Spain are potential sustainable sources, with typical activities of about 1Bq/g depending on the region. Preliminary estimates yielded that a recovery of 50 Ci would require the processing of a 100x100x100m PG volume, which at first glance may not seem cost-effective (assuming 70 - 92% extraction efficiency). Nonetheless, this business case changes significantly when adding important by-products such as gypsum recycling, REE and P (critical raw materials) from PG, and valorizing benefits from ESG-compliant land rehabilitation. A plausible and cost-effective solution would utilize large-scale, automated sorting and processing facilities for effective recovery of Ra-226 which are readily commercially available.



**IAEA-CN-310/19**

**Development and Initial Evaluation of Two <sup>99m</sup>Tc Two Complexes Derived from a Fibroblast Activating Protein (FAP) Inhibitor**

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Tumor microenvironment plays an important role in cancer. Fibroblast activation protein- $\alpha$  (FAP) is a cell-surface serine protease highly upregulated in a wide variety of cancers and therefore constitutes a promising target for the development of potential radiopharmaceuticals.

Objective: The design and development of two <sup>99m</sup>Tc complexes derived from linagliptin, a FAP inhibitor, as potential oncological radiopharmaceuticals.

Two ligands bearing the structure of linagliptin and adequate chelators to coordinate Tc through the formation of a Tc (I) tricarbonyl complex (C1) and a symmetric Tc(V)-nitrido complex (C2) were synthesized and labelled with <sup>99m</sup>Tc. Labelling conditions were optimized and physicochemical studies such as stability, lipophilicity and protein binding were performed

In vitro biological evaluation will be performed using PC3 prostate cancer cells transfected with a human FAP CMV promoter driven expression vector (Acc. BC026250). Uptake, internalisation, efflux and competition studies will be performed.

The labelling strategies rendered the desired <sup>99m</sup>Tc complexes with high radiochemical purity. Both complexes showed high stability in labeling milieu and in human serum for at least 4 hours. Lipophilicity expressed as log P was  $1.02 \pm 0.10$  for C1 and  $0.95 \pm 0.15$  for C2. The complexes had a protein binding of  $17.88 \pm 3.36$  % and  $60.82 \pm 6.44$  % respectively.

Two linagliptin derivative complexes were obtained as potential radiopharmaceuticals for targeting FAP. The products have a high RP and good stability. Physicochemical properties are adequate. In vitro affinity studies will be performed.



**IAEA-CN-310/20**

## **Africa's Next Radiopharmacists- Ways Forward for Education and Career Opportunities**

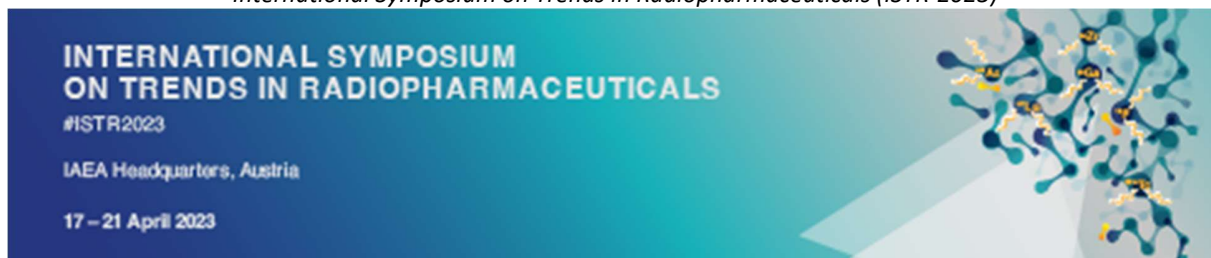
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Africa currently has the highest rates of population growth and studies by the United Nations predict that by the year 2050, a quarter of the world's population will be African (United Nations, 2015). A similar kind of growth however is yet to be seen in the health systems especially as regards the development of special-yet-essential skilled human resources like radio-pharmacists, nuclear medicine and nuclear professionals at large. This is even a bigger problem in Uganda where currently only a single nuclear medicine center is in operation in the capital and no education or training programmes for future radio-pharmacists exist in the country.

There is generally high levels of ignorance about nuclear energy and its application in fields like medicine. It is even doubtful that all university students in scientific and medical fields understand what radio-pharmacy is and its importance. Radio-pharmacy has not been presented to the next generation as a career path option. In addition, there is a widespread misconception in many African countries that nuclear energy is only used for nuclear bombs hence many young Africans have no interest in engaging due to this misinformation.

Nuclear medicine diagnosis and therapy has also not been largely integrated into the medicine and health care sector in many African countries which demotivates many young people from studying radio-pharmacy and other nuclear related courses because there are limited career opportunities. The paper and presentation thereof will examine the level of awareness of, and access to education and career opportunities in the field of radio-pharmacy for young people in Uganda and suggest recommendations towards enhancing the levels of awareness, improving services and attracting young people to the field. It will provide insights for the nurturing of a strong next generation of radio-pharmacists for the African continent.



## IAEA-CN-310/21

### **Effective separation of radiotheranostic $^{47}\text{Sc}$ from natural Ti target using Dowex 50 WX8 cationic exchanger**

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Carrier-free Scandium-47 ( $t_{1/2} = 3.35$  d) is a potential theranostic radioisotope for radiopharmaceutical development. The goal of this research is to employ a commercial cationic exchanger; Dowex 50 WX8 to separate no-carrier-added (NCA)  $^{47}\text{Sc}$  from natural irradiated Ti target quickly and successfully. The influence of pH on the distribution coefficients ( $K_d$ ) of Sc(III) and Ti(IV) ions was studied using the batch approach. The results show that Ti(IV) ions are highly adsorbed by the cationic exchanger, whereas Sc(III) ions are faintly adsorbed with an elution efficiency of  $92 \pm 0.9$  % and excellent radiochemical, radionuclidic, and chemical purities,  $^{47}\text{Sc(III)}$  was radiochemically separated from an irradiated natural Ti target.



**IAEA-CN-310/22**

## **Qualification and Certification Process for Radioisotopes and Radiopharmaceuticals Operators and Supervisors in Indonesia**

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The production of radionuclides for medicine and other applications is one of the most important directions of the nuclear industry, given that nuclear medicine includes diagnostic and therapeutic techniques that use radiopharmaceuticals for applications, which is a key component to personalized medicine, without which patients may be required to undergo more invasive and expensive tests, as well as invasive surgeries. The production of radiopharmaceuticals is reliant on skilled and competent personnel who are qualified to go through the process, as evidenced by a certificate of expertise. Personnel certification in radioisotopes and radiopharmaceuticals is handled in Indonesia by the BATAN Personnel Certification Body (LSP BATAN), which is currently managed by the Directorate of Competency Development National Research and Innovation Agency. The certification procedure is carried out in accordance with BATAN Standard Number 10, which specifies guidelines for the qualification and certification of operators and process supervisors of radioisotopes and isotope-labeled compounds. Qualification and certification are carried out in stages, namely: fulfillment of requirements, qualifying exams, which include general and specific exams, as well as exams, practice for officers, and issuance of certificates of expertise for qualified candidates. The certificate of expertise is then used as one of the requirements for obtaining a Work Permit (SIB) for Operators of Radioisotope Production Facilities and Radiopharmaceuticals issued by the Nuclear Energy Regulatory Agency (BAPETEN). Only personnel with license or SIB could work as operators of Radioisotope Production Facilities and Radiopharmaceuticals.



**IAEA-CN-310/25**

### **Synthesis of [131I]I-queretin/ascorbic Acid Coated Selenium Nanoparticles for Inflammation Theranosis**

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Quercetin offers a promise therapeutic in the treatment and prevention a lot of chronic diseases such as neurological diseases, cancer and cardiovascular, In our study, the combination of quercetin with Selenium nanoparticles (Se-NPs) in presence of ascorbic acid to be radio-iodinated with I-131 forming [131I]I-quer./asc.-Se-NPs via electrophilic substitution reaction giving a radiochemical yield of  $82.24 \pm 2.46$  %. In-vivo study was carried out on muscle inflamed Swiss Albino mice via intravenous injection at different time intervals, the inflamed muscles showed a large accumulation of radioactivity of [131I]I-quer./asc.-Se-NPs reached to  $5.47 \pm 0.27$ % ID/g after 2 hrs. compared with normal muscles which  $1.27 \pm 0.06$ % ID/g at the same time and T/NT reaches 4.31 at this time also. The resulted high antioxidant capacity of the newly synthesized nano-platform and high accumulatio of its radio-iodinated from in inflammation site giving us an opportunity to use this platform as a potential theranostic agent for inflammation.





**IAEA-CN-310/26**

## **Modeling and assessment of Radioactive Iodine dispersion inside Egyptian Radioisotope Production Facility**

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Indoor Air Quality (IAQ) is very important topic in any radioisotope production facility. It is mandatory for some operators to be available behind hot cell that produce radioisotope to practice some tasks concerning maintenance, dosimetry and operation. One of these tasks is redundant transferring Radioiodine from cell to quality control lab and vice versa for measurements. Contam3.2 is a simulation model from NIST (National Institute of Standards and Technology) is used to study and predict I131 concentration in air in hot cell and area of operator behind the cell in emergency case. Emergency is described by dropping small amount of I131 on cell floor. The model predicts the elapsed time to remove contaminants by extraction ventilation system to deposit these contaminants in the dedicated filters and protect operators from inhalation. An emergency situation is also studied in case of opening I131 cell door hole (20 cm) by operators to pick the sample for quality control tests. Pressure interference occurs in this situation permitting some Iodine traces to be available in the areas under consideration. Ventilation system is responsible for removing all radioactive contaminants to settle it inside dedicated charcoal filters to clean the area and keeps it in permissible safe limits.



**IAEA-CN-310/28**

## **Development and In-vivo Evaluation of Chelator Free <sup>123</sup>I/<sup>131</sup>I-silver Nano-probe for Theranostic Applications**

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The emergence of nanoparticles (NPs) is likely to have a significant impact on the drug delivery sector where they are stated at the leading edge with many potential theranostic applications in nuclear medicine. This study demonstrates a facile one pot synthesis technique for the development of <sup>123</sup>I/<sup>131</sup>I-silver nano-probe for tumor diagnosis and/or therapy excluding the utilization of chelating ligands.

The radioactive iodine (I-131) was embedded in the basic structure of the polyethylene glycol decorated silver NPs during the synthesis. The <sup>131</sup>I-nanoprobe was identified via UV-Vis spectroscopy and FT-IR analysis and was characterized for particle size, zeta potential, topography, radiolabeling and entrapment efficiencies, physiological in-vitro stability and cytotoxic behaviour profile. The in-vivo distribution studies in normal and solid tumor bearing mice were investigated following intravenous (IV) and intratumoral (IT) administration.

<sup>131</sup>I-nanoprobe was developed as a spherical structure with average particle size ( $17 \pm 4.92$  nm), hydrodynamic size ( $18 \pm 4.38$  nm), zeta potential (-21 mV), radiolabeling yield ( $97 \pm 0.29$  %), entrapment efficiency (90 % up to 8 h), high in-vitro physiological stability and appropriate cytotoxic behaviour at a concentration below 3  $\mu$ l/104 cells. The in-vivo distribution studies in solid tumor bearing mice revealed that the maximum tumor uptake  $38.32 \pm 0.98$  and  $69.56 \pm 1.53$  % ID/g was achieved at 60 and 15 min post IV and IT injection, respectively. Also, another advanced merit was evolved representing a highly impacted T/NT ratio equal to  $48.32 \pm 1.3$  and  $95.74 \pm 1.85$  at 60 and 15 min post IV and IT injection, respectively.

Stabilized incorporation of radioactive iodine (<sup>123</sup>I/<sup>131</sup>I) into the integral structure of silver nanoparticles elucidated a paradigm shift in the utilization of <sup>123</sup>I/<sup>131</sup>I-silver nano-probe for tumor diagnosis and/or therapy excluding the utilization of chelating ligands.



**IAEA-CN-310/29**

### **Nationalization of Brachytherapy Radioactive Sources in Brazil and the Importance of IAEA Cooperation**

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Brazil has a cancer incidence of about 625,000 cases a year. It is a public health problem, demanding constant efforts to deliver for patients the most efficient treatment modalities, improving their life expectancy and quality. Brachytherapy is a type of Radiotherapy where the radioactive source is placed close to or inside the tumor. The main advantage of the technique is to deliver the maximum dose in the target, saving healthy tissues. In Brazil, Our group had the objective of producing sources nationally, diminishing treatment costs, enabling the treatment to more patients. Some of our projects are developed in collaboration with the International Atomic Energy Agency-IAEA by technical cooperation projects. The IAEA participation is very important to provide technological transfer through scientific visits, expert missions, and contacts with more advanced centers. The financial support is also important, allowing us to buy the necessary equipment to make these cancer treatment sources production feasible in Brazil. Our team has received training through fellowships. We received some experts and organized several workshops to propagate the Brachytherapy technique at national and Latin American level. For producing new sources, five major areas must be considered: 1) source production: nuclear activation and/or radiochemical reaction; 2) welding; 3) quality control: leakage tests; 4) dosimetry and metrology; 5) operational procedures; 6) validation studies. To perform all steps, a multidisciplinary team works together to overcome difficulties. Our major projects are: Iridium-192 pellets: In Brazil there are 150 afterloading machines with pellets that replacement every 4 months (about 450 Iridium-192 sources a year). Our new production line, with the support of IAEA, is in progress, with the hot-cell being installed in a brand-new facility. Iridium-192 wires: In production since 1997, also supported by IAEA. The wire is activated at IPEN's IEA-R1 reactor for 30 hours with  $5 \times 10^{13} \text{ n/cm}^2 \cdot \text{s}^{-1}$  neutron flux resulting in 7.1 GBq (192 mCi) maximum activity. Iridium-192 seed: New seed for ophthalmic cancer treatment. The core presented 90% activity homogeneity. We are making the experimental dosimetry and Monte Carlo simulation. Iodine-125 seeds: Largely used in low dose brachytherapy. I-125 binding yield achieved with our new reaction was 90%; Laser welding presented 70% efficiency. Approved in all leakage tests. Our Iodine-125 seeds laboratory production is 90% ready. Other ongoing projects: polymeric Phosphorus-32 source for spinal cancer treatment, Gold-198 nanoparticles for prostate, breast, and liver cancer treatment, Iodine-125 seed as markers for non-palpable cancers, and dosimetry calculations for all new sources. All the projects are advancing, despite national funding difficulties. Withing those, several mSc, Phd, and Post-doc are getting their degrees. We will continue to develop new products hoping to help the Brazilian population fight against cancer. The support of IAEA has proven to be of the utmost importance for these projects not only in direct funding, but in providing knowledge to our team, the possibility to share information with the scientific community, and to form the next generation of scientists.



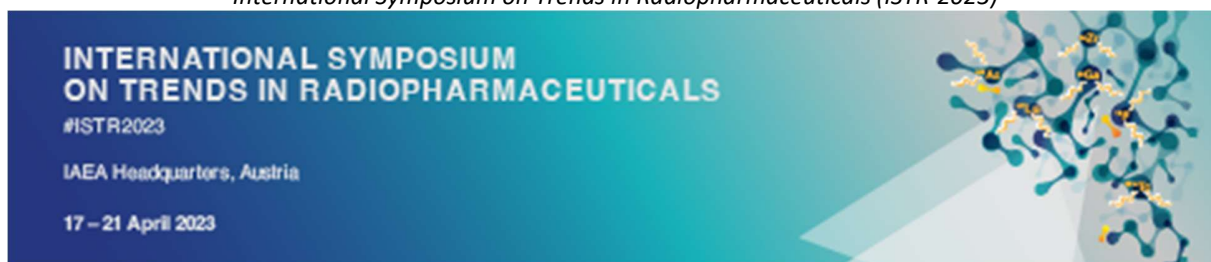
**IAEA-CN-310/30**

### **Synthesis, Activation and Application Testing of Gold Nanoparticles for Nanobrachytherapy**

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For more than 50 years, the Energy and Nuclear Research Institute IPEN, has been offering solutions to Brazil through nuclear technology. Thus, one of the main areas where IPEN has contributed assertively is medicine. Reaching the level of 32 radiopharmaceuticals and radioactive sources intended both for therapy and for the diagnosis of several pathologies, including cancer, which are obtained with the help of the two nuclear reactors and two cyclotrons present in the institution. The Institute has a team for the development, production and distribution of radioactive sources for brachytherapy, such as  $^{192}\text{Ir}$  wires and  $^{125}\text{I}$  seeds. Brachytherapy is a cancer treatment technique where the radioactive source is placed close to or in contact with the lesion. The great advantage of the technique is to save healthy tissues. Currently, we are working on obtaining nanometric materials that can be applied in the emerging nano brachytherapy, because of its properties and characteristics at the nanometric level, gold has been the subject of studies and tests. Elemental Au gold can be activated  $^{198}\text{Au}$  inside a nuclear reactor, and has  $\beta$ - decay and a half-life of 2.7 days, which makes it ideal for short-term irradiations. In addition, gold in the form of nanoparticles has a completely different chemistry, with gold nanoparticles (AuNPs) being easily functionalized by a large part of molecular and polymeric binders, which may present favorable characteristics for the studies, and together with AuNPs they are able to work synergistically to achieve greater efficiencies. Currently, AuNPs have been successfully functionalized with gum arabic (GA), a coating widely used in the cosmetic and food industry, which is low cost and along with nanoparticles has shown biocompatibility with different cell groups and has been shown to be very stable over time. The project includes studies regarding the synthesis of nanoparticles, coating, cytotoxicity of AuNPs in vitro "cold" (non-radioactive) and the development of activation protocols in the nuclear reactor. In the next phase, after activation, in the reactor, "hot" tests will be performed in vitro and in vivo.



## IAEA-CN-310/31

### Challenges in Iodine-125 Sources Production for Cancer Treatment

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There is a great challenge the implantation on assurance quality system in the brachytherapy sources production. It involves to fulfill the Good Manufacturing Practices (GMPs) requirements, involving the process validation and of all supporting activities such as cleaning and sanitization. The purpose of this work was to execute a process validation in the iodine-125 seeds production on Radiation Technology Center located at IPEN- Brazil. Besides this, the sanitization was to evaluate the effectiveness of different surface cleaning products, determining the best to reduce radiological contamination to acceptable levels during the sources production, according to legislation. The fabrication process was performed three times for evaluation. The parameters evaluated in this study were: the source welding efficiency and the leakage tests results (immersion test). The welding efficiency doesn't have an established parameter, since is visually evaluated by the operator, and the leakage detection has to be under 5 nCi / 185 Bq, accordingly with the ISO 9978. In the relation of sanitization, it was established a cleaning program for three production lots of iodine 125 seeds using three types of sanitizers: Lot 1 with extran 1/1 (v/v), Lot 2 with hydrogen peroxide 6% and Lot 3 with sodium hydroxide 1M. Each lots contained seven iodine 125 seeds and was immersed in the sanitizer for 1 hour and then two washes with distilled water. An activity detected in each lots does not exceed 0,2 kBq ( $\approx 5$ nCi). The observed values on process validation were: 75% welding efficiency and 32% leakage detection. Although established values for the global efficiency aren't available in the literature, the results showed high consistency and acceptable percentages, especially when other similar manufacturing processes are used in comparison (average 85-70% found in the literature for other similar metallic structures). According to results of sanitization, the best choice for remove de surface contamination was peroxide hydrogen. Further testing should ensure the sanitizer's choice is based not only on the removal of surface contamination, but also this sanitizer does not leave residues requiring further rinsing with distilled water. Those values will be important data when drafting the validation document and to follow the Good Manufacturing Practices (GMPs).





**IAEA-CN-310/35**

## **Collaborative and Reliance Procedures in the Regulation of Radiopharmaceuticals in the Regional Economic Blocks of Low- and Middle-Income Countries – Prospects for the East African Community**

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One of the biggest challenges to the availability of radiopharmaceuticals in Low- and middle income (L&MI) countries is that their markets are often too small to be attractive to pharmaceuticals companies. This is especially so in L&MI countries which are small discrete markets, with low state funding of tertiary healthcare systems and very low percentages of the population being covered by health insurance.

The above situation faces member states of the East African community (EAC). The EAC is an economic block of seven countries in the great lake's region of Africa, namely: The Democratic Republic of the Congo, the Republics of Burundi, Kenya, Rwanda, South Sudan, Uganda, and the United Republic of Tanzania. The EAC is a home to an estimated population of 300 million people and with a combined gross domestic product (GDP) of US\$ 240 billion. Individual member states have small markets, with Uganda, for example, having a population of 40 million people, a GDP of only US\$ 40.43 billion (World bank, 2021), less than 5% of the population with health insurance cover and a small pharmaceutical market size.

These countries constitute individual pharmaceutical regulatory jurisdictions. For the pharmaceutical companies to be able to bring radiopharmaceutical products to these markets and help the patients while ensuring safety, stringent regulations must be separately met: they have to follow the different marketing authorization processes, undergo audits for Good manufacturing practices, among other regulation. In addition, radiopharmaceuticals pose special challenges compared to other medicinal products, as they are often small scale preparations whose marketing authorization track may need to deviate from the conventional one. This duplication of processes is often not economically sensible for such small markets and may be an inefficient utilization of the technical and financial resources that are evidently limited in the prevailing environment.

This paper seeks to examine the challenges to- and potential of harmonization of legal and regulatory frameworks, as well as collaborations and reliance (such as joint marketing authorization processes and joint audits for compliance with the current Good manufacturing Practices (cGMP)) as a means of allowing cost-effective and timely access to the combined EAC market by radiopharmaceutical companies, while avoiding a trading-off with the assurance of safety, efficacy and quality





**IAEA-CN-310/36**

### **Novel Ubiquicidin Conjugate for bacterial Infection Imaging**

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Antimicrobial peptide, Ubiquicidin (UBI) and its derivatives are reported to show specificity towards broad range of pathogens. UBI (29-41) labeled with  $^{99m}\text{Tc}$  and  $^{68}\text{Ga}$  could distinguish between infection from sterile inflammation. However, there is further scope to enhance specificity of the peptide towards development of an ideal infection imaging probe. In the present study, 2-acetylphenylboronic acid (AB) was integrated as a covalent probe to UBI (29-41) and NODAGA chelator was attached.  $^{68}\text{Ga}$  labeling of NODAGA-UBI (29-41)-AB was optimized. Detailed biological evaluation and comparison with  $^{68}\text{Ga}$ -NODAGA-UBI (29-41) was done.

NODAGA-UBI (29-41)-AB and NODAGA-UBI (29-41) conjugates were synthesized by solid phase peptide synthesis. Conjugates were labeled with  $^{68}\text{Ga}$ . Stability of the radiolabeled peptides in PBS and, human serum was checked and analyses were carried out by HPLC. In-vitro specificity of the formulations towards *S. aureus* was studied. Animal model of infection and inflammation was developed in mice and rats. In vivo evaluation of the formulations was done after injecting in animals through the tail vein. Animals were anesthetized using ~4% isoflurane and imaging was performed at different time points post injection.

$^{68}\text{Ga}$ -NODAGA-UBI (29-41)-AB complex was prepared reproducibly with high RCP (> 97%) and showed stability in serum and PBS for up to 3 h similar to  $^{68}\text{Ga}$ -NODAGA-UBI (29-41). AB conjugation significantly improved the specific uptake of peptide in bacteria. However, in mice model of infection,  $^{68}\text{Ga}$ -NODAGA-UBI (29-41)-AB showed high liver and lung uptake compared to  $^{68}\text{Ga}$ -NODAGA-UBI (29-41). Incidentally, both complexes could distinguish between infection and sterile inflammation in rat model of infection.

$^{68}\text{Ga}$  labeled UBI (29-41)-AB was formulated and its potential for infection imaging was successfully studied.



**IAEA-CN-310/37**

### **68Ga-Labeling of HBED-CC Conjugated Cell Penetrating Peptide Coupled with Tyrosine Kinase Inhibitor, Erlotinib**

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Cell penetrating peptides (CPPs) are capable of traversing biological membranes and therefore act as efficient drug delivery vehicles. With an aim to enhance the entry of tyrosine kinase inhibitor, erlotinib inside the tumor cells it was coupled with a cell penetrating peptide, transactivating transcriptional activator (TAT) and further conjugated with the chelator HBED-CC for <sup>68</sup>Ga-labeling.

The protected TAT decapeptide Lys(N3)-Arg(Pbf)-lys(Boc)-lys(Boc)-Arg(Pbf)-Arg(Pbf)-Glu(tBu)-Arg(Pbf)-Arg(Pbf)-Arg(Pbf)-NH<sub>2</sub> was synthesized manually using standard Fmoc solid phase peptide synthesis methodology. Erlotinib was conjugated with TAT by performing on-resin Cu(I)-catalyzed click reaction between the azide group of lysine and alkyne group of erlotinib. Subsequently, N-terminus of TAT-erlotinib was coupled with HBED-CC, cleaved, purified using semi-preparative HPLC and characterized by MALDI-TOF spectrometry. <sup>68</sup>Ga-labeling of HBED-CC-TAT-erlotinib was carried out at pH 4 at room temperature (10 min) and radiolabeling yield was determined by analytical RP-HPLC.

HBED-CC-TAT-erlotinib conjugate (yield: 6 mg; purity: ≥95%) was characterized by MALDI TOF. The radiolabeling yield of <sup>68</sup>Ga-HBED-CC-TAT-erlotinib was >95% and radiotracer was observed to be stable in saline (3 h) with no change in the HPLC chromatogram pattern. <sup>68</sup>Ga-HBED-CC-TAT-erlotinib was observed to be highly hydrophilic with log P value -3.02±0.1.

The TAT peptide was successfully synthesized and conjugated with erlotinib as well as chelator HBED-CC for <sup>68</sup>Ga radiolabeling. Further studies in order to assess the internalization of peptide-drug conjugate in EGFR over-expressing cell lines are underway.



**IAEA-CN-310/39**

**Developing Questions Bank for Radioisotopes Radiopharmaceuticals Personnel Certification Based on the Result of Validity Analysis**

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In producing radioisotopes and radiopharmaceuticals, an officer must have a certificate of expertise issued by the Person Certification Agency (LSP BATAN) to obtain a Work Permit (SIB) from the Nuclear Energy Supervisory Agency (BAPETEN). To obtain a certificate of expertise, candidates must pass a certification exam, which consists of a written exam and a practical exam. Exam questions are the primary tool for verifying the expertise of officers, so it must be tested and evaluated for validity and reliability. The test and evaluation had been completed, and conclude to develop a question bank based on the validity results in order to improve the quality of the personnel certification process and avoid question leakage. The development of the question bank is by using manually categorize for each material based on standard state on SB 010-BATAN: 2011 in accordance with the result of test and evaluation existing question. The categorization method questions are carried out by dividing the ratio of the number of exam questions by the indicators of the trainees' training success listed in the training syllabus. Each sub-number category's of question banks is assigned a special code that will be used at random in the distribution of exam questions.



**IAEA-CN-310/40**

### **Route of Administration Studies for Brain Targeting by Optimized <sup>99m</sup>Tc-Olanzapine**

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Formulation of potent brain imaging nanoradiopharmaceutical with high brain targeting is challenging because of the presence of the blood-brain barrier (BBB). Olanzapine is an antipsychotic drug with low brain targeting because of P-glycoproteins and the first hepatic-pass metabolism. The study aimed to formulate the <sup>99m</sup>Tc-olanzapine solution (<sup>99m</sup>Tc-OLZ) and <sup>99m</sup>Tc-olanzapine loaded polymeric micelles (<sup>99m</sup>Tc-OLZ-PM) to be used as intranasal brain imaging nanoradiopharmaceutical. The study assessed the brain targeting between the different routes of administration and different formulations. <sup>99m</sup>Tc-olanzapine was prepared in high labeling yield ( $96.30 \pm 0.09\%$ ) by direct technique using sodium dithionite as reducing agent. <sup>99m</sup>Tc-OLZ-PM was radioformulated via thin film hydration method with appropriate particle size and high entrapment efficiency. The comparative biodistribution study between the different routes of administration (intravenous and intranasal) for <sup>99m</sup>Tc-OLZ and intranasal <sup>99m</sup>Tc-OLZ-PM was done in normal albino mice. The intranasal <sup>99m</sup>Tc-OLZ showed the higher brain uptake and brain to blood ratio than intravenous <sup>99m</sup>Tc-OLZ that prove the potency of intranasal administration. <sup>99m</sup>Tc-OLZ-PM presented highest brain uptake ( $7.3 \pm 0.1\%$  ID/g) and highest brain to blood ratio ( $18.3 \pm 0.53$ ) in the fastest time (0.25 h) post intranasal administration demonstrating the efficacy and astonishing brain targeting of intranasal <sup>99m</sup>Tc-OLZ-PM as a novel nanoradiopharmaceutical for brain imaging.



**IAEA-CN-310/41**

### **Synthesis and Characterization of High Purity Lu-177-Dotanoc: In-House Production Experience and the Way Forward**

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Peptide Receptor Radionuclide Therapy (PRRT) plays a major role in radionuclide therapy for patients who have failed to respond to conventional chemotherapy. Lutetium-177-DOTANOC is one of the promising radiotracers for the treatment of a number of neuroendocrine tumors (NETs), particularly for well-differentiated NETs with overexpressed somatostatin receptor on the cancer cells. Somatostatin receptor (SST) analogs have been labeled with various types of radionuclides and have been reported elsewhere as promising theranostic radiopharmaceuticals for NETs. DOTANOC (DOTA-NaI3-Octreotide) peptide having the ability to specifically bind SST receptor subtypes 2, 3 and 5, which show over-expression in neuroendocrine tumors. Lu-177 is a beta emitting radionuclide that decays with a half-life of 6.65 days. The simultaneous emission of imageable gamma photons [208 keV (11%) and 113 keV (6.4%)] along with particulate beta emission [ $\beta(\text{max}) = 497 \text{ keV}$ ] makes it an ideal candidate for theranostic applications. In this work, commercially available conjugated peptide, DOTA-NOC, was labeled with reactor-produced Lu-177 for preliminary quality investigation. Due to the lack of automated synthesis module, we performed manual radiosynthesis of Lu-177-DOTANOC. The aim was to evaluate the radiolabeling efficiency and stability *in vivo* for up to 7 days. We report on our first experience in the manual handling and in-house synthesis of Lu-177-DOTANOC. The synthesis was carried out in ultrapure water with 18.5MBq of Lu-177, adjusted to pH 5.5-6.0 by acetate buffer, and the reaction vial was incubated at 100C for 30 minutes. Lu-177-DOTANOC radiochemical purity averaged was more than 99.5%, and the complex was stable for up to 7 days. In addition, bovine serum was used to investigate *in vivo* stability. A small amount of Lu-177-DOTANOC was added into the serum and incubated at 370C. The radiochemical purity results showed high complex stability with more than 98% remaining intact after 7 days. The manual labelling proved to be robust, cost effective and feasible in our available resources. This paper will also discuss briefly the key challenges of in-house Lu-177 isotope production using current research nuclear reactor, and possibilities for the near future, such as initiating a study using custom-made semi-automated system for the synthesis of Lu-177 radiopharmaceuticals.





IAEA-CN-310/42

## A Nanoliposomal Formulation for Dosimetry and Combination Radionuclide Therapy of Breast Cancer

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Combination radionuclide therapy (CRT) is an emerging concept in the management of cancer. CRT is the combination of radionuclide therapy with other complementary anti-tumour therapeutic modalities to envisage a better therapeutic index with minimal side effects than monotherapies. Combined monotherapies aid each other in overcoming resistance and bypassing survival selection mutations developed by cancerous cells resulting in enhanced therapeutic effect. Aim of this study is to develop  $^{177}\text{Lu}/^{99\text{m}}\text{Tc}$  labeled liposomes loaded with doxorubicin for dosimetry and combination therapy of breast cancer. Liposomes incorporating phosphoethanolamine-DTPA (PE-DTPA) for radiolabeling with  $^{177}\text{Lu}$  and  $^{99\text{m}}\text{Tc}$  were prepared by the ethanol injection method. Doxorubicin (dox) was actively loaded in liposomes using the pH gradient method (lip-dox). Radiolabeling with  $^{177}\text{Lu}$  in acetate buffer, pH-5 and  $^{99\text{m}}\text{Tc}$  in phosphate buffer, pH-7 was optimized. Characterization and stability of the formulations were studied. In-vitro studies in SKBR3 and 4T1 cells to assess cytotoxicity and cell cycle analysis in SKBR3 cells were carried out. A tumor uptake study using  $^{99\text{m}}\text{Tc}$  labeled lip-dox and tumor regression study using  $^{177}\text{Lu}$  labeled lip-dox in SKBR3 xenograft tumor to assess the synergistic effect of the combination therapy was performed. Liposomes of 87.4 nm size were prepared and ~100% radiolabeling of lip-dox was achieved with  $^{177}\text{Lu}$  and  $^{99\text{m}}\text{Tc}$ . Both  $^{177}\text{Lu}$  and  $^{99\text{m}}\text{Tc}$  radiolabeled formulations were found to be stable in serum and PBS at  $37^\circ\text{C}$  and  $4^\circ\text{C}$ , when estimated by TLC.  $^{99\text{m}}\text{Tc}$  labeled lip-dox showed  $8.4 \pm 0.7$  and  $5.1 \pm 1.2$  % tumor /  $\text{cm}^3$  uptake at 6 h and 24 h in SKBR3 xenograft tumor in SCID mice. Enhanced cytotoxic effect of  $^{177}\text{Lu}$ -lip-dox due to combination compared to monotherapies,  $^{177}\text{Lu}$ -lip and lip-dox were observed at microcurie level of  $^{177}\text{Lu}$  and nanomolar concentration of dox in SKBR3 and 4T1 cancer cells. G1 arrest was observed in cells in response to (100  $\mu\text{Ci}$  & 200  $\mu\text{Ci}$   $^{177}\text{Lu}$ ), (5  $\mu\text{M}$  & 2.5  $\mu\text{M}$  dox) and combination  $^{177}\text{Lu}$ -lip-dox (100  $\mu\text{Ci}$  + 2.5  $\mu\text{M}$ , 200  $\mu\text{Ci}$  + 5  $\mu\text{M}$ ). Results of tumor regression study corroborated with in-vitro studies and enhanced therapeutic response due to combination therapy using  $^{177}\text{Lu}$ -lip-dox than monotherapy of lip-dox and  $^{177}\text{Lu}$ -lip were observed.

CRT is a new paradigm which warrants promising results. If pursued systematically, it might contribute immensely to the personalized treatment of cancer.





**IAEA-CN-310/44**

**Clinical Pharmaceutical Screening as a tool to improve Radioiodine Therapy Safety: Descriptive study of two Years' Experience**

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Radioiodine therapy (RIT) is used to treat differentiated thyroid carcinoma (DTC) and requires extensive evaluation to ensure effectiveness and safety. However, studies covering clinical pharmaceutical screening (CPS) for radiopharmaceutical users are still incipient (1, 2).

Descriptive study regarding two years of a CPS service carried out in a reference oncology hospital in Brazil. Descriptive analysis was used to describe the clinical situations identified, as well as correspondent drug therapy problems (DTP) and pharmaceutical interventions performed.

Eighty-four patients were included, 82,1% women; 61,9% < 55 years (47,8 years mean age), using a mean of 4,2 medications. The following critical situations were identified in CPS: (i) Twelve patients' (needing additional drug therapy to acute pain management (33,3%) and hypertensive crisis (41,6%); (ii) two patients needing medicines dosage adjustment; (iii) five patients in reproductive age without contraceptive methods needed additional medicines. All pharmaceutical interventions were accepted.

CPS to DTC patients during the RIT is feasible and effective, representing an important tool to improve RIT safety through the identification, prevention, and resolution of critical drug-related clinical situations.



## **IAEA-CN-310/45**

### **Training the Future Generation of Trainers in Radiopharmacy as a Strategy to Strengthen the Human Resources in Latin America**

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With the objective to overcome the limited availability of educational programs in Radiopharmacy in Latin America, the IAEA project RLA6084 has proposed to strengthen the regional system of training, evaluation and accreditation of human resources in the different areas of Radiopharmacy. The 16 countries participating in this project are cooperating to develop regional strategies to overcome human resource development gaps in a sustainable manner.

Initially, a survey on the status of human resources and training opportunities was conducted to establish base line which clearly demonstrated the need for formal training in Radiopharmacy competencies. The second step was the development of a regional training strategy for the different categories of personnel required for effective operation of different levels Radiopharmacy facilities. Training contents were developed which consists in 5 modules, covering all the topics required for the Radiopharmacy practice and 2 additional modules that are required to be taken by the participants based on their education background and practical experience in Radiopharmacy. These modules would ideally include e-learning, synchronic virtual and presential practical lessons. The syllabus for the modules was harmonized through discussion with international experts. Finally, 12 young professionals participated in a virtual “train the trainers” course that included the use of the Lanent virtual platform and the preparation of a series of lectures by the participants. The participants are also committed to act as teachers in 3 future IAEA pilot courses to put into practice the acquired skills of the trainers. This group will constitute the initial seedbed of trainers or teachers in order to generate an educational offer in their countries in the future.

In conclusion, project RLA 6084 constitutes an important initial effort for the human resources capacity building in Latin America in Radiopharmacy.



**IAEA-CN-310/48**

### **Hospital Radiopharmacy Training Program for Pharmacists: Experience in a Reference Hospital in Brazil**

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Radiopharmacy has experienced recently regulatory and technical advances, however, training centres either in graduation or post graduation level are still scarce, especially in Latin-America. In this context, we started the incorporation of Hospital Radiopharmacy theme to Residence Program in Oncology for pharmacists at National Cancer Institute in Rio de Janeiro, Brazil. After a pilot in 2013, the subject was officially incorporated to the program in 2014 as a 40-hours theoretical and 80 hours-observational practice. This course is offered to 10 pharmacists per year. This first experience demonstrated lead to two additional specific training programmes in 2016: (i) Fellowship in Hospital Radiopharmacy (FHR) and (ii) Post-residence practice in research and development applied to hospital radiopharmacy (PRHR), both one-year length, 40-hours a week training. FHR prepare pharmacists to routine planning, radiolabelling and quality control of  $^{99m}\text{Tc}$ -radiopharmaceuticals, register and investigate nonconformities, track the use of dispensed radiopharmaceuticals and monitor adverse events, with a focus on good manufacturing practices and patient safety. At the end it is also possible to visit another radiopharmacy centre for at least 15 days. PRHR offers an experience in research and development, which can be continued in MSc course. Since the beginning of these two programs, six students have graduated, three entering radiopharmaceutical job market, two of them starting MSc with projects in hospital radiopharmacy and one started direct a MSc course, showing that these two training programs are important tools to develop radiopharmacy practical skills and insert professionals into the job market.



**IAEA-CN-310/49**

### **Radiobiological and Dosimetric Characterization of Molecular Radiopharmaceuticals at the Cellular Level**

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Targeted radionuclide therapy (TRT) has proven to be one of the treatment options with the greatest capacity to achieve total remission of cancer in a non-invasive, specific manner and with minimal side effects. Clinical trials conducted to date have demonstrated the excellent uptake and good response rate of the radiopharmaceutical  $^{177}\text{Lu}$ -iPSMA, however, exacerbation of bone lesions has also been observed in some patients. These undesirable responses could be related to the Bystander phenomenon, which consists of the radioinduced release of mediators that modify intercellular signaling, causing remote effects. As part of the radiobiological and dosimetric characterization of  $^{177}\text{Lu}$ -iPSMA, the effects at a distance produced in non-target cells of the stroma (fibroblasts) as a consequence of the treatment of prostate cancer target cells as well as the impact of heterobivalence on the relative biological effectiveness (RBE) were evaluated. The estimated RBE value for  $^{177}\text{Lu}$ -iPSMA (4.6 - 2.3) was significantly higher compared to that for X-rays (1.0 - 0.5). Our findings demonstrate the superiority of radiopharmaceuticals as a therapeutic option over Linac systems and it was also found that both stromal cells and tumor cells are capable of eliciting distant responses in a reciprocal and dose-dependent manner. As a future perspective, it is intended through three-dimensional co-cultures to evaluate the importance of the spatial distribution of the dose and the linear energy transfer (LET) in the Bystander effect.



## **IAEA-CN-310/51**

### **68Ge/68Ga Generator in Nuclear Medicine and Licensing Aspects: Brazil's Situation**

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Currently, Brazil has 130 nuclear medicine facilities that perform positron emission tomography diagnostics, of these services, 92 are authorized by Brazilian National Nuclear Authority (CNEN) to operate with  $^{68}\text{Ga}$ . The number of services that use a  $^{68}\text{Ga}$  generator has been growing in recent years and, since the beginning of 2022, CNEN has implemented minimum requirements to be adopted by each of these services that acquire the generator. Among the requirements to be met are: a) establishment of procedures related to radiation protection adopted from elution to administration of the radiopharmaceutical to the patient; b) implement additional shields for the  $^{68}\text{Ge}/^{68}\text{Ga}$  generator in service; c) specific training of occupationally exposed individuals who operate the  $^{68}\text{Ge}/^{68}\text{Ga}$  generator and workers who handle and inject the  $^{68}\text{Ga}$ ; d) record the dose rates, weekly, close to the  $^{68}\text{Ge}/^{68}\text{Ga}$  generator, approximately at the following heights: gonads, chest and face – simulating the position of the worker and also in the following steps: elution, labeling and fractionation of the radiopharmaceutical; e) submit a report of doses of professionals (whole body and extremity) to CNEN every six months. Based on data obtained from dose rate records, individual dosimetry and operational procedures implemented aiming at radiological protection for each installation, CNEN will be able to improve the licensing of these services.



**IAEA-CN-310/53**

## **Virtuality As a Tool to Expand Educational Offer in Radiopharmacy in Latin-America**

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One of the key aspects of GMP is the education of human resources. According to WHO the production of radiopharmaceuticals requires postgraduate training and appropriate practical experience. However, the postgraduate specialized educational offer in Radiopharmacy is almost inexistent in Latin-America.

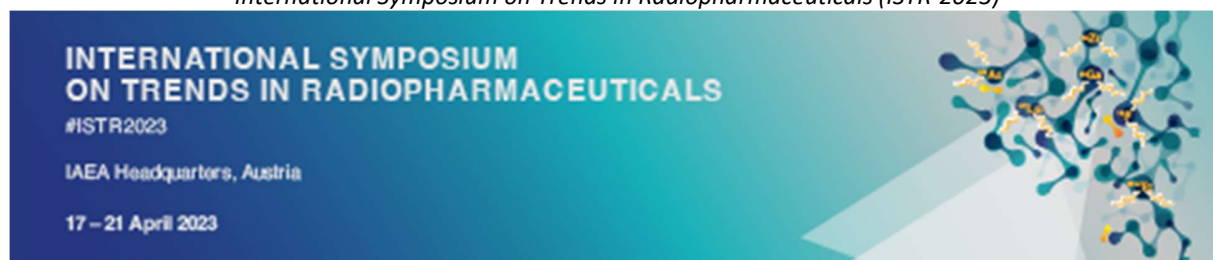
The Radiochemistry Area of the Faculty of Chemistry in Uruguay has been teaching Radiopharmacy at undergraduate level for more than 20 years and since 2016 also a postgraduate Diploma of specialization in Radiopharmacy (DSRF) that already has graduates from Colombia, Costa Rica and Uruguay. Nevertheless, a major difficulty for participating has been the need to attend presential lessons in Uruguay for a minimum of 6 to 12 months.

Due to the restrictions caused by Covid-19, we adapted our courses to the virtual modality offering synchronous and recorded theoretical classes and the lack of laboratory practices was compensated with demonstrative videos. This modality promoted the regional visibility of our courses leading to a significant participation of professionals from Peru, Bolivia, México, Dominican Republic, Costa Rica and Panamá, who will have the opportunity of obtaining the DSRF after a short internship of 2 months to acquire the practical skills required for the clinical practice.

Concomitantly we implemented a virtual course of actualization in Radiopharmacy for technologists with students from Chile, Costa Rica, Dominican Republic and Peru.

In conclusion, virtual tools are extremely important to facilitate access to education in Radiopharmacy in Latin-America and should be encouraged to strengthen the human resources development of the different categories of Radiopharmacy professionals in our region.





**IAEA-CN-310/55**

**Development of  $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$  Generator Based on Low Specific Activity of Molybdenum-99 ( $^{99}\text{Mo}$ ) in Indonesia**

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A  $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$  generator based on the low specific activity of molybdenum-99 ( $^{99}\text{Mo}$ ) in Indonesia has been developed. The  $^{99}\text{Mo}$  radioisotope was produced by neutron-irradiating of natural molybdenum in G.A. Siwabessy multi-purpose reactor, Indonesia, and it has a specific activity of  $\sim 25.9 - 29.6$  GBq/g of Mo. The  $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$  generator consists of two columns. The main column contains mesoporous gamma-alumina as high capacity adsorbent while the second column contains acidic-alumina. The  $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$  generator has been applied for the  $^{99}\text{Mo}$  activity up to 19.6 Gbq (530 mCi). The  $[^{99\text{m}}\text{Tc}]\text{TcO}_4^-$  eluate produced by the  $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$  generator has an average yield above 97% and satisfied the US Pharmacopoeia regulations: clear solution with a pH of 5.0–5.5, high radiochemical purity (>99%),  $^{99}\text{Mo}$  breakthrough below 0.010%, and aluminium breakthrough below 5  $\mu\text{g}/\text{mL}$ . The resulting  $[^{99\text{m}}\text{Tc}]\text{TcO}_4^-$  eluate was used for the preparation of  $[^{99\text{m}}\text{Tc}]\text{Tc}$ -radiopharmaceuticals namely  $[^{99\text{m}}\text{Tc}]\text{Tc}$ -MDP,  $[^{99\text{m}}\text{Tc}]\text{Tc}$ -DTPA, and  $[^{99\text{m}}\text{Tc}]\text{Tc}$ -MIBI with radiochemical purity above 97%. Based on the measurement of the radiation exposure rate on the surface and at a distance of 1 m of the  $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$  generator, the  $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$  generator is classified into type II-yellow packaging.



**IAEA-CN-310/64**

## **Sustainable REE Production by Th-232 Processing Into Ac-225 for Radiopharmaceutical Cancer Treatment**

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The Steenkampskraal monazite mine in South Africa has an NI 43-101 Mineral Resource Estimate that indicates the presence of 86 900 tons of rare earth oxides at an average grade of 14.4%, and 11 700 tons of thorium oxide at an average grade of 2.14%. Anglo American Corporation mined Steenkampskraal for 11 years from 1952 until 1963 and produced and exported 53 939 tons of monazite concentrate to England. This monazite contained about 4 315 tons of thorium. When the British government stopped buying thorium, AAC closed the mine. Steenkampskraal now has a Mining Right and a Certificate of Registration (COR) with the National Nuclear Regulator that allow Steenkampskraal to mine, process, transport, and store naturally occurring radioactive material (NORM), including thorium. Recent research has shown that Th-232 may be processed using high-energy proton spallation to produce Actinium-225 (Ac-225). Ac 225 is a key raw material to produce radiopharmaceuticals utilized for medical diagnostic and alpha-therapeutic applications. There is currently no robust raw material supply chain for Ac-225, leaving currently about 50,000 cancer patients untreated (status June 2022 USA). The Th content at Steenkampskraal holds great potential to produce radiopharmaceuticals for cancer treatment. Steenkampskraal is the highest-grade rare earth mine in the world and has great investment potential; the production of radiopharmaceuticals will increase this investment potential.



**IAEA-CN-310/66**

### **Separation of Ge-68 from Ga-Ni Alloy Target for <sup>68</sup>Ge/<sup>68</sup>Ga Generator Production**

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Gallium-68 is an important positron emitting radionuclide with 68 min physical half-life and decays by  $\beta^+$  (89%) used in PET imaging for prostate cancer and neuroendocrine tumor. At present BRIT Kolkata supplies <sup>68</sup>Ga radiopharmaceutical by direct production from enriched Zn-68 solid target using 30 MeV Medical Cyclotron to local hospitals. However due to a very short half-life of <sup>68</sup>Ga, the supply of cyclotron produced <sup>68</sup>Ga-radiopharmaceutical is limited to local regions only. Therefore, it is important to prepare Ge-68 ( $t_{1/2} = 271$  days) radiochemical for the manufacture of <sup>68</sup>Ge/<sup>68</sup>Ga generator to cater to various nuclear medicine centers. BRIT, Kolkata has produced Germanium-68 for the first time in India using 30MeV VECC Medical Cyclotron from an indigenously developed Ga-Ni alloy electroplated target. The Ga-Ni alloy target was prepared from sulphate bath (pH = 1.5) using constant current electrolysis technique on a gold-plated Cu-base material. The target was irradiated with 28 MeV proton beam for 80 hours continuously and chemically processed using Sephadex G-25 column after sufficient cooling in an indigenously developed automated module. The electroplated target remained intact after irradiation without any damage.

The irradiated target was dissolved in H<sub>2</sub>SO<sub>4</sub> and H<sub>2</sub>O<sub>2</sub> mixture by repeated circulation of the hot acid solution in a closed loop. The dissolved solution mixed with 1M Na-citrate (pH = 12-13) and NaOH solution followed by loading on a preconditioned Sephadex G-25 column. The column was washed with 1M Na-citrate (pH = 12-13), dilute Na-citrate (pH = 12-13), dilute NaOH solution and deionized water successively. <sup>68</sup>Ge-chloride was eluted using 0.1M HCl solution. The chemical separation yield and radionuclidic purity of Ge-68 was about 70% and more than 98% respectively.

Pure <sup>68</sup>Ge-chloride was thus successfully produced for preparation of <sup>68</sup>Ge/<sup>68</sup>Ga generator. Therefore, large scale production of <sup>68</sup>Ge-chloride can be achieved in future by irradiating Ga-Ni targets for prolonged periods.

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**IAEA-CN-310/67**

**Imaging of the Tumor Microenvironment Via SPECT/CT with [99mTc]Tc-Ifap: Kinetics, Radiation Dosimetry and Imaging in Patients**

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A [99mTc]Tc-iFAP SPECT/CT radioligand was developed for the detection of FAP, with >98% radiochemical purity. The aim of this research was to study the kinetics and carry out the dosimetric calculations of [99mTc]Tc-iFAP in healthy volunteers and evaluate the radioligand uptake in three different cancer treatment-naive patients with different solid tumors (overexpressing FAP).

Subjects were scanned (whole body) at 0.5, 2, 4, and 24 h after administration of 740 MBq of [99mTc]Tc-iFAP. Activity quantification was carried out by a 2D-planar/3D SPECT hybrid method to fit the biokinetic models of the source organs (volume of interest). The radiation doses were estimated employing the OLINDA code. Cancer SPECT/CT images of [99mTc]Tc-iFAP (740 MBq) were acquired after [18F]FDG PET/CT, for visual and quantitative comparison. [99mTc]Tc-iFAP biodistribution and kinetics exhibited favorable characteristics due to rapid blood clearance ( $t_{1/2\alpha} = 2.22$  min and  $t_{1/2\beta} = 90$  min) predominant renal excretion, and an effective dose of  $2.3 \pm 0.4$  mSv. An adequate concentration of the [99mTc]Tc-iFAP was achieved in the primary tumors and lymph node metastases (cancer patients), proving is a potential tool to assess FAP expression in the tumor-microenvironment.



## IAEA-CN-310/68

### Feasibility Study on Production of $^{195m}\text{Pt}$ in Tehran Research Reactor

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Platinum agents are important chemotherapeutic compounds being used for the treatment of various cancers like lung, breast, ovarian, and colon cancers. Cisplatin agents labeled with platinum- $^{195m}\text{Pt}$  theranostic radionuclide can potentially be a useful tool for Auger radionuclide therapy. In addition, it can be used for determining the patient's dose and assist in the investigation of the mechanism of Cis-platinum's action and its metabolism in the human body.

$^{195m}\text{Pt}$  radionuclide with suitable nuclear properties ( $T_{1/2} = 4.02$  days,  $E_{\gamma} = 60-100$  keV, Auger electrons with  $E = 2.417$  keV,  $LET = 9.5$  keV/ $\mu\text{m}$  and range =  $0.25$   $\mu\text{m}$ ) can be easily used in the synthesis of platinum-based cytotoxic compounds.

In this study, production calculations of platinum- $^{195m}\text{Pt}$  in the Tehran research reactor were performed through the simultaneous solution of differential equations of the decay chains for natural platinum and natural iridium targets, and while calculating the activity and specific activity, the theoretical results were compared with the experimental values. The results showed that there is good compatibility between the measured values experimentally and the results of the theoretical calculations. The results of this research can be used in studies of Cis-platin labeling with platinum- $^{195m}\text{Pt}$ .



**IAEA-CN-310/69**

### **Human Dosimetry Calculation of $^{188}\text{Re}$ -Hynic-Bombesin**

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Due to having a high affinity to bind to gastrin-releasing peptide receptor (GRPr), the Hynic-Bombesin peptide is a good candidate for targeted radionuclide therapy in prostate cancer. Because of the suitable nuclear properties and achieving carrier-free radionuclide from the  $^{188}\text{W}/^{188}\text{Re}$  generator,  $^{188}\text{Re}$  can be well used to develop the labeled compounds for therapeutic goals.

In this research, the adult human absorbed dose for different organs was calculated based on biodistribution data of  $^{188}\text{Re}$ -HYNIC-BBN in rats. The results showed that a considerable amount of  $^{188}\text{Re}$ -Hynic-BBN (0.08mGy/MBq) was accumulated in the pancreas. Moreover, all other tissues except for the kidneys approximately received an insignificant absorbed dose and therefore  $^{188}\text{Re}$ -Hynic-Bombesin can be regarded as a new potential agent for prostate cancer therapy.





**IAEA-CN-310/70**

### **Scandium-47 Production by Cyclotron Irradiation of Titanium Targets**

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Recently, the development of theranostic radionuclides has been vastly interested in targeted radionuclide therapy. Scandium-47 is a novel theranostic radionuclide with decay characteristics comparable to  $^{177}\text{Lu}$  in terms of average  $\beta$  energy and  $\gamma$  energy. In this study, cyclotron production of  $^{47}\text{Sc}$  via  $^{nat}\text{Ti}(p,x)$  nuclear reaction was investigated. The excitation function of the proton-induced reaction on  $^{48,49,50}\text{Ti}$  was calculated using the TALYS 1.9 software to settle the optimum range of the incident-proton energy. The Monte Carlo MCNPX and SRIM codes were used to determine the integral yield based on the medium cyclotron and calculate the target thickness respectively. In addition to theoretical calculations, design and construction of a developed targetry system was carried out.

The experimental yield for  $^{nat}\text{Ti}(p,x)^{47}\text{Sc}$  nuclear reaction, at  $5\mu\text{Ah}$  total current beam &  $E_p = 29.5 \rightarrow 23.1$  MeV, was found to be  $4.25 \text{ MBq}/\mu\text{Ah}$ . However,  $^{44m}\text{Sc}$ ,  $^{44g}\text{Sc}$ , and  $^{46g}\text{Sc}$  were observed as the main impurities. The radiochemical impurities were separated with the Liquid-Liquid Extraction (LLX) method. Quality control of the final production was performed by gamma ray spectrometry. The obtained results showed that there was a good agreement between experimental and theoretical results.

In order to minimize the impurities, based on the simulated integral yield of products, the  $^{50}\text{Ti}(p,\alpha)^{47}\text{Sc}$  was the proper reaction. So, the  $5.29 \text{ MBq}/(\mu\text{A}\cdot\text{h})$  production yield, without any isotopic impurity by  $E_p = 20 \rightarrow 8$  MeV induced on enriched  $^{50}\text{Ti}$ , will be the best candidate for medical applications.



## **IAEA-CN-310/71**

### **Development of the Affordable Automatic System for Production of Small Batches of Technetium-99m Generators**

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The production of technetium-99m generators often requires large material investments, especially because it is a complex product that is classified as a sterile radiopharmaceutical. We developed a simple and affordable automatic system suitable for small manufacturers in developing member states. The entire process takes place in just one hot cell divided into three compartments. In the first section, the vial with the molybdenum-99 solution is unpacked. The second part of the hot cell is used to prepare the molybdenum-99 solution that will be loaded into the generators. In the third section, there is a charger that prepares the generators for loading, dispenses the molybdenum-99 solution into generators, samples the eluates for quality control, and puts protective caps on the generators, after which the generators are ready to be packed in transport packaging. The charger can have a capacity of 12-36 generators. If necessary, to produce a larger number of generators, charging can be repeated. The preparation of the Mo-99 solution, as well as dispensing it into the generators, is carried out in a class "A" sterile environment in accordance with EU-GMP regulations. The whole process is automated and controlled by a PC, which is equipped with the appropriate software.



**IAEA-CN-310/74**

### **Preparation and Preclinical Evaluation of $^{90}\text{Y}$ - and $^{177}\text{Lu}$ -Labeled Nanoparticles for Solid Tumor Therapy**

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The application of nanotechnology in drug formulation is a field that is currently being extensively developed. Nanomaterials, as a platform for drug delivery, enable improved pharmacokinetic properties and reduced toxic effects on healthy tissues. The nanodelivery of drugs into tumor tissues is of particular importance. The Laboratory for radioisotopes of the "Vinča" Institute of Nuclear Sciences has developed a number of nanomaterials designed for the delivery of therapeutic radioisotopes ( $^{90}\text{Y}/^{177}\text{Lu}$ ) to tumors. Such materials include superparamagnetic iron oxide nanoparticles (SPIONs) functionalized with biocompatible moieties such as citrate, dextran, (3-aminopropyl)triethoxysilane, mesoporous silica, 1,2-dimercaptosuccinic acid (DMSA), or hydrophilic phosphate ligands such as imidodiphosphate (IDP) and inositol hexaphosphate (IHP). The micromaterials such as  $^{90}\text{Y}$ -labelled microspheres were also developed and shown to be suitable for use in radioembolization (SIRT) therapy. The functionalized nanoparticles were labeled with therapeutic radioisotopes ( $^{90}\text{Y}$  or  $^{177}\text{Lu}$ ) with high yield and radiochemical purity. All developed materials show high antitumor activity both *in vitro* and *in vivo* in mouse tumor models. Also, all nanomaterials show high retention of radioactivity in the tumors after direct intratumoral injection. Nevertheless, the biodistribution studies after intravenous application show high accumulation in the organs of the reticuloendothelial system such as the liver and spleen. This issue remains the major challenge in the delivery of nanoparticles to solid tumors.



**IAEA-CN-310/75**

**Preliminary Studies for the Implementation of a Synthesis Method and Quality Control of [18F]PSMA-1007: A New Radiotracer for Prostate Cancer in the Chilean Public Health System**

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Prostate cancer is the oncological pathology with the highest incidence and mortality in Chile, being responsible for around 2000 deaths each year. That number becomes relevant when considering, with current tools, the diagnosis is carried out in late stages where metastatic processes are already triggered.

[18F]PSMA-1007 is a membrane-specific antigen radioligand and uses positron emission tomography to obtain an early diagnosis of prostate cancer. In the current work, a production method for PSMA-targeted radiopharmaceutical was implemented and put into practice at the Cyclotron Laboratory from the Chilean Nuclear Energy Commission. Likewise, a fast physicochemical analysis methodology was developed that ensures its safety, assessing compliance with critical radiopharmaceutical quality attributes such as chemical purity, radiochemical purity, radionuclide purity, radioisotope half-life and final pH of the finished product. In addition, the interference of sodium ascorbate in chemical purity tests, performed by High Performance Liquid Chromatography (HPLC) and Spot-Test was studied.

This work lays the foundations for the first stage required to make [18F]PSMA-1007 available from the public system, providing a powerful tool for the early detection of prostate cancer in Chile.



**IAEA-CN-310/76**

**Development of New Type Target for Production of  $^{177}\text{Lu}$  of High S.A. in Reactors of Low-Medium Neutron Flux**

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CNEA Argentina has a reactor for radioisotopes production of low neutron flux  $0.8 \cdot 10^{14} \text{ n.cm}^{-2} \cdot \text{s}^{-1}$  (RA3) where is not possible the production  $^{177}\text{Lu}$  of S.A. for treatment ( $\text{S.A.} \geq 21 \text{ Ci/mg}$ ) using  $^{176}\text{Lu}$  target of 74.5% enrichment currently available. Neither via indirect method using  $^{176}\text{Yb}$ , the low CS for this reaction requires neutron flux around  $5 \cdot 10^{14} \text{ n.cm}^{-2} \cdot \text{s}^{-1}$ . To overcome limitations imposed by low neutron flux a new type of target was designed and under study in RA3 having  $^{176}\text{Lu}$  and  $^{176}\text{Yb}$  in a mixture. Current results are showing strong increments of S.A. compared with  $^{176}\text{Lu}$  only-target, first set of experiment made at two cycles (63 hs/each) showed increments on S.A. of 44% over a  $^{176}\text{Lu}$  only-target, experiment at three and four cycles are giving further increments on S.A. More experiment are in progress to found the maximum S.A. achievable in our reactor. This method might help member states having low-medium neutron flux reactor for making indigenous production of  $^{177}\text{Lu}$  at high S.A.



**IAEA-CN-310/77**

**Gap Analysis Review of Lsp Batan's Radioisotopes and Radiopharmaceuticals Personnel Certification Management System Following the Organizational Merger with Brin**

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The competence of the personnel responsible for the process is highly dependent on the operation of the radiopharmaceutical radioisotope process installation in terms of safety, process effectiveness, product quality, and the validity of the analysis results. As a result, officers in radioisotope and radiopharmaceutical manufacturing facilities must be certified. Furthermore, officers are required to have a Work Permit, according to the regulation of the Head of BAPETEN No. 16 of 2014. The officer obtains the Work Permit after receiving a competency certificate from an LSP accredited by KAN or BNSP. LSP BATAN was accredited by KAN in 2017 with authorization number LSP-010-IDN. LSP BATAN is currently the only LSP that performs nuclear personnel certification. Personnel certification for radioisotope and radiopharmaceutical manufacturing facilities must adhere to the scheme based on BATAN STANDARD (SB) 010:2011. The merger of the BATAN organization into BRIN was accompanied by changes in the structure and function of each work unit previously under the BATAN organization, including the appointment of PSMN as the manager of the LSP-BATAN function managed by the Directorate of Competency Development. As a consequence, a gap analysis related to changes in the LSP organization is required. The method used is a literature review, and it is hoped that this paper will provide input or follow up on changes that occur, ensuring that the certification process for personnel working in radioisotope and radiopharmaceutical production facilities runs smoothly.





**IAEA-CN-310/78**

**Development of a New Radiopharmaceutical of  $^{99m}\text{Tc}$ -Hynic-Ifap for the Detection of Different Types of Cancer of Epithelial Origin by Spect Images.**

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Several studies have shown that the over-expression of the fibroblast activating protein denominated FAP promotes tumor growth, while its inhibition helps to increase the response of the immune system [1]. FAP is over-expressed in 90% of human epithelial carcinomas such as breast, lung, colorectal and ovarian cancer among others [2].  $^{99m}\text{Tc}$ -FAP-34 is the only FAP inhibitory radiopharmaceutical that has been radiolabeled with  $^{99m}\text{Tc}$  for SPECT imaging of the microenvironment in cancer [3]. In this research, a new boronic acid derivative iFAP was designed as a new radiopharmaceutical with specific molecular recognition directed to the tumor microenvironment for the diagnosis of more than twenty types of cancer of epithelial origin [4]. To synthesize and evaluate the in vitro and in vivo ability of  $^{99m}\text{Tc}$ -iFAP boronic acid derivative to target the FAP protein associated with cancer processes in the tumor microenvironment for SPECT imaging. For the synthesis of the molecule, a boronic acid derivative was coupled to the D-Alanine and HYNIC molecules. The chemical characterization was performed by spectroscopy of FT-IR, UV-VIS, H-NMR. The labeling of radiopharmaceutical was performed by adding 0.2 phosphate buffer (pH 7.0) and perterrenato de sodium obtained from a  $^{99}\text{Mo}/^{99m}\text{Tc}$  generator (ININ, Mexico) to a lyophilized formulation with the HYNIC-D-alanine-boroPro (HYNIC-iFAP) followed by incubation at  $95^\circ\text{C}$  for 15 min. The radiochemical purity was evaluated by reversed-phase HPLC analyses. Stability studies in human serum were performed by size-exclusion HPLC. In vitro Cellular Uptake and Internalization was tested using N30 and normal fibroblast cells with blocked and non-blocked receptors. In vivo studies were performed by biodistribution and Images were obtained in athymic mice with induced Hep-G2 tumor by using a micro-SPECT/CT system. A chemical purity of 92% was obtained after iFAP synthesis. The main functional groups of the molecule were demonstrated by spectroscopic techniques. The radiochemical purity was greater than 98%. The radiopharmaceutical was stable in human serum at 24 hours (PR<95%). High uptake in N30 cells ( $7.8 \pm 1.2\%$  of total activity) and specific recognition for FAP was observed. In vivo studies showed high tumor uptake ( $7.05 \pm 1.13\%$  ID/g at 30 min) and renal elimination. The  $^{99m}\text{Tc}$ -iFAP developed in this research shows suitable properties as a new FAP inhibitor based on the  $^{99m}\text{Tc}$ -HYNIC-D-alanine-boroPro structure for SPECT tumor microenvironment imaging.



IAEA-CN-310/79

## **Radiolabeling of Novel Alpha Mangostin derivate, Physico-chemical Properties and Cellular Uptake to T-47D human Cell Line as a Theranostics Radiopharmaceutical Candidate for Breast Cancer**

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Alpha mangostin is known as the potential isolates for breast cancer drugs. Several drug candidates have been successfully synthesized which are derivatives of the alpha mangostin compound, i.e 1,3, -dihydroxy-7-methoxy-2,8-bis (3-metillbut-2-en-1-il) -9-oxo-9H- xanthen-3-il 2-chloromethylbenzoate (AMB10). In order to find radiopharmaceutical candidates for breast cancer, synthesis of AMB10 with Iodine-131 has been carried out. Iodine is a radioactive compound which emits alpha and gamma, that  $^{131}\text{I}$ -AMB10 can be used as a theranostics agent. Synthesis was carried out by the radioiodination method using chloramine T as an oxidizing agent and several optimizations were carried out including the amount of AMB10, the amount of oxidizing agent, and temperature and incubation reaction time. This study aimed to determine the physicochemical characteristics of  $^{131}\text{I}$ -AMB10 (plasma protein binding and lipophilicity) and internalization study of  $^{131}\text{I}$ -AMB10 using T-47D human cell line. Determination of Radiochemical purity  $^{131}\text{I}$ -AMB10 was carried out by electrophoresis method, using phosphate buffer pH 7,4, and Whatman 1 paper as stationary phase. A total of 5mL of  $^{131}\text{I}$ -AMB10 (70-100mCi) was added in a test tube containing 1.5 mL plasma protein and incubated for 10 minutes. Plasma was precipitated with 10% TCA and centrifuged. The percentage of filtrate and precipitate was calculated to determine the percentage of plasma protein binding. Lipophilicity test was carried out by mixing  $^{131}\text{I}$ -AMB10 into a test tube containing octanol and water, then separated the two layers to determine the percentage. Internalization test was carried out by inserting  $^{131}\text{I}$ -AMB10 into T47D cell culture medium, incubated for 10, 30 and 60 minutes. Cells were lysed with the addition of 2M NaOH. The optimization results were obtained radiochemical purity of  $97.53 \pm 1.08 \%$  (n=9) with incubation reaction time for 15 minutes at low temperature (2-4 °C). The percentage of plasma protein binding was  $73.66 \pm 4.99\%$  with a log P of 0.672. Internalization of  $^{131}\text{I}$ -AMB10 using T-47D cells at 10, 30 and 60 minutes was obtained  $28.47 \pm 14.55\%$ ;  $29.52 \pm 6.41\%$  and  $33.11 \pm 8.47\%$  respectively. Further research will be carried out in vitro and in vivo testing to prove the radiopharmaceutical capability as a radiopharmaceutical for breast cancer.  $^{131}\text{I}$ -AMB10 has physicochemical characteristics in accordance with the role of five. Internalization of  $^{131}\text{I}$ -AMB10 showed penetration into the T-47D cell line and the highest internalization at the 60 minutes.



## **IAEA-CN-310/81**

### **“From a participant’s perspective: IAEA Sponsored MSc Radiopharmacy – Experience, outcomes and recommendations”**

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Radiopharmacy and Nuclear Medicine are complementary. Mauritius was no exception in dealing with the lack of qualified radiopharmacists in Africa. The laudable effort of the IAEA to award fellowships (under RAF 6054) to eligible participants was warmly welcomed. Mauritius seized the opportunity. The country now has a fully qualified radiopharmacist, working full-time at the Nuclear Medicine Department. A radiopharmacist is necessary to ensure quality of nuclear medicine services offered, especially with the imminent setting up of a PET-CT service at the New Cancer Hospital. The fellowship was hosted by Morocco in collaboration with CNESTEN (Centre National de l’Energie, des Sciences et des Techniques Nucléaires). Several other stakeholders were also involved. The IAEA and the university made sure that the level and quality of the training and course content was up to the norms. Radiopharmacy, in all its aspects, was dissected and made easy to understand by the very competent lecturers. Hands-on practice enhanced laboratory skills. Radiation protection culture was inculcated throughout the course. Although Covid-19 was a major obstacle, the IAEA and the host institution devised measures to ensure the successful completion of the course. Radiopharmacy education is pivotal. Africa needs more qualified radiopharmacists and more academics. Achieving quality nuclear medicine service is not insuperable if Inter-African collaboration is nurtured, with the help of international organisations.



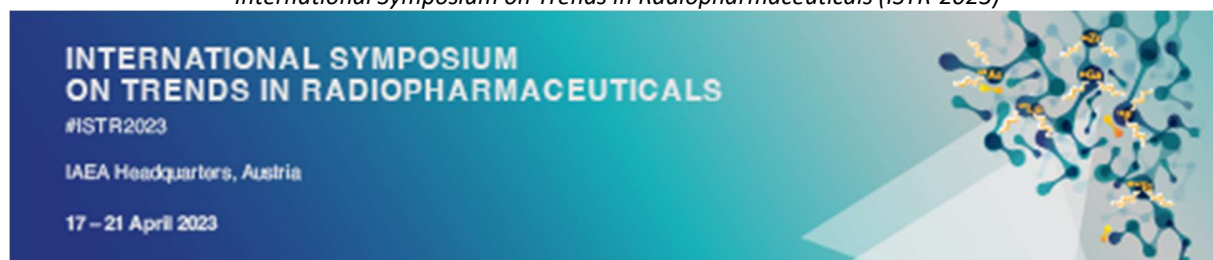
## IAEA-CN-310/82

### **Synthesis and preclinical evaluation of $^{177}\text{Lu}$ -NP(RGF)-CXCR4L as a new nanoradiopharmaceutical for colorectal cancer treatment**

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Recently, our group developed a novel HYNIC-CXCR4 ligand (CXCR4L) for specific targeting of CXCR4 positive tumors. Regorafenib (RGF) is multikinase inhibitor FDA-authorized in patients with metastatic colorectal cancer with no optimal results (6.4 months median overall survivor, side effects on 93 % of patients). Taking advantage of the CXCR4 overexpression in colorectal cancer, this research aims to synthesize, characterize and evaluate a new targeted nanoradiopharmaceutical (NRP) for the chemo/radiotherapy provided by RGF and  $^{177}\text{Lu}$  with therapeutic potential against colorectal cancer. To synthesize and biochemically characterize  $^{177}\text{Lu}$ -NP(RGF)-CXCR4L as well as to evaluate their behavior in normal mice and its potential as an agent to provide chemo/radiotherapy in colorectal cancer cells. Empty PLGA nanoparticles (NP) and RGF-encapsulated PLGA nanoparticles [NP(RGF)] were prepared using a 3D flow-focusing microfluidic Dolomite device, from an experimental design (Design Expert 11.1.2.0 software). Once synthesized NP and NP(RGF), they were conjugated to DOTA-NH<sub>2</sub> and HYNIC-CXCR4L. In this stage, 1 mg DOTA-NH<sub>2</sub> (Macrocyclics, USA) dissolved in 20  $\mu\text{L}$  of HCO<sub>3</sub> 0.02 M p.H. 9.0/100  $\mu\text{L}$  of PVA 0.5% w/v and 1 mg HYNIC-CXCR4L (ININ)/100  $\mu\text{L}$  of PVA 0.5% w/v were individually added to a previously HATU activated carboxylate NP and NP(RGF) nanoparticles solution [HATU 10 mg, DIPEA (10 $\mu\text{L}$ ) and DMF (200  $\mu\text{L}$ )]. DOTA-NP(RGF)-CXCR4L, DOTA-NP(RGF), DOTA-NP-CXCR4L and DOTA-NP were prepared using this scheme. All systems were physicochemically characterized by DLS, TEM, FT-IR, UV-Vis and the stability was evaluated. The RGF entrapment and release profile was also determined. The prepared NP was evaluated alongside with the intermediates for cytotoxicity, proliferation, uptake/internalization and cell viability. For radioisotopic imaging a colorectal cancer HCT116 tumoral model in athymic mice was used. Optimized NP and NP(RGF) with suitable polydispersity was obtained. A monomodal distribution was demonstrated. Physicochemical analyses suggest the correct NPs functionalization and characterization. The final size of NP(RGF)-CXCR4L was 302 nm with a z potential higher than 80 mV which means excellent stability due to strong repulsive forces. Spectroscopic techniques demonstrated the correct functionalization of NP with DOTA and CXCR4L. Entrapment RGF efficiency was  $91.46 \pm 0.47$  %. The NP(RGF)-CXCR4L formulation was lyophilized and redispersed for further radiolabeling. Radio-HPLC analysis showed the formation of  $^{177}\text{Lu}$ -NP(RGF)-CXCR4L with radiochemical purity >99%. In vitro studies demonstrated inhibition of 74% of viability and 61% of HCT116 colorectal cancer cells proliferation through inhibition of Erk and Akt activation, attributed to RGF effect. Late apoptotic/dead was promoted by  $^{177}\text{Lu}$ -NP(RGF)-CXCR4L rather than intermediate nanosystems. After iv administration in normal mice, both renal and hepatobiliary excretion were observed. Once demonstrated the targeted drug effect on viability and cell proliferation,  $^{177}\text{Lu}$  dosimetry studies and therapeutic efficacy is needed.  $^{177}\text{Lu}$ -NP(RGF)-CXCR4L obtained from lyophilized formulation showed high synthesis reproducibility through microfluidics technique. High in vitro stability and specific uptake/internalization in HCT116 colorectal cancer cells was observed. Therapeutic multikinase inhibition was demonstrated. This well characterized nanoradiopharmaceutical demonstrated potential as a new nanoradiopharmaceutical for colorectal cancer treatment. Since  $^{177}\text{Lu}$  radiotherapeutic effect is well documented, further therapeutic efficacy and dosimetric studies are required. This study was supported by the Mexican National Council of Science and Technology Grant CONACyT-A1-S-38087 and the COMECYT grant CAT2021-0036.



## **IAEA-CN-310/83**

### **Status, Opportunities and Future Direction of Radiopharmacy Practice in Africa**

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In Africa, radiopharmacy services are still inadequate. The Society of Radiopharmaceutical Sciences organized a congress (eSRS Africa 2021) where scientists gathered to discuss the status, gaps and the way forward to improve radiopharmacy services in African countries. Opportunities were introduced including improved communication and established networking, enhanced education, research and practice of radiopharmacy. The current Abstract summarises those opportunities and future directions.

A survey was performed to identify the status of radiopharmacy practice and the results show that African participants were mainly early career people (23%) and students (19%). Scientific work presented showed the scope of research.

Opportunities described included introducing new technology, training personnel across the various Radiopharmacy fields, establishing partnerships with experienced research groups, using research models adapted to African perspectives and sharing experience.

A practical partnership developed between the IAEA and the SRS provides a significant opportunity for enhancing radiopharmacy practice in Africa. Twenty-one Member States in Africa established the first coherent radiopharmacy network in Africa, the African Association of Radiopharmacy. The Association will organize the first conference of Radiopharmacy in Africa by the end of 2023.





**IAEA-CN-310/84**

**Registered radiopharmaceuticals, trends in clinical trials, the role of Rosatom State Corporation**

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A tremendous growth of target therapy radiopharmaceuticals on clinical trials requires more isotopes. Isotope products are mainly manufactured by national corporations. Rosatom State Corporation has the largest capacity in the world, exploiting 8 reactors. To use Rosatom's facilities effectively and to make them available worldwide it is essentially important to have a proper view upon isotopes and molecules on multinational clinical trials, radiopharmaceuticals indications, doses, time terms, infrastructure conditions and other information that may influence current and future demand for isotope products. This presentation is an attempt to summarize what is highly needed worldwide and what role may particular Rosatom's plants play currently and potentially.





**IAEA-CN-310/85**

### **Production of Terbium-161 as an Auger Emitter in Tehran Research Reactor**

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$^{161}\text{Tb}$ , as an alternative to  $^{177}\text{Lu}$  due to similar decay properties, is a promising radionuclide owing to its favorable properties for treating small-size cancer by emitting a substantial number of conversion and Auger electrons. No Carrier Added  $^{161}\text{Tb}$  can be obtained by neutron irradiation Gd through  $^{160}\text{Gd}(n,\gamma) ^{161}\text{Gd} \rightarrow ^{161}\text{Tb}$  nuclear reaction. The existence of an effective Gd/Tb separation method is critical to obtaining NCA  $^{161}\text{Tb}$  with high specific activity.

In this study separation of  $^{161}\text{Tb}$  from Gd/Tb matrix has been done using Ln resin column based on the extraction chromatography method. The eluted bed volumes from the column containing Gd/Tb matrix were quantified using Gamma Spectrometry. Due to obtaining high radionuclidic purity and yield, different experimental parameters for the effective separation of Gd/Tb such as concentration of eluting solutions and flow rate of load and elution were investigated to optimize the radio-chemical separation. The results showed that optimum Gd/Tb isolation condition was obtained using  $\text{HNO}_3$  solution with a concentration of 0.8 and 3N to separate gadolinium and terbium radionuclides, respectively. The separation yields of Tb and Gd were obtained at 83.51 % and 81.8% respectively. Finally, no carrier added radionuclide ( $^{161}\text{Tb}$ ) was prepared. The resultant NCA  $^{161}\text{Tb}$  can be used for the preparation of NCA  $^{161}\text{Tb}$  labeled radiopharmaceuticals.



**IAEA-CN-310/86**

**Diagnostic Multidose Preparation of Ready-to-Use [64Cu]Cu-ATSM for Hypoxia Targeting Using Copper-64 Produced at GE PETtrace 860**

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PETtrace 860, is a biomedical cyclotron with dedicated liquid-targets ports. In view of extending its utility towards production of Copper-64 from solid target, existing ports were modified to assemble non-commercial indigenously developed solid target irradiation unit. The present work envisages on production of clinical-grade, multi-doses [64Cu]Cu-ATSM, utilizing [64Cu]Cu<sup>2+</sup> produced in PETtrace-860.

Multiple patient-doses of [64Cu]Cu-ATSM was formulated using in-house produced [64Cu]CuCl<sub>2</sub> in 0.2N CH<sub>3</sub>COONa (28°C, 30min, pH~5.5) with H<sub>2</sub>-ATSM(2µg/µL), purified with light-tC18. In-vitro stability was ascertained by sodium-ascorbate(~7.0µg/MBq). RCP was evaluated by radio-TLC and radio-HPLC. Melanoma CA cell-line (B16F10) was used for in-vitro evaluation. In-vivo biodistribution was performed in C57BL/6-mice bearing syngeneic tumor with B16F10 cell-lines.

Using ~18mCi of [64Cu]CuCl<sub>2</sub>, ~17mCi of [64Cu]Cu-ATSM was produced with RCY ~95%(n=5). The RCP was >98%(Rt: 13.25min). In-vitro stability was upto 6h post-radiolabeling at 4°C (Ethanol <5%).

[64Cu]-ATSM showed significant retention with B16F10-melanoma cells(~18.5%) in hypoxic condition, reaching plateau after 30 min. In bio-distribution study, radioactivity in most of the organs decreased after 12h post-injection. High retention of radioactivity was found in liver and tumor.

The quality control parameters of the produced [64Cu]Cu-ATSM were validated, thus establishing the potential of PETtrace-860 for producing Copper-64 and its further uses in formulation of clinical-grade multiple patient-doses of 64Cu- based radiopharmaceuticals.



**IAEA-CN-310/87**

### **[68Ga]Ga-FAPI-4 and [18F]FDG in the Detection Non-Iodine Concentrating Thyroid Carcinoma**

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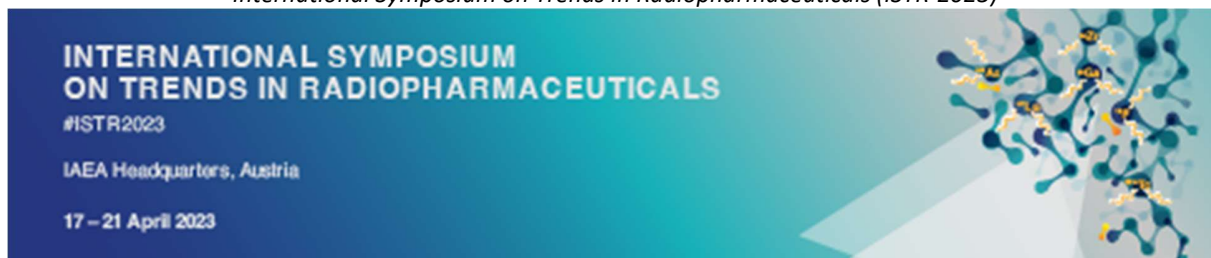
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The fibroblast activation protein (FAP) is a type-II transmembrane glycoprotein which is overexpression of cancer-associated fibroblasts (CAFs) in different epithelial tumors. The present study aims to compare the diagnostic performances of [68Ga]Ga-FAPI-4 PET/CT and [18F]FDG PET/CT in Non Iodine concentrating Poorly differentiated thyroid Carcinoma (PDTC) cell lines at in-vitro and xenograft SCID mice model and in thyroglobulin elevated negative iodine scintigraphy (TENIS) patients.

FAPI-4 was radiolabeled with pre-concentrated [68Ga]GaCl<sub>3</sub> (sourced from 68Ge/68Ga Generator) in 1N-CH<sub>3</sub>COONa buffer [95°C:15min:pH~4.0] and purified using light C-18 SPE-column. PDTC cell-line, FRO, expressing FAP, was used for in-vitro receptor binding and internalization study. In-vivo biodistribution studies were performed in SCID mice bearing tumor xenograft of FRO cell-lines. Study with PDTC patients are in progress using both [18F]FDG and [68Ga]Ga-FAPI-4 followed by PET/CT scan.

[68Ga]Ga-FAPI-4 showed rapid binding with FRO cells (30%). Bio-distribution study showed clearance of radioactivity 1H PI. Uptake and long-term retention were found in the tumor, which corroborated with scintigraphy results. [68Ga]Ga-FAPI-04 showed a comparable sensitivity with [18F]FDG PET/CT.

[68Ga]Ga-FAPI-04 PET/CT is of comparable sensitive with [18F]FDG PET/CT in detecting Thyroid CA lesions, and SUVmax is correlated well with tumour volume.



**IAEA-CN-310/88**

**Multidoses formulation of [68Ga]Ga-WL12 and Its Preclinical Evaluation for Clinical Translation in Patients with Metastatic Breast and Cervical Cancer**

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Programmed cell death ligand-1 (PDL-1) are overexpressed in cervical and breast cancer patients. The present work was aimed to establish a protocol for radiochemical-synthesis of bulk-doses of [68Ga]Ga-WL12. The in-vitro cell-lines and in-vivo bio-distribution studies was carried out towards envisaging its use as a promising diagnostic radiotracer in cervical and breast CA patients.

WL-12 was conjugated with p-NCS-benzyl-DOTA at 1:10 molar ratios (pH~8.0) and purified using PD-10. The DOTA-benzyl-WL12 were radiolabeled with pre-concentrated [68Ga]GaCl<sub>3</sub> in acetate-buffer (95°C, 15min, pH~4.0) and purified using C-18 SPE column. RCP was evaluated using radio-TLC and radio-HPLC. Cervical and breast CA cell-line (HeLa and MCF7), used for in-vitro evaluation. In-vivo biodistribution carried out in nude mice bearing tumor-xenograft induced by MCF7 cell-lines.

Using 22mCi of [68Ga]GaCl<sub>3</sub>, ~16mCi of [68Ga]-DOTA-WL12 was prepared. The RCP was >98%. In-vitro saline stability was upto 3h post-radiolabeling

[68Ga]-DOTA-WL12 showed rapid binding with MCF7(~25%) and HeLa(~16%) cells, reaching plateau after 30 min. In bio-distribution study, radioactivity in most of the organs decreased after 5h post-injection. High retention of radioactivity was found in tumor.

Clinical multiple patient doses formulation of [68Ga]-DOTA-WL12 was successfully developed. Pre-clinical results demonstrate the promising potential of radiotracer for clinical translation in cervical and breast CA patients.



**IAEA-CN-310/89**

**Patient Doses formulation of [177Lu]Lu-DOTA-Atezolizumab Using Low Specific Activity [177Lu]LuCl<sub>3</sub> : A Potential Therapeutic Agent for PD-L1 Targeting**

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Programmed cell death ligand-1 (PDL-1) proteins are overexpressed in variety of cancers namely cervical, small-cell lung, breast etc. The present work thus envisages to establish a radiolabeling protocol for [177Lu]Lu-DOTA-Atezolizumab using low specific-activity (<15mCi/μg) [177Lu]LuCl<sub>3</sub>. In-vitro stability, immunoreactivity and cell-binding studies carried out in HeLa and MCF7 cell-lines. In-vivo biodistribution were carried out in suitable animal model.

Pre-concentrated Atezolizumab was coupled to p-NCS-benzyl-DOTA at 1:10 molar-ratios (pH:8) and purified using PD-10. DOTA-benzyl-Atezolizumab was radiolabeled with [177Lu]Lu-Acetate (37°C, 90min, pH~6.5). In-vitro stability was ascertained by ascorbic-acid (~240μg/37MBq). RCP was evaluated by radio-TLC and radio-HPLC. Cervical and breast CA cell-lines (HeLa and MCF7) were used for in-vitro evaluation. In-vivo biodistribution was carried out in SCID-mice bearing tumor-xenograft induced by MCF7 cell-lines.

Using 175mCi of [177Lu]LuCl<sub>3</sub>, ~148mCi of [177Lu]Lu-DOTA-Atezolizumab was prepared. The RCP was >98%. In-vitro saline stability was upto 96H post-radiolabeling at -20°C.

[177Lu]Lu-DOTA-Atezolizumab showed rapid binding with MCF7(~25%) and HeLa(~16%) cells, reaching plateau after 30min. In bio-distribution study, radioactivity in most of the organs decreased 3days post-injection. High retention of radioactivity was found in tumor.

Patient doses formulation of [177Lu]Lu-DOTA-Atezolizumab was successfully developed. Promising pre-clinical results demonstrates, [177Lu]Lu-DOTA-Atezolizumab is a potential therapeutic radiopharmaceutical for clinical translation in cervical/breast CA patients.



## IAEA-CN-310/90

### **Gallium-68 Radiolabeled Bioactive Naphthoquinonoid Derivatives and its Pre-clinical Evaluation: PIN1 Potential Diagnostic Agents for Targeting PIN1 Positive Cancers**

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Bioactive naphthoquinonoid derivatives, Juglone and Plumbagin are potential agents for diagnosis of PIN1 positive breast cancers. The present work envisages to establish a radiolabeling protocol for DOTA-benzyl-plumbagin and DOTA-benzyl-juglone with  $[^{68}\text{Ga}]\text{GaCl}_3$ . In-vitro pharmacokinetic and in-vivo bio-distribution studies were carried out for radioactive formulations.

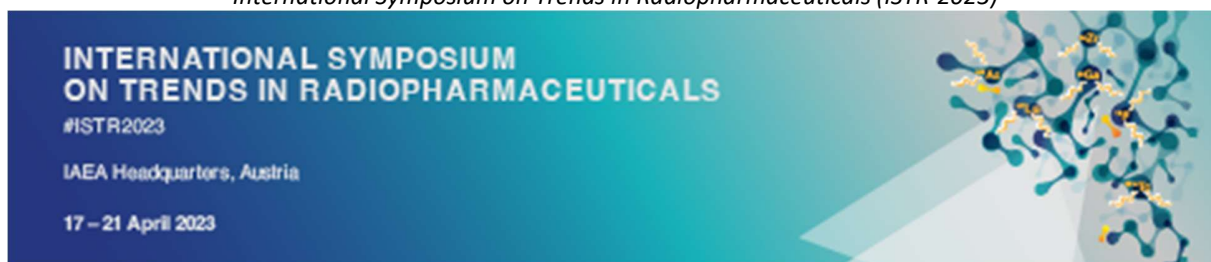
Juglone and plumbagin propyl-amine derivatives were synthesized using N-Boc-3-bromopropylamine and purified. Both derivatives were conjugated with p-NCS-benzyl-DOTA at 1:10 molar-ratios (pH~8.0). DOTA-benzyl-plumbagin and DOTA-benzyl-juglone (50 $\mu\text{g}$  each) were radiolabeled with  $[^{68}\text{Ga}]\text{GaCl}_3$  in acetate-buffer (95 $^\circ\text{C}$ , 15min, pH~4.0) and purified. RCP was evaluated using radio-TLC and radio-HPLC. Human breast-cancer cell-lines, MCF7 and MDA-MB-231, expressing PIN1 were used for in-vitro evaluation. In-vivo biodistribution studies were performed in SCID-mice bearing tumor xenograft induced by MCF7 cell-lines.

$[^{68}\text{Ga}]\text{-DOTA-plumbagin}$  (~19mCi) and  $[^{68}\text{Ga}]\text{-DOTA-juglone}$  (~16mCi) were prepared from 25mCi of  $[^{68}\text{Ga}]\text{GaCl}_3$ , The RCP for both formulations were >95%. In-vitro saline stability was upto 3h post-radiolabeling.

Rapid binding was observed for  $[^{68}\text{Ga}]\text{Ga-DOTA-juglone}$  (~25%) and  $[^{68}\text{Ga}]\text{Ga-DOTA-plumbagin}$  (~15%) with MCF7 cells, reaching plateau after 30-60min. In bio-distribution studies, radioactivity in most of the organs decreased after 6h post-injection, while high retention of radioactivity was found in tumor.

Clinical dose formulation of  $[^{68}\text{Ga}]\text{-DOTA-naphthoquinonoid}$  derivatives was successfully developed. Pre-clinical results demonstrate the promising potential of  $[^{68}\text{Ga}]\text{Ga-DOTA-naphthoquinonoid}$  derivatives for clinical translation in PIN1 positive breast cancers patients.





## **IAEA-CN-310/91**

### **Moving forward of radiopharmacy education in Thailand**

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Over the last decade, nuclear medicine service in Thailand has become increasingly important. However, the lack of qualified personnel is one of the limitations to enhancing capacity and capability of radiopharmaceuticals to fulfil international quality standard.

In 2006, the first radiopharmacy training course in cooperated with the IAEA and Thailand Institute of Nuclear Technology (TINT) was launched and 22 participants attended. The emerging of radiopharmacy into academic programme was begun in 2016 for undergraduate programme of Pharmacy, Faculty of Pharmacy, Mahidol University. Professional elective course in Radiopharmaceutical chemistry and Professional practice in hospital radiopharmacy laboratories are available for a fifth-year student. For graduate programme, both master's and doctoral degrees related to radiopharmaceuticals development are additionally offered.

Consequently, the continuing professional programme on radiopharmacy was initially planned in 2019 by Nuclear Medicine Society of Thailand (TSNM) to standardise and update knowledge of the personnel involved in radiopharmacy operation. However, covid-19 pandemic disrupted the plan. Currently, TSNM and TINT resume this course and will be held in 2023. The 2-week certification course will provide basic and advanced lectures including practical sections.

Therefore, success and sustainability of radiopharmacy education are essentially required support from professional societies, academic sectors and nuclear medicine centres.



## IAEA-CN-310/94

### Cyclotron Production and Quality Control of $^{68}\text{Ga}$ using High Power Solid Target for Theranostic Applications

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$^{68}\text{Ga}$  ( $E_{\beta^+ \text{max}}=1.8$  MeV,  $\beta^+$  89%,  $T_{1/2} = 68$  min) has played a remarkable role in clinical applications worldwide. Specially as a diagnostic isotope for pairing with therapeutic radiometal isotopes, particularly when targeting molecules that can utilize the same chelator for both  $^{68}\text{Ga}$  and the therapeutic radioisotopes (for example,  $^{177}\text{Lu}$ ,  $^{225}\text{Ac}$  and  $^{90}\text{Y}$ ). In this work we develop a well-established method for the production of  $^{68}\text{Ga}$  cyclotron-based production via the nuclear reaction  $^{68}\text{Zn}(p,n)^{68}\text{Ga}$  using high power electroplated solid target (150  $\mu\text{A}$ , 13 MeV proton beam). The target is made of copper pre-electroplated with silver then electroplated by enriched  $^{68}\text{Zn}$ .

The irradiation of the prepared target for 60 min of proton beam yield of  $92.5 \pm 3.7$  GBq EOB ( $n=3$ ). High grade HCl is used for dissolution of enriched  $^{68}\text{Zn}$  layer. The separation and purification of  $^{68}\text{Ga}$  is performed in two steps using Dowex 50W-X4 for adsorption of trace metals (Fe, Cu and Zn) then DIPE is used for high purity  $^{68}\text{Ga}$  extraction.

The analysis of trace metal was performed by anodic stripping voltammetry method. The level of Zn and Fe was  $0.1 \pm 0.05$  and  $0.2 \pm 0.07$   $\mu\text{g}/\text{GBq}$  of  $^{68}\text{Ga}$  respectively ( $n=3$ ).



**IAEA-CN-310/97**

**Production and Radiochemical Separation of  $^{89}\text{Zr}$  via  $^{89}\text{Y}(p,n)^{89}\text{Zr}$  Route Using an Indigenously Developed Solid Target Irradiation Assembly**

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The 16.5 MeV GE PETtrace-800 at the Radiation Medicine Centre, Mumbai India is routinely used to produce and supply  $^{18}\text{F}$ -radiopharmaceuticals. To extend the utility of PETtrace-800, a semi-automated solid target assembly has been indigenously designed and fabricated to source other medically useful radioisotopes.

$^{89}\text{Zr}$  a positron emitter with a half-life of 78.4 h is a promising radionuclide for immuno-PET studies. This work reports on the production of  $^{89}\text{Zr}$  via the  $^{89}\text{Y}(p,n)^{89}\text{Zr}$  route and the radiochemical separation from the irradiated Y target.

The target was prepared by sandwiching 150  $\mu\text{m}$  thick natural yttrium foil (99.9%) between two copper disks. This foil target was irradiated with 10  $\mu\text{A}$  proton current for 30 minutes. After irradiation, chemical separation of  $^{89}\text{Zr}$  from its target material  $^{89}\text{Y}$  was carried out using Sephadex G-25 resins. Offline gamma spectrometry was used to determine the radionuclidic purity (RNP) and the radiochemical yield (RCY).

The EOB yield of  $^{89}\text{Zr}$  was 3.38  $\text{MBq}\mu\text{A}^{-1}\text{h}^{-1}$ . The RCY of the purified  $^{89}\text{Zr}$  using the Sephadex G-25 resins was 55%. The recorded  $\gamma$  spectrum of purified  $^{89}\text{Zr}$  shows only the 511 and 909 KeV peaks indicating high RNP (99%).

The indigenously developed solid target irradiation assembly has allowed broader access to several promising radionuclides, including copper-64 and zirconium-89. Research level production of  $^{89}\text{Zr}$  has been demonstrated. The quality control parameters of the produced  $^{89}\text{Zr}[\text{Zr}^{4+}]$  were validated.



IAEA-CN-310/99

## **Theoretical Estimation of Radiation Safety Parameters in $^{111}\text{In}$ Production via $^{111}\text{Cd}(p,n)^{111}\text{In}$ Route Using Indigenously Developed Solid Target Assembly**

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A prototype solid target assembly has been designed to be used for medical radioisotope production, at Radiation Medicine Centre (RMC). This study is aimed at evaluating the radiation safety aspects during the production of  $^{111}\text{In}$  using this assembly design.

During the production of  $^{111}\text{In}$  via the  $^{111}\text{Cd}(p,n)^{111}\text{In}$  route, the radiation safety parameters such as neutron and photon yields, corresponding ambient dose-equivalent rates, radioactivation in different parts of the solid target assembly and photon ambient dose equivalent decay rates with time after EOB have been evaluated for the proposed design using Fluka code.

While the neutron and photon ambient dose rate at 30 cm from the target assembly were found to be  $6.35\text{E}+02 \text{ mSvh-}1\mu\text{A-}1$  and  $3.78\text{E}+01 \text{ mSvh-}1\mu\text{A-}1$  respectively along the beam direction, the corresponding values were  $1.53\text{E}+03 \text{ mSvh-}1\mu\text{A-}1$  and  $6.80\text{E}+01 \text{ mSvh-}1\mu\text{A-}1$  respectively, along the perpendicular to the beam direction. The theoretically estimated yield of  $^{111}\text{In}$  obtained is  $3.66\text{E}+01 \text{ MBq}\mu\text{A-}1\text{h-}1$ . The photons dose rate becomes reasonably low at 30 cm from the assembly, after 30 h decay.

This study illustrates that a sufficient quantity of  $^{111}\text{In}$  can be produced with adequate radiation safety at RMC with proposed solid target assembly design. Post irradiation, a 30 h decay is essential to minimize the radiation hazards involved in subsequent handling of the system.



**IAEA-CN-310/100**

**“Regulatory Practices to Ensure Safe and Secure Production and Use of Radiopharmaceuticals in Pakistan”**

zahra kousri

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In Pakistan, Technetium-99m, generated from decay of Mo-99, which is produced locally is used in most of the nuclear medicine procedures. In order to ensure the special quality of radiopharmaceuticals, Pakistan follows all the regulations of PNRA and European/US Pharmacopeia.

Pakistan Nuclear Regulatory Authority (PNRA) ensures the implementation of the regulatory requirements to improve the quality, safety and security of radiopharmaceuticals during production, dispensing, storage, transport and use of radioisotopes via licensing, authorizations, review & assessment and inspection & enforcement tools. PNRA has established regulatory framework for licensing of nuclear installations and radiation facilities, safe transport of radioactive material, radiation protection, radioactive waste management, management of nuclear/radiological emergency and to perform enforcement actions in case of non-conformances. Accordingly, PNRA has licensed MPF-I and has registered the site for construction of another such facility namely Molybdenum Production Facility-2 (MPF-2). Currently, processes for revalidation of operating license of MPF-1 and issuance of construction license to MPF-2 are underway at PNRA.

This paper will discuss detailed regulatory requirements, PNRA practices to license the radioisotope production facilities and regulatory inspections during production, storage, transport and dispensing of radiopharmaceuticals. The challenges during implementation of regulatory requirements will also be discussed.



**IAEA-CN-310/101**

## **Radionuclidic Impurities in Medical Radiosotopes Andregulatory Concerns in Patient Dose**

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The radioactive by-products called impurities are also produced during production of desired medical radioisotope. The impurities should be eliminated to meet the quality standards before injection to avoid undue radiation dose to the patient. The removal of impurities with chemical process is sometimes challenging, however these impurities be minimized by careful selection of target, incident beam, beam energy and decay process. During the production of medical radioisotopes such as  $^{68}\text{Ga}$ ,  $^{64,67}\text{Cu}$ ,  $^{89}\text{Zr}$ ,  $^{90}\text{Y}$  through proton and alpha reactions, the by-products like  $^{62,63,65}\text{Zn}$ ,  $^{58,60}\text{Co}$ ,  $^{89\text{g,m},90,91\text{m},92\text{m}}\text{Nb}$  are also produced. This is because different reaction channels open at different beam energies. In this paper, radionuclidic impurities in the production of medical radioisotopes ( $^{68}\text{Ga}$ ,  $^{64,67}\text{Cu}$ ,  $^{89}\text{Zr}$ ,  $^{90}\text{Y}$  etc.) through proton and alpha reactions and methods to eliminate or minimize impurities will be discussed. In addition, the paper will include detailed discussion on activation of different targets with proton and alpha beams, production yields, isotopic ratios, and decay characteristics of main product and by-products.





## IAEA-CN-310/102

### Radiochemical Isolation of Cyclotron Produced Positron-Emitting $^{51}\text{Mn}$ Using N,N,N',N'-tetra-n-octyldiglycolamide (DGA) resin

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N,N,N',N'-tetra-n-octyldiglycolamide (DGA, normal) and N,N,N',N'-tetra-2-ethylhexyldiglycolamide (DGA, branched) resins (Eichrom, Lisle, IL) were investigated for the purification of  $^{51}\text{Mn}$  ( $t_{1/2}=46.2$  min,  $E_{\beta^+}=960\pm 2$  keV,  $I_{\beta^+}=97 \pm 3\%$ ) produced from 16 MeV proton irradiation of  $^{54}\text{Fe}$  targets. Batch resin experiments were conducted with both resins in 0.1-5.0 M HCl. Solutions contained stable  $\text{Fe}^{2+/3+}$  and  $\text{Mn}^{2+}$  (1.1 mg/mL and 0.6 mg/mL, respectively). 30% (w/v)  $\text{H}_2\text{O}_2$  was added to oxidize  $\text{Fe}^{2+}$  to  $\text{Fe}^{3+}$ . MP-AES determined the concentration of both  $\text{Fe}^{3+}$  and  $\text{Mn}^{2+}$  eluted from each column for varying concentrations of HCl. At 5 M HCl,  $1.1 \pm 0.5$  mg/mL of  $\text{Mn}^{2+}$  and  $0.0 \pm 0.1$  mg/mL of  $\text{Fe}^{3+}$  was detected for normal DGA and  $1.4 \pm 1.2$  mg/mL of  $\text{Mn}^{2+}$  and  $0.1 \pm 0.1$  mg/mL of  $\text{Fe}^{3+}$  for branched DGA. The measured  $\text{Fe}^{3+}$  affinity ( $D_w$ ) for normal and branched DGA resin was of order  $10^3$  and  $10^2$ , respectively, at 5 M HCl;  $\text{Mn}^{2+}$  was not retained by either resin (A). These results informed dynamic column experiments with unbranched DGA resin, achieving decay corrected separation yields of  $90 \pm 6\%$  ( $n=4$ ) and a separation factor of  $(1.03 \pm 0.2) \times 10^6$  ( $n=4$ ) (B). High-pressure ion chromatography (HPIC) confirmed the concentrations of toxic metals met Chemistry, Manufacturing, and Controls (CMC) acceptance criteria ( $\text{Cu} < 6$  ppm,  $\text{Ni} < 2$  ppm,  $\text{Co} < 0.5$  ppm) (C). Gamma spectroscopy confirmed a  $^{51}\text{Mn}$  radionuclidic purity of 99.8% at end of chemistry, with the balance  $^{51}\text{Cr}$  (D). This work motivates exploration of  $^{51}\text{Mn}$  as a clinical diagnostic tool in PET imaging



### IAEA-CN-310/103

#### **In House Preparation and Biodistribution of $^{90}\text{YCl}$ , $^{90}\text{Y-DOTATATE}$ , $^{90}\text{Y-FHMA}$ and $^{90}\text{Y-EDTMP}$ for Therapeutic Application**

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In this work the radiolabeling and biodistribution of  $^{90}\text{YCl}$ ,  $^{90}\text{Y-DOTATATE}$ ,  $^{90}\text{Y-FHMA}$  and  $^{90}\text{Y-EDTMP}$  were carried out. A routine production method of  $^{90}\text{YCl}$  was performed using an  $^{90}\text{Sr}/^{90}\text{Y}$  generator (KAMADHENU) with a yield of  $> 98\%$ . All compounds were successfully labeled with  $^{90}\text{Y}$  and the Radiolabelling yields were greater than  $98\%$ . Experiments in rats were carried out in accordance with appropriate European Community directive guidelines (86/609/EEC). Biodistribution studies were performed in healthy Wister Han rats (male, 160–220 g). The animals were anesthetized and sacrificed, routinely 1, 3, and 24 h post-intravenous injection (p.i.) for  $^{90}\text{YCl}$ ,  $^{90}\text{Y-DOTATATE}$ , and  $^{90}\text{Y-EDTMP}$ , Whereas Biodistribution of  $^{90}\text{Y-FHMA}$  was performed at 1 hours. Selected organs were taken out. The radioactivity of weighted samples of femur, heart, liver, lungs, kidneys, spleen, stomach, intestine, and blood were measured using a gamma counter CE/SN:03 L 504. The uptakes in the different selected organs, expressed as  $\%ID(\pm SD)/g$ , of the organs for all the radiolabeled compounds. Femur was taken as a representative of the skeleton and observed uptakes in femur were  $2.62\%/g$ ,  $13\%/g$ ,  $10.72\%/g$  and  $17.57\%/g$  for  $^{90}\text{YCl}$ ,  $^{90}\text{Y-DOTATATE}$ ,  $^{90}\text{Y-FHMA}$  and  $^{90}\text{Y-EDTMP}$ , respectively, at 1 h post injection. Normal uptake in kidney was observed for all compounds, no increase of the uptake in any of the organs and tissues were observed, except for  $^{90}\text{YCl}$ , and  $^{90}\text{Y-EDTMP}$  the activity of bone was increased after 3 h post injection from ( $2.62\%/g$  and  $17.57\%/g$ ) to ( $8.86\%/g$  and  $49.86\%/g$ ) and then it decreased after 24h post injection to ( $0.38\%/g$  and  $1.154\%/g$ ) respectively.  $^{90}\text{Y-DOTATATE}$  was located in the bones closely to distribute  $^{90}\text{YCl}$  after 2 hours ( $10.09\%/g$  and  $8.86\%/g$ ), then decrease to  $4.166\%/g$  and  $0.38\%/g$  respectively,. Normal  $^{90}\text{Y-DOTATATE}$  uptake in kidney ( $2.07\%/g$ ) and high uptake in blood ( $6.24\%/g$ ) were observed after 24 hours post injection.



## IAEA-CN-310/104

### **Project Concept Paper (PCP) presented in IAEA-KOICA-KAERI Joint Training Programme: CNEA Coordinated Project for Clinical Translation of Theragnostic Radiopharmaceuticals in Argentina**

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A PCP for Clinical Translation of Theragnostic RPs based on a management system (MS) that coordinates the CNEA resources in a centralized way has been designed with the help of IAEA-Koica is presented with the goal to provide innovative therapies in the field of nuclear medicine and improve the quality of life of Argentina population

Several radioisotopes are proposed for the PCP under design:  $^{68}\text{Ga}$ ,  $^{99\text{m}}\text{Tc}$ ,  $^{177}\text{Lu}$  and  $^{225}\text{Ac}$  for theragnostics pairs RPs based on PSMA inhibitors analogues. The MS proposed coordinates the clinical translation in all its development stages, through two thematic axes: Non-clinical trial and clinical trial axes (Fig.1). Non-clinical trial stages were design according FDA and EMA preclinical guidelines, resulting in a ten-steps non-clinical development strategy (Fig.2). Clinical Trials will be design by CNEA Clinical Committee. Besides, training on Clinical Translation issues, close linkage with regulatory organisms and concept paper publication are proposed.

In the framework of IAEA-KOICA-KAERI Joint Training Programme we could design a PCP which integrates the existing resources in CNEA clinical translational chain, and coordinates them in an orderly and efficient manner through an internal MS.



## IAEA-CN-310/105

### Ac-225 production Using the Experimental Fast Reactor Joyo

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Ac-225 can be applied to cancer treatment of various sites, but world supply is scarce. In this study, the feasibility of producing Ac-225 using fast neutrons in the experimental fast reactor Joyo was investigated.

The reaction chain is shown in Fig. 1. The amount of Ac-225 produced by irradiation with Ra-226 in Joyo was evaluated by burnup calculation using ORIGEN2.2 code. In addition, the uncertainty of the amount of Ac-225 produced was evaluated.

Figure 2 shows the results of the burnup calculation. Ra-225, which is the parent nuclide of Ac-225, is produced by irradiating 1 g of  $^{226}\text{Ra}$  in Joyo for 60 days. Since the Ac produced immediately after irradiation contains highly toxic Ac-227, it is separated and discarded. A pure Ac-225 newly generated from the decay of Ra-225 can be extracted. Milking of Ra-225 extracts about 0.64 Ci of Ac-225. The uncertainty of production was estimated to be 55% by propagation from the uncertainties of Ra-226 cross section and neutron flux.

As a result, it was shown that a large amount of Ac-225 could be produced in Joyo by irradiating Ra-226. In the future, we will confirm the accuracy of the evaluation of the generated amount through demonstration experiments.



## IAEA-CN-310/106

### Challenge for Mo-99/Tc-99m production by JRR-3

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Japan depends on foreign countries for many medical isotopes, and in order to realize domestic production from the viewpoint of enhancing the security of the medical system, the Atomic Energy Commission formulated the "Action Plan for the Production and Use of Radioisotopes for Medical Purposes" on May 31, 2022. In this Action Plan, one of the goals is to "manufacture and supply approximately 30% of the domestic demand for Mo-99/Tc-99m by utilizing Japan Research Reactor No.3 (JRR-3)".

JRR-3 stopped operation after the Great East Japan Earthquake in 2011 to meet the new regulatory standard, but resumed operation at the end of February, 2021. JRR-3 has several utilization facilities for neutron beam experiments, irradiation tests of reactor material, and manufacturing radio isotopes for medicine use and silicon semiconductor by transmutation.

JAEA is aiming to establish production technology of Mo-99 by neutron capture method, making effective use of the performance of JRR-3. The demonstration test is scheduled to be completed in 2025, and the prospect for domestic production of Mo-99 is expected to be established. In this issue, we will introduce the current status of the test.



**IAEA-CN-310/107**

### **Development of [<sup>89</sup>Zr]Zr-DFO-Trastuzumab for Immune PET Imaging of HER2+ tumors**

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In this study, [<sup>89</sup>Zr]Zr-DFO-trastuzumab was prepared and preclinical evaluation of this immune-PET imaging agent was studied. [<sup>89</sup>Zr]Zr-DFO-Trastuzumab was prepared with radiochemical purity of >98% at the optimized conditions (chelator: mAb ratio of 10:1, <sup>89</sup>Zr/mAb ratio of 74 MBq:1 mg, temperature of 37 °C and pH=7). The radioimmunoconjugate was stable both in PBS buffer and in human serum for at least 48 h. Cell studies including binding assay and internalization were carried out on HER2+ BT474 cell line and HER2- CHO cell line indicating the high affinity of the radioimmunoconjugate to HER2+ cells. Biodistribution and imaging studies in HER2+ BT474 tumor-bearing mice demonstrated the significant uptake values of [<sup>89</sup>Zr]Zr-DFO-Trastuzumab in tumor sites. Also, a women with HER2+ metastatic breast cancer that was under treatment with Herceptin underwent both [<sup>89</sup>Zr]Zr-DFO-Trastuzumab and [<sup>18</sup>F]FDG PET/CTs. Notably, [<sup>89</sup>Zr]-DFO-Trastuzumab PET/CT revealed metastatic lesions almost similar to the [<sup>18</sup>F]FDG PET/CT scan findings. According to the results, [<sup>89</sup>Zr]Zr-DFO-Trastuzumab can be considered as a high potential radiopharmaceutical for PET imaging of the patients with HER2+ tumors.





**IAEA-CN-310/108**

### **Development of [<sup>89</sup>Zr]Zr-PSMA-617 for Prostate Cancer PET Imaging**

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In this study, preparation and preclinical studies of [<sup>89</sup>Zr]Zr-PSMA-617 was evaluated. [<sup>89</sup>Zr]ZrCl<sub>4</sub> was prepared by passing [<sup>89</sup>Zr]Zr(ox)<sub>2</sub> through a preactivated strong cation exchange cartridge (QMA, Waters). [<sup>89</sup>Zr]Zr-PSMA-617 was produced according to published papers with slight modifications [74 MBq [<sup>89</sup>Zr]Zr-PSMA-617, 25 μg (20.5 nmol) PSMA-617, temp. = 95°C in two steps, Step 1: time = 30 min; pH=3-4 and Step 2: time = 30 min; pH=4-5). The final preparation was passed through a preconditioned C18 cartridge. The final radioligand was prepared with radiochemical purity > 96% (RTLC, HPLC) and specific activity of 3.4 TBq/mmol. [<sup>89</sup>Zr]Zr-PSMA-617 was stable in PBS buffer (4°C) and in human serum (37°C) for at least 48 h. Cell studies including binding assay and internalization were carried out on PC3 and LNCaP cell lines as well as CHO cell line indicating the high affinity of the radioligand to PC3 and LNCaP cells. The biodistribution and imaging of [<sup>89</sup>Zr]Zr-PSMA-617 in PC3 tumor-bearing mice at different intervals post-injection showed the significant uptake of the radioligand in tumor sites. The results indicated the high potential of [<sup>89</sup>Zr]Zr-PSMA-617 for PET imaging of prostate cancer.



## IAEA-CN-310/109

### Study of the Molybdenum Recovery from Used $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ Gel Generators

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The Institute of Nuclear Physics in Almaty, Kazakhstan, produces  $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$  gel generators using  $^{99}\text{Mo}$  with a specific activity from 0,8 to 1,8 Ci/g obtained by irradiation of natural molybdenum oxide in WWR-K research reactor with a neutron flux of  $1,7$  to  $2,0 \cdot 10^{14} \text{ n} \cdot \text{cm}^{-2} \cdot \text{s}^{-1}$ .

Use of molybdenum enriched to at least 95% of  $^{98}\text{Mo}$  increases the specific activity of  $^{99}\text{Mo}$  up to 3,5 times, depending on target geometry, with a corresponding increase of the generator activity and/or time of precalibration. Recycling of valuable enriched  $^{98}\text{Mo}$  would improve economic efficiency of the process.

This paper presents the results of study of the molybdenum recovery from zirconium polymolybdate gel remaining in used  $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$  gel generators for its future reuse in the production of new generators.

Molybdenum was extracted by sequential leaching with a 4M solution of ammonium hydroxide. The content of molybdenum and zirconium in the zirconium polymolybdate gel before and after leaching was determined by X-ray fluorescence analysis. It was experimentally found that 95% molybdenum extraction is achieved by triple leaching at  $70\text{-}75^\circ\text{C}$  for 60 minutes with intensive stirring. Further purification of the leached molybdenum was done by precipitation with 8-hydroxyquinoline in the form of  $\text{MoO}_2(\text{C}_9\text{H}_6\text{ON})_2$ . After filtration, washing and drying, the precipitate was annealed in a muffle furnace at  $500^\circ\text{C}$  until the formation of molybdenum oxide.



**IAEA-CN-310/110**

### **Strengthening radiopharmacy practices in Morocco**

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The first applications of nuclear and radiation techniques for medical purposes in Morocco were introduced since 1950s. Following technological developments and establishing the necessary infrastructures, nuclear medicine has been developed over the last decades and will likely continue to rise in the future by opening new nuclear medicine centres across the country in addition to the current 25 centres operating at level 2b.

Diagnostic radiopharmaceuticals are the majorly applied radiopharmaceuticals in the hospital Radiopharmacies, while therapeutic and theranostic applications except internal iodine radiotherapy are still in the growing process.

To meet the growing domestic demand, Morocco has developed capacities in radiopharmaceutical production for nuclear medicine. The National Center for Nuclear Energy, Science and Technology (CNESTEN) has recently obtained the marketing authorization of Iodine 131 produced using the research reactor Triga Mark II. Other radiopharmaceuticals for SPECT applications are in the process of development and production by CNESTEN. Two industrial cyclotrons are regularly producing short lived radiopharmaceuticals (mainly FDG-18) for PET imaging since 2010.

Furthermore, Morocco has established its own regulatory framework for radiopharmaceuticals which are combining two very restrictive regulatory requirements for both nuclear and pharmaceutical aspects, depending on two independent authorities.

Regarding the human resources, it worth to mention that the Faculty of Medicine and Pharmacy of Rabat, jointly with CNESTEN, is running a master's programme in radiopharmacy in collaboration with the IAEA for French-speaking countries with the objective to ensure sustainability and Improvement of Radiopharmacy Services at national and regional level.



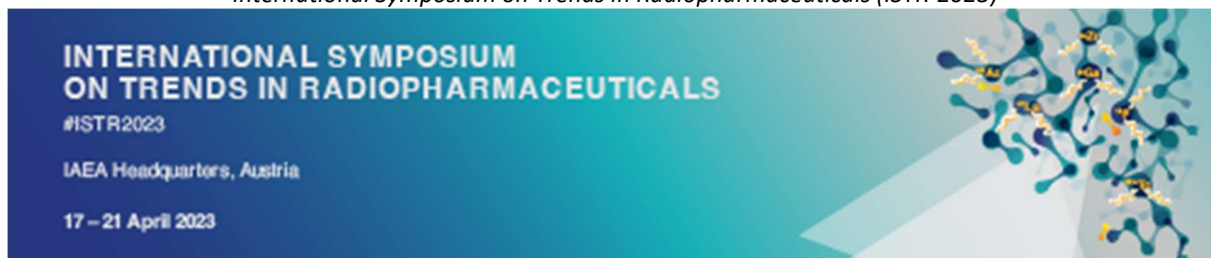
**IAEA-CN-310/111**

## **Establishing Good Radiopharmacy Practice in Mauritius: A case study for Africa**

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In Mauritius, only two nuclear medicine centres are currently established: a national hospital department providing diagnostic services with radiopharmaceuticals for Single Photon Emission Tomography (SPECT) and a private clinic mostly producing 2-deoxy-2-[<sup>18</sup>F]fluoro-D-glucose (FDG) for Positron Emission Tomography (PET). The construction of other diagnostic centres is underway and, considering approximately a 2-million inhabitants, a satisfactory coverage of the national diagnostic demand could be envisaged. However, there are still unsolved issues that can compromise the quality and reliability of the diagnostic service, and it is argued that these problems also affect many other countries in the African region. In this context, the Mauritius case could be conveniently used as a reference paradigm. A critical problem is the absence of a national regulatory framework for handling the preparation and quality control of radiopharmaceuticals according to internationally accepted standards as dictated by the principles of Good Radiopharmacy Practice (GRP). It is worthy to remind that since radiopharmaceuticals are medicinal products including a radioisotope, they should be prepared before use and their pharmaceutical quality must be ensured for the safety and benefit of the patient. This implies that the production and control of radiopharmaceuticals must necessarily be carried out by qualified personnel with all the necessary knowledge to guarantee the quality of the final product. This highly specialized staff must possess a broad spectrum of knowledge ranging from basic chemistry, physics, biology, and pharmacy and is commonly recognized with the name of 'Radiopharmacist' and 'Radiopharmacy' is its field of application. In Mauritius, no official recognition of this professional role has been pursued and, consequently, no specific educational programs in Radiopharmacy have been implemented nationwide. Since no rigorous procedures are applied for the preparation and quality control of radiopharmaceuticals, this may seriously question the reliability of the diagnostic outcome. Evidently, to ensure the efficacy of a diagnostic procedure it is mandatory to first develop a framework of guidelines, inspired by GRP, that can be applied at the national level and that can serve as a reference for regulatory authorities for evaluating the quality of radiopharmaceuticals. These guidelines can be conveniently elaborated at the national level by each African country and subsequently harmonized throughout the continent. In this perspective, IAEA is playing a crucial role in helping Mauritius to introduce regulations for radiopharmaceuticals through ongoing national and regional projects. These efforts are of the utmost importance to build a new generation of Radiopharmacists in the region with an in-depth understanding of the science of radiopharmaceuticals and of the principles of GRP. They will also contribute to promoting a solid educational system in Radiopharmacy that can avoid flaws and defects in the clinical use of radiopharmaceuticals, and ultimately ensure the benefit of patients.



**IAEA-CN-310/113**

**Platinum Nanoparticles Labeled with Iodine-125 for Combined „Chemo-Auger Electron” Therapy of Hepatocellular Carcinoma**

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Novel concepts of treatment heterogenic and therapy-resistant neoplasms should be a combination of different therapeutic routes, in order to enhance their efficacy through the multidirectional biological activity. According to this concept, **\*\*we propose a “chemo-Auger electron” therapy\*\*** combining the high radiotoxicity of Auger electrons emitted by  $^{125}\text{I}$  with the chemotoxicity of 2 nm platinum nanoparticles (PtNPs) located in the cell nucleus.

Our results show synergistic effect of  $^{125}\text{I}$ -PtNPs against hepatocellular carcinoma cells with the efficacy enhancement from around 50% to over 90% after 72 h for PtNPs and  $^{125}\text{I}$ -PtNPs (50 MBq/mL) respectively. Moreover, significant DNA double-strand breaks were induced when the cells were incubated with radioconjugate for 12 and 24 h. Synthesized radioconjugate was also effective against 3D tumor spheroid model resulting in its growth inhibition during 5th day and subsequent complete disintegration after 12 days. Negligible effects were observed during parallel experiments with  $^{125}\text{I}$ .

Taking into account lack of efficient therapeutic routes for HCC treatment, these results are promising for further assessment, especially with more comprehensive in vitro studies followed by in vivo evaluation. This is crucial for rational evaluation of application potency for this type of combined therapy.



**IAEA-CN-310/114**

**Development and Validation method of Gas chromatography for Quality Control of Organic Solvents in [F-18] Florbetapir**

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[F-18] Florbetapir is one of the PET/CT radiopharmaceuticals used for the diagnosis of amyloid pathology. In the radiopharmaceutical production stages, there have been many hazardous organic solvents used in the radiopharmaceutical production, separation, purification and dry-up steps. Thus, according to the United States Pharmacopeia (USP43 NF38) monograph. All organic solvents containing ethanol (EtOH), acetonitrile (ACN), and dimethyl sulfoxide (DMSO) must be controlled under the specification level before injection into patients. In this study, we aimed to optimize and validate a user-friendly, fast, and reproducible analytical procedure for determining organic solvents in [F-18] Florbetapir. The organic solvents were determined by gas chromatography–flame ionization detector (GC-FID) on a 0.320 mm x 30 m x 1.80 m film sickness (DB-624 UI) column. The analytical characteristics in this work consisted of specificity, system suitability, linearity, precision (repeatability and intermediate), accuracy, range, the limit of quantitation, and robustness following (ICH) Q2 (R2) guideline. All the results met acceptable limits and this validated analytical procedure can be used as an in-house method for [F-18] Florbetapir residual solvent determination, apart from its well accepted in the United States Pharmacopeia (USP) monograph.





**IAEA-CN-310/115**

### **Bioconjugates of $^{103}\text{Pd}/^{103\text{m}}\text{Rh}$ in-vivo Generator for Targeted Auger Electron Therapy**

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In our studies, we propose delivering of  $^{103\text{m}}\text{Rh}$  and  $^{109}\text{Ag}$  to the cell nucleus by in-vivo  $^{103}\text{Pd}/^{103\text{m}}\text{Rh}$  and  $^{109}\text{Pd}/^{109}\text{Ag}$  generators.  $^{103}\text{Pd}$  and  $^{109}\text{Pd}$  as the parent radionuclide will immobilized in the Pd or Au nanoparticles together with trastuzumab.

Due to the low availability of  $^{103}\text{Pd}$ , in the first step we used  $^{109}\text{Pd}$  obtained by neutron irradiation of natural Pd.  $^{109}\text{Pd}$  is an emitter of  $\beta^-$  particles and conversion and Auger electrons. Like  $^{103}\text{Pd}$ , it forms an in-vivo  $^{109}\text{Pd}/^{109}\text{Ag}$  generator. Up to now, 3nm and 6nm  $^{109}\text{Pd}$ NPs and 15nm Au@ $^{109}\text{Pd}$  nanoparticles have been successfully synthesized. Nanoparticles got conjugated with trastuzumab as a vector. In vitro cell studies indicated specific binding  $^{109}\text{Pd}$ -radiobioconjugates to Her2 receptor on SKOV-3 cells and 38 % and 28 % of cell and nucleus internalization respectively. Cytotoxicity studies showed  $^{109}\text{Pd}$ -radiobioconjugates were toxic to SKOV-3 cells specially at the highest concentration of 40 MBq/ml 24h after incubation. The obtained results show that trastuzumab-functionalized  $^{109}\text{Pd}$ -labeled nanoparticles can be suitable for the application in mixed  $\beta^-$ -Auger electron targeted radionuclide therapy. In the next stage, we will continue our studies using the  $^{103}\text{Pd}/^{103\text{m}}\text{Rh}$  in-vivo generator.



**IAEA-CN-310/116**

## **Organic Boron-Derivatives for Radiohalogenation of Biomolecules**

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In nuclear medicine, various radionuclides are used in diagnosis and treatment of cancer disease. Halogen elements are very interesting for medical applications, especially fluorine, astatine, and iodine. The latter has been used for a long time because of its radioactive isotopes ( $^{123}\text{I}$ ,  $^{124}\text{I}$ ,  $^{125}\text{I}$ , and  $^{131}\text{I}$ ) have optimal half-lives and are used in different applications such as SPECT or PET imaging, and therapy; whereas,  $^{18}\text{F}$  and  $^{211}\text{At}$  have shorter half-lives, but still can be used either for PET imaging or therapy.

These radionuclides are used to label biomolecules directly or via prosthetic groups which contain two functional moieties. The first one is an active functional group, either ester or maleimide, that allows conjugation to biomolecules like peptides or monoclonal antibodies which have free amine (lysine) or sulfhydryl group (cysteine). The second functionality is the organometallic group that achieves regio-selectivity of radionuclides by undergoing an electrophilic or nucleophilic aromatic substitution reaction. The most widely used organotin precursors suffer from potential contamination of final product with a tin residue that makes purification process more challenging taking into account known tin toxicity. Also, silicon precursors are used but the silicon-carbon bond is not enough reactive for electrophilic aromatic substitution reaction.

In this work, we are interested in boron precursor due to its advantages including low toxicity, ease to be handled and most of the boron precursors being stable to air and moisture. Kabalka et al. showed the radioiodination of different arenes starting from boronic acid precursors and he obtained high radiochemical yields in short times. Based on those reports we are proposing development of organic boron-derivative precursors for radiohalogenation of biomolecules to obtain a potential diagnostic or therapeutic radiopharmaceutical.



**IAEA-CN-310/117**

### **Optimal Radiolabeling Conditions for [18F]AlF-NOTA-moiety**

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The use of versatile chemistry, such as nucleophilic and electrophilic substitutions, allows the direct or indirect incorporation of fluorine-18 ( $^{18}\text{F}$ ) into molecules of interest, the former being the most used. Despite some exceptions, bioactive molecules such as peptides, proteins, and oligonucleotides are not stable under the typical reaction conditions used in  $^{18}\text{F}$  radiolabeling reactions. High temperatures and alkaline solutions are usually required for the formation of carbon-fluorine (C-F) bonds in nucleophilic fluorination reactions. Under these conditions, the reaction is often unsuitable for the radiolabeling of bioactive molecules and often too long for practical use. Therefore, the development of new bioactive molecules of medical interest labeled with  $^{18}\text{F}$  and not with the radionuclide  $^{68}\text{Ga}$  is hindered.

$^{18}\text{F}$  radiolabeling using the aluminum-fluoride (Al-F) technique results in low-to-moderate radiochemical yields, ranging from 5 to 20%. Therefore, in the work described herein, the optimal radiolabeling condition for the formation of  $^{18}\text{F}[\text{AlF}_2]^+$  and  $^{18}\text{F}[\text{AlF-NOTA}]$  moieties with radiochemical yield (RCY) and radiochemical purity (RCP) greater than 90% is described as a prerequisite for radiopharmaceutical preparation using the  $^{18}\text{F}[\text{AlF}]$ -bifunctional chelator technique. The proposed method is not only simple but also practical and relevant for beginners interested in radiolabeling with the  $^{18}\text{F}[\text{AlF}]$ -chelate complex technique or for researchers who want to proceed on a larger scale.



**IAEA-CN-310/119**

## **Regulatory Approach to the Use of Radiopharmaceuticals in Developing Countries**

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The use of radiopharmaceuticals has increased in many developing nations, necessitating the establishment of a suitable regulatory framework for radiation protection. To conduct an adequate safety evaluation of the design and shielding of a radiopharmaceutical bunker, regulatory bodies must identify sources of exposure in order to enhance safety. Due to this, qualified regulatory staff who can verify compliance with safety regulations are required. The primary factor in approving a facility employing radiopharmaceuticals is justification, therefore the physical half-life, the energy released, and the decay mechanism of the radionuclides in use must be known in order to conduct adequate safety evaluations. The regulatory body should collaborate with the relevant parties in order to develop diagnostic reference levels, which offer broad guidance for clinical operations. A thorough quality assurance procedure is necessary because equipment must be used safely within the parameters and guidelines outlined in the technical specifications and license requirements. The regulatory body should examine the processes for producing radionuclides, preparing radiopharmaceuticals, transporting, receiving, and unpacking radionuclides, administering radiopharmaceuticals to patients, caring for patients during nuclear medicine procedures, managing radioactive waste, and storing radiation sources for the protection of workers, patients, and the general public. Contamination must be routinely monitored.



## **IAEA-CN-310/120**

### **Development of PSMA kit as Ga-68 Radiopharmaceutical for Diagnosis of Prostate Cancer**

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The radiopharmaceutical  $^{68}\text{Ga}$ -PSMA has been increasingly used in Thailand since 2017. As the main radiopharmaceutical manufacturer in the country, Radioisotope Center, Thailand Institute of Nuclear Technology, is providing and conducting research on radiopharmaceuticals including pharmaceutical cold kits. The research on development of a PSMA kit for  $^{68}\text{Ga}$  focused on the formulation in a form of lyophilized kit, on the production in accordance with GMP, and on the quality control following European Pharmacopoeia. The kit formulation was designed for a batch size of 50 vials. The lyophilization was carried out for 44 hours and all processes were performed under sterile conditions. The quality control of the kit was analyzed in terms of water content, PSMA amount, pH after reconstitution, sterility, bacterial endotoxins, radiochemical purity and stability. The results showed that the kit can be radiolabeled with 5 – 20 mCi of  $^{68}\text{Ga}$  at room temperature and is stable for at least 4 hours. Its chemical and biological qualities conform to pharmacopeial regulations.



**IAEA-CN-310/122**

**Estimated Human Dose of Technetium-99m Derived from Low Specific Activity 99Mo/99mTc GENERATOR: Preliminary Study**

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Technetium-99m ( $^{99m}\text{Tc}$ ) has been successfully produced from a low specific activity  $^{99}\text{Mo}/^{99m}\text{Tc}$  generator developed in Indonesia. Before used in human, certain test must be conducted to ensure the safety of the  $^{99m}\text{Tc}[\text{NaTcO}_4]$  product including the biodistribution test in animal. The aims of this study are to carry out the biodistribution test of the  $^{99m}\text{Tc}[\text{NaTcO}_4]$  derived from the low specific activity  $^{99}\text{Mo}/^{99m}\text{Tc}$  generator in mice and to determine its estimated human dose. Approximately  $11.1 \text{ MBq}/100 \mu\text{L}$  of  $^{99m}\text{Tc}[\text{NaTcO}_4]$  were then injected to each mice intravenously. Selected organs were then collected after 0.5, 1, 3, 5 and 24 h after injection and the radioactivity was measured by using gamma counter stated in  $\% \text{ID}/\text{g}$  organ. The OLINDA/EXM was used to determine the estimated human dose of  $^{99m}\text{Tc}$ . The biodistribution result showed that thyroid has the highest  $^{99m}\text{Tc}$  activity for all groups followed by stomach and bladder. The estimated dose of  $^{99m}\text{Tc}$  showed that the highest internal doses for man were found in thyroid, stomach and liver with the distribution of  $1.67 \times 10^{-2}$ ,  $3.01 \times 10^{-3}$  and  $2.48 \times 10^{-3} \text{ mSv}/\text{MBq}$ , respectively, while for the woman the highest internal doses were found in thyroid, stomach and lung with the distribution of  $2.12 \times 10^{-2}$ ,  $3.94 \times 10^{-3}$  and  $3.13 \times 10^{-3} \text{ mSv}/\text{MBq}$ , respectively.





**IAEA-CN-310/123**

## **Quality control of the $^{18}\text{F}$ -FDG radiopharmaceutical at the Center for Nuclear Medicine and Oncology in Semey**

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Fluorodeoxyglucose  $^{18}\text{F}$  (2-fluoro- $^{18}\text{F}$ -2-deoxy-D-glucose) remains the most widely used radiopharmaceutical for PET diagnostics. Since 2021, this type of diagnostics has become available for residents of the East Kazakhstan region. The report presents experimental data on quality control parameters obtained during the production of radiopharmaceuticals. Particular attention is paid to the choice of LAL test conditions for serial control of the finished radiopharmaceutical. The purpose of this study is to highlight the potential value of continuous quality control of finished  $^{18}\text{F}$ -FDG products and share our initial experience in this area.

An overview of the quality control dossier for each new batch of  $^{18}\text{F}$ -FDG includes radionuclide identification, radiochemical purity, chemical purity, pH, residual solvents, sterility, and bacterial endotoxin levels. High purity reagents and solvents purchased from Sigma-Aldrich were used in the quality control assay. The main indicators of the quality of a radiopharmaceutical (total activity, availability of radionuclides, radiochemical purity, chemical purity, pH, osmolarity) and meets the requirements of the European Pharmacopoeia. The LAL test was carried out using the Endosafe PTS portable test system (Charles River, USA), which is the only method suitable for express analysis of the finished radiopharmaceutical in terms of "bacterial endotoxins". To eliminate interfering factors, the finished product was diluted with LAL-water in ratios of 1:10, 1:75, 1:100, 1:200, 1:350, 1:3500. The test results confirmed the reproducibility and specificity of the LAL test method. For the analysis of bacterial endotoxins,  $^{18}\text{F}$ -FDG preparation at a dilution of 1:100 and cartridges with a sensitivity of 0.5-0.005 EU/ml were chosen.

Investigated the stability of the obtained  $^{18}\text{F}$ -FDG. During the ten-hour shelf life of  $^{18}\text{F}$ -FDG, the drug quality parameters remained constant.

In conclusion, constant and strict quality control of  $^{18}\text{F}$ -FDG is important for patient and staff safety, as well as good image quality.



**IAEA-CN-310/124**

### **Education and Training of Radiochemists in a GMP Certified Cyclotron Facility**

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A major problem faced by new cyclotron centers is the availability of trained staff for operation of the cyclotron as well as production and quality control of radiopharmaceuticals. While support for training of staff is provided by IAEA for government sponsored projects such support is not available for private manufacturers. Moreover, radiochemistry is not one of the courses taught in most Universities. Our experience in developing in-house training of both cyclotron operators and chemists in in our cyclotron center is described in this paper. Fresh students with Master's degree in physics and chemistry or bachelor's degree in pharmacy are recruited and put through the in-house training as follows:

- Good radiation protection practices are imparted by the Radiation Safety officer (RSO) in a four week training module. This includes, biological effects of radiation, measurement of radiation, radiation dosimetry, dose limits, radiation protection practices etc.
- The second module is in quality control and GMP documentation related to PET radiopharmaceuticals production and this extends to almost 6 months
- The third module is on the preparation of chemicals, cartridges, columns, cassettes for various PET radiopharmaceuticals production and it extends to 3 months during which time the trainee also is allowed inside the clean room to observe the production.
- The fourth module is on operation of the hot cell and associated systems and operation of the synthesis module. The trainee matures to the final step of dispensing the radiopharmaceuticals towards the end the 9-12 month module.
- On successful completion of the quality control, production, dispensing and dispatch the training of operation of the cyclotron starts.

As the training need to be done without disruption of the routine production, fresh recruitment is done on a spaced manner of six months. By following the above training program we have developed highly skilled PET radiopharmaceutical scientists for our present and future projects.



**IAEA-CN-310/125**

### **Setting Up a Clean Room Facility for GMP Based Production of Freeze-Dried Kits for Formulation of $^{99m}\text{Tc}$ and $^{68}\text{Ga}$ Radiopharmaceuticals**

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Nuclear medicine practice flourished in the past thanks to the availability of freeze-dried kits and  $^{99}\text{Mo}/^{99m}\text{Tc}$  generator. The same trend is likely to happen with  $^{68}\text{Ge}/^{68}\text{Ga}$  generator and  $^{68}\text{Ga}$  radiopharmaceuticals. In this paper we report the setting up of a clean room facility complying with EU GMP standards for the manufacture of freeze dried kits. The kit manufacturing laboratory consists of a series of clean room with gradation and change areas. Production of kits are carried out in a laminar flow bench of Class A placed inside a Class B clean room. A freeze drying unit with a 6L capacity is installed with opening inside the Clean room. There are also two additional Class C clean room one used for reagent preparation and the other for microbiological quality control. The manufacturing formulae of the kits for  $^{99m}\text{Tc}$  is adapted from the IAEA TRS 466: Technetium-99m radiopharmaceuticals: Manufacture of kits. Freeze dried kits of DTPA, DMSA and MDP are already standardized and released for clinical use. Our experience can be adapted by MS wanting to start cold kit manufacturing which will bring down the cost of practicing nuclear medicine.



**IAEA-CN-310/127**

## **[18F]FDG Production: A Retrospective Analysis of 2300 Batches Using Different Synthesis Modules**

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A Siemens Eclipse HP 11 MeV cyclotron together with Von Gahlen hot cells equipped with Siemens Explora (SFE4) and Neptis mosaic-RS (NRS) modules have been in use since 2017. The center is catering to the PET radiopharmaceuticals requirement of 17 hospitals in the Southern part of India. Among the PET radiopharmaceuticals FDG is the most widely used and the main revenue stream of this cyclotron center. This paper presents a retrospective analysis of the first 2300 batches of FDG production done in our center. 2078 batches were done using SFE4 and 239 batches with NRS module. The uncorrected yields for SFE 4 ranged from of 53-75% whereas it ranged from 10-80% in NRS module over 5 years. Batch failures were 1.6% and 5.8 %, respectively for SFE4 and NRS. With a thorough understanding of the process, improved chemistry, modified program as well as routine preventive maintenance, the yields of FDG using both the modules could be improved over the time and failure rate reduced from 0.2% to 0 in SFE4 and 3.8% to 0.8% in NRS. FDG yield is higher in NRS module as compared to SFE4 as the latter being acid hydrolysis takes 45 min for completion of synthesis where as it is just 20 min for NRS module which rely on base hydrolysis. The data presented as well as improvements done in the chemistry will be useful for MS having PET radiopharmaceuticals production.



**IAEA-CN-310/128**

**Method Development and Validation for the Determination of Residual Solvents in [F-18]FPSMA-1007 Radiopharmaceutical by Using Gas Chromatography.**

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[F18]FPSMA-1007 is a radiopharmaceutical for prostate cancer diagnosis. Ethanol, acetonitrile, and dimethyl sulfoxide are used in the 18F-PSMA production procedures as residual solvents which must be identified and quantified for safety reasons. A gas chromatographic technique with FID detector (GC-FID) is one of the most widely used method for residual solvents analysis and quantitative determination in the radiopharmaceutical products, but our current method takes at least 16 minutes to complete one analysis. The aim of this research is to develop and reduce the analytical time by half via analytical parameters' adjustment. Development and validation of a GC- FID method for the analysis of the residual solvents in 18F-PSMA radiopharmaceutical was done through evaluation of method, linearity, precision, accuracy, limit of detection (LOD) and limit of quantitation (LOQ). The results show that the new condition passed the method validation criteria of the International Council for Harmonization (ICH). The linearity of all residual solvents had a correlation coefficient ( $r$ )  $> 0.99$ . The precision was determined in the term of percentage of recovery which was in the range of 98 – 102% for all 3 residual solvents. For the accuracy, the %RSD value was less than 2% in all residual solvents. The LOD was 0.004, 0.74, and 0.08 ppm, while the LOQ was 0.012, 2.24, and 0.24 ppm for ethanol, acetonitrile, and dimethyl sulfoxide respectively. Moreover, with the new condition, the analysis time was reduced to 50% or 8 minutes.

In conclusion, the new validated condition can be used for residual solvents analysis and determination of 18F-PSMA radiopharmaceutical's chemical purity in which the analytical time was reduced by 50%.



**IAEA-CN-310/129**

**Preparation and Characterization of Palladium-103/109 Bisphosphonate - 2,2' Bipyridyl Complexes for the Treatment of Bone Cancer Metastasis – Preliminary Studies.**

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Radiopharmaceuticals based on Auger electron emitters may find application in bone metastasis treatment because the emitted energy is deposited over a very short range without damaging the bone marrow. Among others Auger emitters also  $^{103}\text{Pd}/^{103\text{m}}\text{Rh}$  and  $^{109}\text{Pd}/^{109}\text{Ag}$  in vivo generators are promising for such therapy. The aim of our studies is synthesis and characterization of the  $^{109}\text{Pd}$  and  $^{103}\text{Pd}$  2,2' bipyridyl- bisphosphonate complexes for the treatment of bone cancer metastases. Synthesis was performed using 2,2' bipyridyl, Alendronate ligand and  $\text{Pd}^{2+}$  in  $\text{K}_2\text{PdCl}_4$  form with the molar ratio of 1:2. FTIR spectrum confirmed the presence of 2,2' bipyridyl ligand and bisphosphonates in the complex. Obtained complex was yellow and soluble in water. Obtaining of  $\text{Pd}(\text{alendronate})_2\text{bpy}$  complex was confirmed by Mass spectroscopy. At the HPLC chromatograms both, the radioactive and stable compounds have a retention time of around 6 min in the water/acetonitrile gradient. To mimic the sorption of the studied complex on the bones, the sorption on hydroxyapatite was performed. As a result of the sorption process using  $^{109}\text{Pd}$  complex, the maximum adsorption was 86%. Further studies with breast and prostate cancer cell lines will be performed to determine the toxicity of the complex.





**IAEA-CN-310/130**

## **Regulatory Control of Ventilation Systems of Radiopharmaceuticals Production Facilities with Cyclotron**

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Regulatory control of the ventilation systems of radiopharmaceutical production facilities represents a challenge for all regulatory bodies in the field of radiological protection, because of the complexity involved in assessing the eventual presence of radioactive material in the air.

In Argentina, the authorization process for a radiopharmaceutical production facility with cyclotron has 4 stages, since it is classified as Class I: construction, commissioning, operation and decommissioning. In each stage, it is required to analyze that radiological protection criteria related to the design and operation of the ventilation system are met, for which it is necessary to evaluate these systems, understanding the production processes and the impact that the appliance of these criteria could have on biological safety and considering a graded approach.

As far as inspection processes are concerned, the objective is to verify compliance with the authorized design and the maintenance of safe operating conditions for workers, the public and the environment. This involves the development of numerous tasks and controls by the inspector's team of the regulatory body that must be carried out with adequate frequency.

The Nuclear Regulatory Authority of Argentina, through the "Class I Particle Accelerators Control Department", describes in the present paper its regulatory action in the control of ventilation systems; during the authorization and inspection processes of the radiopharmaceuticals production facility with cyclotron.



IAEA-CN-310/133

## **Synthesis and Radioiodination of (z)-3-ethoxy-methylene) 2,3 dihydro-5,7-dimethylthiopyrano [2,3-b]pyridine -4-one as a Potential Antitumor**

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A compound of (z)-3-ethoxy-methylene) 2, 3 dihydro-5, 7-dimethylthiopyranol [2, 3-b] pyridine -4-one has been synthesized as antitumor agent and characterized to give high chemical yield. Radiolabeling was conducted with iodine-125 giving about 94.9% labeling yield. Many factors like amount of substrate, pH, reaction temperature, amount of oxidizing agent, reaction time and the stability have been systematically studied to optimize the iodination yield. Biodistribution studies indicate the suitability of the labeled iodo-DTPP14 ((z)-3-ethoxy-methylene) 2, 3 dihydro-5, 7-dimethylthiopyranol [2, 3-b] pyridine -4-one) as a novel tracer to image solid tumor. In addition, the cell viability assay showed high toxicity of synthetic compound, DTPP14 against human tumor cell lines as a new cytotoxic agent. Radioiodinated DTPP14 showed a high selectivity for cancerous tissues indicating the possibility of its promising use as a theranostic radiotracer for human solid tumor and further studies need to be performed on human being.



**IAEA-CN-310/134**

### **Rationale Radiosynthesis of $^{68}\text{Ga}$ -tri- $\gamma$ -glutamic Acid Polypeptide**

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Most of  $^{68}\text{Ga}$ -based radiopharmaceuticals enroll in diagnostic part of theranostics using DOTA as a versatile chelator. In fact, stability constant of DOTA is low ( $\log K_{\text{cal}} = 21.3$ ) if compare to NOTA ( $\log K_{\text{cal}} = 31.0$ ). Recently, some small peptides have gained attention to develop as a new bifunctional chelator. Herein, we rationally designed a new tri- $\gamma$ -glutamic acid polypeptide (tri- $\gamma$ -GAP) to mimic chemical structure of NOTA to serve an assessment of precise Ga-68 chelation.

Linear tri- $\gamma$ -GAP was assembled by solid phase peptide synthesis (SPPS). Subsequently,  $^{68}\text{GaCl}_3$  4.0 mL 7.0 mCi was added to solution of tri- $\gamma$ -GAP 50 mg in  $\text{H}_2\text{O}$  100 mL with acetate buffer 1.5 mL and heated at  $90^\circ\text{C}$  for 15 min. Sep-Pak C18 cartridge was used in purification.

Tri- $\gamma$ -GAP was synthesized in 5 steps to give 24% total yield. It was analyzed by HRMS (ESI) calculated for  $\text{C}_{15}\text{H}_{23}\text{N}_3\text{O}_{10}$  405.1383, found: 406.1378  $[\text{M}+\text{H}]^+$ . The radioactivity of  $^{68}\text{Ga}$ -tri- $\gamma$ -GAP was found to be 3.5–3.8 mCi ( $n = 5$ ), radiochemical yield was 77%. After purification, radiochemical purity was 98% and specific activity was in the range of 29.17–31.67 mCi/ $\mu\text{mol}$ . In addition, pH of radiolabeled product was in range of 4.5–5.0. Tri- $\gamma$ GAP was designed to contain three N-dentate and four OH-dentate, which can forms  $\text{N}_3\text{O}_3$  hexadentate at ambient temperature in the same manner to NOTA. Moreover, it can be conjugated to anti-cancers, other bioactive pharmacological molecules via peptide or ester linkage. Moreover, tri- $\gamma$ -GAP possibly enhances its conjugated molecule to uptake into targeted cell through glutamic acid transporter.

Tri- $\gamma$ -GAP was successfully synthesized by SPPS methodology and labeled with Ga-68. It has potential to utilize as a novel small peptide chelator for theranostics.



**IAEA-CN-310/135**

### **Ac-225/Bi-213 Generator System Based on $\alpha$ -zirconium Phosphate Ion Exchanger**

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The capacity study of prepared  $\alpha$ -zirconium phosphate monohydrate ( $\alpha$ -ZrP) ion exchanger granulated in polyacrylonitrile matrix (70% loading) was carried out with Eu as a homologue of Ac-225 using column model of future high activity generator and a stock solution Eu with Eu-152 of activity 57.2 kBq. The fractions of Eu-152 solution were collected after pumping the stock solution through the column at various times for gamma measurements and further calculations of theoretical sorbent capacity for Ac-225 which was evaluated as 36.7 TBq/g.

The model high activity (75 MBq of parent Ac-225) generator with length of bed of 7.5 cm and diameter of 0.4 cm containing  $\alpha$ -ZrP (particle size 0.8-1.0 mm) as a stationary phase eluted with mixture of 0.01M diethylenetriaminepentaacetic acid (DTPA) in 0.005M nitric acid provided Bi-213 with yields in the range from 80 to 95 % in 2.6 ml of eluate and the contamination by parent Ac-225 was in tens of ppm up to forty days of using with flow rate of 0.33 ml/min.

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**IAEA-CN-310/136**

### **Cerium(IV) Oxide As a Matrix for a Radionuclide Generator**

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This work was focused on a comprehensive characteristics of cerium(IV) oxide regarding its potential as a matrix of a radionuclide generator. Cerium(IV) oxide was prepared by calcination of cerium(III) nitrate and characterized with FT-IR spectrometry and X-ray powder diffraction. The mechanism of sorption on a surface of prepared material as well as active sorption sites and functional groups were studied via potentiometric titrations in pH range 2-11. The kinetic and sorption studies of prepared material were carried out with Ge-68 and Ga-68 as a model radionuclide pair in acidic media.

In order to confirm the long-term radiation and chemical stability of prepared material, prepared oxide was granulated in polyacrylonitrile and used as a matrix in column experiments with Ge-68 and Ga-68. Gallium-68 was regularly eluted from the column for 18 months. As an elution solution, 0.1M HCl was chosen on the basis of batch sorption experiments. The leakage of cerium was determined via ICP-MS.

To sum up, described experiments provided the first comprehensive characteristics of cerium(IV) oxide as an ion-exchanger. It provides fast kinetics of sorption as in the timespan of 5 min, 99 % of Ge-68 is adsorbed. It can also be stated that the contamination of eluate by cerium was constant and held under 4 ppm for the whole tested period, which confirms the radiation and chemical stability of prepared material. It could also lead to conclusion that using cerium(IV) oxide in Ge-68/Ga-68 radionuclide generator could significantly extend the shelf-life of such a device.

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**IAEA-CN-310/137**

### **Development of $^{64}\text{Cu}$ -Dotatate for Pet Imaging of Somatostatin Receptor Positive Neuroendocrine Tumors**

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In this study,  $^{64}\text{Cu}$ -DOTATATE was produced at the optimized conditions and its preclinical evaluations including cellular studies and biodistribution in normal and tumor-bearing mice were performed.  $^{64}\text{Cu}$  was prepared using  $^{68}\text{Zn}(p,\alpha n)^{64}\text{Cu}$  reaction at 30 MeV cyclotron.  $^{64}\text{Cu}$ -DOTATATE was produced with the radiochemical purity of higher than 99% (RTLC and HPLC) at the optimized conditions (370 MBq, 15  $\mu\text{g}$  of DOTATATE, 95  $^{\circ}\text{C}$ , 20 min). The results indicated the radiochemical purity of 94.9% and 95.5% in PBS buffer and human serum after 12 h. Cell studies were carried out on C6 glioma cell lines. Constant values of  $K_d = 21.7 \pm 3.8$  nM and maximum binding of  $B_{\text{max}} = 0.16 \pm 0.41$  nM was obtained indicating the high affinity of  $^{64}\text{Cu}$ -DOTATATE to C6 cells overexpressed somatostatin receptors. Internalization studies of  $^{64}\text{Cu}$ -DOTATATE showed more than 58% internalization at 6 h post incubation. The imaging studies of  $^{64}\text{Cu}$ -DOTATATE in tumor-bearing mice with somatostatin receptors indicated significant accumulation in the tumor and pancreas, stomach and intestine as the organs with cells expressing somatostatin receptor. The obtained results indicated the high potential of  $^{64}\text{Cu}$ -DOTATATE for PET imaging of somatostatin receptor positive neuroendocrine tumors.





**IAEA-CN-310/138**

**Radiolabelled Plerixafor As a Theranostic Molecule for Targeting CXCR4 Receptor Over-Expression: Radiolabelling and In-Vitro Bioevaluation and Preclinical Biodistribution Study**

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Lymphomas are a heterogeneous group of neoplasm comprising proliferating lymphoid cells or their precursors. Current treatment modalities include chemotherapy; radiation therapy; passive immunotherapy; radio-immunotherapy, and small-molecule inhibitors. Over-expression of chemokine receptors, specifically chemokine receptor 4 (CXCR4), in various cancers like lymphoma, breast cancer etc. favors chemotaxis, promotes angiogenesis and metastasis. CXCR4 antagonists disrupt the specific interaction of chemokines with their CXCR4 receptor and may elicit therapeutic potential. Therefore, CXCR4 receptor over-expression and cytotoxicity in various cell-lines has been evaluated.

Standardization of conjugation of plerixafor with bifunctional chelating agents (DTPA, NOTA, etc.). Optimization includes radiolabelling of conjugated plerixafor with  $^{68}\text{Ga}$  and  $^{177}\text{Lu}$  for imaging and therapeutic purposes, respectively. Quality control of radiolabelled plerixafor included radionuclide, radiochemical purity, sterility, pyrogenicity, and serum stability. CXCR4 binding efficacy and toxicity studies were performed on CXCR4 expressing cancer cell lines. The biodistribution studies were conducted in normal rats.

DTPA (1087 Da) and NOTA (1014 Da) conjugation of plerixafor was confirmed with MALDI-TOF. Radionuclide and radiochemical purity of  $^{68}\text{Ga}$  and  $^{177}\text{Lu}$  plerixafor was >99%. The synthesized radiopharmaceuticals were sterile and pyrogen-free. Radio-ligand binding assay confirmed high specificity ( $K_d = 57.16 \text{ nM}$ ) towards CXCR4 expressing cancer cells. Furthermore, the cytotoxicity studies indicated a log absolute  $\text{IC}_{50}$  concentration of 2.628 nM. Immunocytochemistry depicted positive nuclear staining of CXCR4 receptors in SKBR3 and MDA-MB-231 cancer cells. In-vivo physiological biodistribution of  $^{68}\text{Ga}$ - plerixafor was found in the liver, lung, and spleen. The radiotracer showed faster renal clearance, low liver and blood pool activity.

In vitro studies with radiolabelled plerixafor depicted high CXCR4 receptor affinity, eliciting theranostic potential for CXCR4 expressing tumors.



IAEA-CN-310/139

### **Simple Preparation of Novel [99mTc]-Pramipexole Radiopharmaceutical As a Potential Agent for Brain Imaging**

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Brain imaging is a noninvasive clinical tool that is very useful for the early detection of pathophysiological changes in the brain and is considered very important for prognostic purposes, therapeutic decision-making, and follow-up therapy. This study aims to develop radiopharmaceutical technetium-99m based for brain imaging so that it can be used worldwide. Pramipexole (a drug that has the ability to penetrate the blood-brain barrier) has been successfully labeled technetium-99m [ $^{99m}\text{Tc}$ ] through direct labeling methods using stannous chloride as reducing agent and optimization of several labeling parameters such as incubation times that produce radiochemical purity above 90%, as well as testing stability at room temperature. In addition, in this study, computation simulation was also conducted. From the computation simulation results, binding affinity with receptors from Pramipexole and [ $^{99m}\text{Tc}$ ]-Pramipexole was not significantly different. Whereas from the results of the labeling optimization, the optimum number of pramipexole was 400  $\mu\text{g}$ , the optimum number of stannous chloride was 20  $\mu\text{g}$ , optimum pH 7, 15 minutes incubation time at room temperature, and maximum storage stability at room temperature was 5 hours. The radiochemical purity was obtained  $92,48 \pm 2.43\%$  using the paper chromatographic method, where the stationary phase used was Whatman No. 1 paper chromatography. The mobile phase using acetone and a mixture of ethanol : water : ammonium hydroxide (2:5:1). The optimization of labeling optimization of pramipexole compounds using technetium-99m obtained high radiochemical purity is a potential candidate to be developed for brain imaging radiopharmaceutical.



**IAEA-CN-310/140**

### **Validation of Analytical Methods: Determination of Sodium Thiosulfate in Sodium 131-I Iodide Solutions by High Performance Liquid Chromatography**

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Iodine-131, with a half-life of 8.02 days, is one of the most widely used radionuclides in medical diagnosis and therapy for a variety of thyroid disorders. Sodium iodide [<sup>131</sup>I] solutions has been produced on 2018 by CNESTEN. The manufacturing process and the formulation of the product have yielded a high quality finished product and shown to be stable up to 21 days. The formulation is an aqueous solution of the active substance sodium iodide [<sup>131</sup>I] containing sodium thiosulfate as a reducing agent to minimize the oxidation of sodium iodide [<sup>131</sup>I] and liberation of free iodine [<sup>131</sup>I]. Molecular iodine [<sup>131</sup>I] is not a desirable chemical species because it may contaminate the laboratory, the personal and users by vaporization and can lower down the radioactivity content of preparations during the manufacturing process. The current formulation use  $0,08 \pm 10\% \text{mg/mCi}$  of sodium thiosulfate. The objective of this validation is to demonstrate in respect to the ICH Harmonised Guidelines Q2(R1) that the compendial European Pharmacopoeia method for the determination of iodide content as well as for the estimation of the radiochemical purity according to monograph 04/2021:0281 of the Eur. Pharm., is suitable for the identification and quantification of the sodium thiosulfate which is performed at the same time and in the same HPLC runs using a suitable concentration of an external thiosulfate reference standard. The analytical method used is the HPLC high performance liquid chromatography with detection by UV spectrophotometry. This method is the official and mandatory method of the European pharmacopoeia for the determination of iodide content as well as for the estimation of the radiochemical purity of the finished product by using a second radioactivity detector. By using the operating chromatographic conditions indicated in the monograph 04/2021:0281 of the European pharmacopoeia, results revealed high linearity of the method “ $R^2 = 0.9999$ ” in the working concentration range (60 % -140 %). The RSD% of Peak areas was used for evaluation of the repeatability of the analyte using five different preparations at the same concentration and was found to be equal to 1.17%. DL and QL limits were determined using the linearity calibration data of sodium thiosulfate pentahydrate; the method has a DL and QL lower than 1 ng/ml. The method is found to be also accurate, precise, specific it thus suitable for its intended purpose: the identification and the quantification of sodium thiosulfate in the finished product: Sodium Iodide (<sup>131</sup>I) Solutions. Moreover the method is performed at the same time and in the same HPLC runs using the suitable concentration of the external thiosulfate reference standard. The method makes it possible to save a lot in terms of analysis time before the release of the finished products if other methods were used, as well as the minimization of the iodinated organic waste produced by the HPLC.



**IAEA-CN-310/142**

### **Synthesis of New Azobenzene Derivatives Radiolabelled with Gallium-68 As New Imaging Agents for the Diagnosis of Alzheimer's Disease**

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The goal of this work was synthesis and assessment of clinically relevant physicochemical properties of a series of newly-designed azobenzene analogues radiolabelled with diagnostic radionuclide gallium-68.

The lipophilicity of the in silico-designed and synthesized compounds was determined by the logarithm of their distribution coefficients, log D, in the n-octanol/PBS (pH 7.40) system. The stability of the <sup>68</sup>Ga-radiocomplexes, isolated from the reaction mixture, was investigated in a function of time (by the HPLC), in the challenge experiments and in human serum. All obtained <sup>68</sup>Ga-radioconjugates were tested on mice by means of PET-CT scans and ex-vivo biodistribution. The affinity of the compounds toward amyloid beta was assessed by docking and MD simulations. Finally, for all radioconjugates their non-radioactive reference compounds were synthesized in milligram scale and characterised by the MS. We synthesized new <sup>68</sup>Ga-labelled azobenzene conjugates with good yield and purity. All radioconjugates show high stability in human serum, the optimal lipophilicity and exhibit promising amyloid beta binding properties. The <sup>68</sup>Ga-labelled azobenzene conjugates can be considered promising candidates for diagnostic radiopharmaceuticals.

This work has been done within a collaborative project financed by NCN (Opus grant 2018/31/B/ST4/03809) and statutory activities of the Institute of Nuclear Chemistry and Technology.



**IAEA-CN-310/143**

### **Radiolabeled Inhibitors of VEGF-A165/NRP-1 Complex for Pathological Angiogenesis Imaging**

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The aim of the study was to label various inhibitors (of peptide structure, e.g. A7R and its retro-inverso analogue, of peptidomimetic structure, e.g. Lys(hArg)-Dab-Pro-Arg, and a simple organic molecule, e.g. EG01337) of the VEGF-A165/NRP-1 complex with diagnostic (<sup>68</sup>Ga) or therapeutic (<sup>177</sup>Lu) radionuclides and to evaluate their physicochemical and biological properties.

The lipophilicity of the synthesised radiocompounds was characterized as a decimal logarithm of their distribution coefficients, logD, and stability was investigated in a function of time in challenge experiments and in human serum. For the research of biological properties, the study of affinity on cell lines with the overexpression of the NRP-1 receptor was used.

All radioconjugates have been synthesized with good yield and radiochemical purity and turned out to be highly hydrophilic (logD parameters ranged from -4.6 to -3.4). All radioconjugates, except those based on retro-inverso A7R and EG01337, showed unsatisfactory stability in human serum. Biological properties studies are in progress.

Among the radioconjugates tested, radiopreparations based on retro-inverso A7R peptide and EG 01337 molecule can be considered as potential radiopharmaceuticals.

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IAEA-CN-310/144

## Cyclotron Production of $^{68}\text{Ga}$ Via the $^{68}\text{Zn}(p,n)^{68}\text{Ga}$ Reaction from Solid Target for Preparation of Radiotracers

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Due to the use of the positron emitter  $^{68}\text{Ga}$  in radiopharmaceuticals for the diagnosis of malignant tumors using PET / CT, the demand on this short live radionuclide has increased rapidly in the recent years. This need can hardly be met by GMP-approved  $^{68}\text{Ge}/^{68}\text{Ga}$  generators. The shortage of  $^{68}\text{Ge}/^{68}\text{Ga}$  generators could not be entirely closed despite the temporarily tolerated access to unauthorized generator systems. To meet the demand on the radionuclide  $^{68}\text{Ga}$  a cyclotron-based production via the nuclear reaction  $^{68}\text{Zn}(p,n)^{68}\text{Ga}$  (started from the stable isotope  $^{68}\text{Zn}$ ) provide an opportunity to ensure the patient care with  $^{68}\text{Ga}$  radiopharmaceuticals. At the moment various production routes are being intensively investigated. Since liquid targets based on the use of  $^{68}\text{Zn}$  probably are not capable of meeting the demand for  $^{68}\text{Ga}$ , more promising methods are based on solid-targets. Here we present a cyanide-free method for the electrochemical target preparation and promising results of the cyclotron-based production of  $^{68}\text{Ga}$  using solid-targets of  $^{68}\text{Zn}$ . A comparison of radiolabeling and preclinical PET imaging was performed with both cyclotron and generator produced  $^{68}\text{Ga}$ . The  $^{68}\text{Zn}$  electrolyte solution was prepared using the following procedure:  $^{68}\text{Zn}$  oxide was dissolved in 0.6 mL concentrated HCl and subsequently diluted with 4.6 mL water. The solution was adjusted to pH = 9.2 using  $\text{NH}_4\text{OH}/\text{NH}_4\text{Cl}$ -buffer. The plating-step of the target was carried out electrochemically using an Alceo system from Comecer. The electrolysis took place overnight at 3.2 V. The deposited amount of  $^{68}\text{Zn}$  in the target body ranged between 20–60 mg. After the target transfer to the PTS-unit,  $^{68}\text{Zn}$  was irradiated with a proton beam of 16.5 MeV at 20  $\mu\text{A}$  for max. 30 min (IBA-30 MeV). During the post-processing in the EDS-unit,  $^{68}\text{Zn}$  and the formed  $^{68}\text{Ga}$  were dissolved in hydrochloric NaCl solution.  $^{68}\text{Ga}$  was trapped on an anion exchange cartridge (MK-GA). Further reduction of zinc content in the final product can be achieved by washing with NaCl solution. 0.1 M HCl was added into the final vial. The remained  $^{68}\text{Ga}$  on the anion exchange cartridge was eluted into the final vial with a small amount of diluted NaOH solution. The radionuclidic purity was determined using a high-purity germanium detector (HPGe, Ortec). The concentration of iron and zinc was determined using colorimetric tests. Radiolabeling was investigated using the PSMA-derived peptide DOTA-PSMA. PET imaging was performed using [ $^{68}\text{Ga}$ ]GaDOTA-PSMA in a PC3 xenograft model. Our initial results showed that up to 4.8–5.2 GBq of  $^{68}\text{Ga}$  (n. d. c.) could be obtained after irradiation of  $^{68}\text{Zn}$  with a proton-beam at 20  $\mu\text{A}$  for 30 min including a semi-automatic purification (approx. 15 - 25 minutes). The electrochemical preparation of the  $^{68}\text{Zn}$  target, as well as the post-processing, does not require any organic solvents. Moreover, the 0.5 M HCl used for the semi-automated separation of  $^{68}\text{Ga}$  from the irradiated target material is fundamentally gentler on materials than reported methods, which usually use higher concentrations of HCl. Radionuclide impurities were determined and could be identified as  $^{66}\text{Ga}$  and  $^{67}\text{Ga}$ . The radionuclidic purity was determined to be > 99,9 %. The concentration of Fe ions in the final product was less than 0.1  $\mu\text{g} / \text{mL}$ . The content of Zn was significantly higher than 0.1  $\mu\text{g}/\text{mL}$  in a first trial. The concentration on zinc can be reduced by including a washing step using NaCl-solution after collecting of  $^{68}\text{Ga}$  onto the anion exchanger cartridge. The amount of  $^{68}\text{Ga}$  can be increased by higher beaming time as well as by using higher target currents. Preclinical PET imaging comparison between generator and cyclotron produced  $^{68}\text{Ga}$  showed identical radiotracer tumor uptake and biodistribution profiles in PC3 tumor bearing mice. In conclusion, we could show an alternative production method for  $^{68}\text{Ga}$  using solid targets. This method provides highly scalable production with equivalent or superior quality  $^{68}\text{Ga}$  to a  $^{68}\text{Ge}/^{68}\text{Ga}$  generator, while providing identical bio-distribution and tumor uptake profiles.





IAEA-CN-310/145

## Preparation and Preclinical Evaluation of Anti ROR1 Labeled with $^{64}\text{Cu}$ As a Radioimmunoconjugate for ROR1+ Breast Cancer Imaging

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Radioimmunosciintigraphy (RIS) has attracted considerable clinical application in tumor detection. Receptor-tyrosine-kinase-like orphan receptor 1 (ROR1) is extensively expressed during embryogenesis but it is absent within most mature tissues. However, expression of ROR1 has been reported in multiple human malignancies including breast cancer. High level expression of ROR1 in breast adenocarcinoma was associated with aggressive disease. So breast cancer radioimmunosciintigraphy targeting ROR1 expression is an attractive object in molecular imaging especially nuclear medicine researches. In this study, we have developed an efficient indirect labeling method of anti-ROR1 with  $^{64}\text{Cu}$  ( $T_{1/2} = 12.8$  h,  $\beta^+ = 17\%$ ,  $\beta^- = 39\%$ ,  $EC = 43\%$ ) through using NOTA (p-SCN-Bn-NOTA) bi-functional chelator and performed preliminary biodistribution studies in mouse bearing breast adenocarcinoma. Anti-ROR1 was conjugated with NOTA (Macrocyclics B-605), the average number of the chelator conjugated per mAb was calculated and total concentration was determined by spectrophotometrically. NOTA- anti-ROR1 was labeled with  $^{64}\text{Cu}$  then Radiochemical purity and immunoreactivity by 4T1 cell line and serum stability of  $^{64}\text{Cu}$ -NOTA- anti-ROR1 were determined. The biodistribution studies and radioimmunosciintigraphy were performed in female BALB/c mouse bearing breast carcinoma tumor ( $^{64}\text{Cu}$ -NOTA- Anti-ROR1 i.v., 100  $\mu\text{l}$ ,  $20 \pm 5$   $\mu\text{g}$  mAb, 6, 12, 24 and 48 h).  $^{64}\text{Cu}$ -NOTA- anti-ROR1 was prepared (RCP  $>97\% \pm 0.7$ , Specific activity  $4.3 \pm 0.7$   $\mu\text{Ci}/\mu\text{g}$ ). Conjugation reaction of chelator (50 molar excess ratio) to antibody resulted in a product with the average number of chelators attached to a mAb (c/a) of  $3.8 \pm 0.4$ . Labeling yield with  $^{64}\text{Cu}$  in 400  $\mu\text{g}$  concentration of bioconjugate was  $94.9\% \pm 1.1$ . Immunoreaction of  $^{64}\text{Cu}$ -NOTA- anti-ROR1 complex towards ROR1 antigen was determined by RIA and the complex showed high immunoreactivity towards ROR1. In vitro and in vivo stability of radioimmunoconjugate was investigated respectively in PBS and blood serum by RTLC method. In vitro stability showed more than  $92\% \pm 2.2$  in the PBS and  $78\% \pm 2.7$  in the serum over 24 h. The Immunoreactivity of the radiolabeled anti-ROR1 towards 4T1 cell line was done by using Lindmo assay protocol. Under these conditions, the immunoreactivity of the radioimmunoconjugate was found to be 0.77. The biodistribution of  $^{64}\text{Cu}$ -NOTA- anti-ROR1 complex in the mice with normal and breast tumor at 6, 12, 24 and 48 h after intravenous administration, expressed as percentage of injected dose per gram of tissue (%ID/g). Biodistribution and imaging studies at 24 and 48 h post-injection revealed the specific localization of complex at the site of tumors.  $^{64}\text{Cu}$ -NOTA- anti-ROR1 is a potential compound for molecular imaging of PET for diagnosis and follow up of ROR1 expression in oncology.



**IAEA-CN-310/146**

### **Production and Quality Control of $^{99m}\text{Tc}$ -Radiopharmaceuticals**

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The radioisotope production division of Bangladesh atomic energy commission is performing a marvelous job of supporting public health sector by producing and supplying medically important radioisotopes. Several commonly used radiopharmaceuticals are also produced in cleanroom facility installed under ADP and IAEA TC project.  $^{99m}\text{Tc}$ -MDP (Methylene Diphosphonate),  $^{99m}\text{Tc}$ -DTPA (diethylene-triamine-pentaacetate),  $^{99m}\text{Tc}$ -DMSA (iii) (dimercapto succinic acid) and  $^{99m}\text{Tc}$ -DMSA (iv) are the most commonly used radiopharmaceutical in nuclear medicine. Test production of a number of small batches for checking quality control parameters of these radiopharmaceutical was performed. All these radiopharmaceuticals were prepared using analytical grade chemicals according to the guidelines described in IAEA Technical Reports Series No. 466. Both wet and dry labelling was carried out with freshly eluted  $^{99m}\text{Tc}$  from  $^{99}\text{Mo}/^{99m}\text{Tc}$  generator and the labelled compound was tested for quality control. Test for apyrogenicity and sterility were performed according to the pharmacopoeias and the results were found negative. Radiochemical purity test was performed with HPGe detector by paper chromatography using acetone and saline (0.9% NaCl) as mobile phase. The radiochemical purity of these radiopharmaceuticals was found >95%. The bio-distribution in Wistar rats was carried out for different organs (%dose/organ). Bio-distribution showed acceptable high uptake. Shelf-life study of this radiopharmaceutical showed satisfactory result. It can be concluded that, in-house production of  $^{99m}\text{Tc}$ -radiopharmaceuticals under aseptic condition in clean room facility following the guidelines of IAEA and other pharmacopeia provide better results to be used in nuclear medical center and prove the competency in future radiopharmaceutical production sector.



**IAEA-CN-310/147**

### **Advancement of Radioisotope Production and Nuclear Medicine: Perspective Bangladesh**

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Radioisotopes as well as radionuclides guided treatment in nuclear medicine has grown tremendously during the last few years. Different new techniques in nuclear medicine using radioisotopes gives valuable diagnostic and therapeutic guidelines to doctors. Radioisotope production is one of the important activities of Bangladesh Atomic Energy Commission (BAEC). It has an enormous service for the patients at nuclear medicine sector of the country. There are 16 (sixteen) nuclear medicine centers under the umbrella of BAEC and 06 (six) other private and government run hospitals. 08 (eight) new nuclear medicine centers are going to start their activities very soon.  $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$  generators are solely supplied from Radioisotope Production Division (RIPD) of BAEC using imported fission Molybdenum-99 to all the centers. Import of  $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$  generators is completely substituted by RIPD generators since 2005. The cGMP-compliant generator production plant was established at RIPD in May, 2005 with the help of IAEA TC project and is working till now successfully. Increasing demand for more  $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$  generators for the newly established nuclear medicine centers tends to change the internal arrangements of generator production hot cell to meet the entire demand. For PET radiopharmaceuticals, currently, BAEC is producing  $^{18}\text{F}$ -FDG in its own 18 MeV cyclotron. Another project is going on for the establishment of 02 (two) new cyclotrons. The nuclear medical institute of BAEC is also serving patients with radiotherapy using Linear Accelerator (LINAC). Another diagnostic and therapeutic medical radioisotope Iodine-131 is also supplied from RIPD on weekly basis and fulfilling the country's own demand. New theranostic radiopharmaceuticals are yet to be introduced. Bangladesh is planning to produce more radioisotopes using a new 20MW research reactor (proposed) for the patients to lead a better and healthy life.



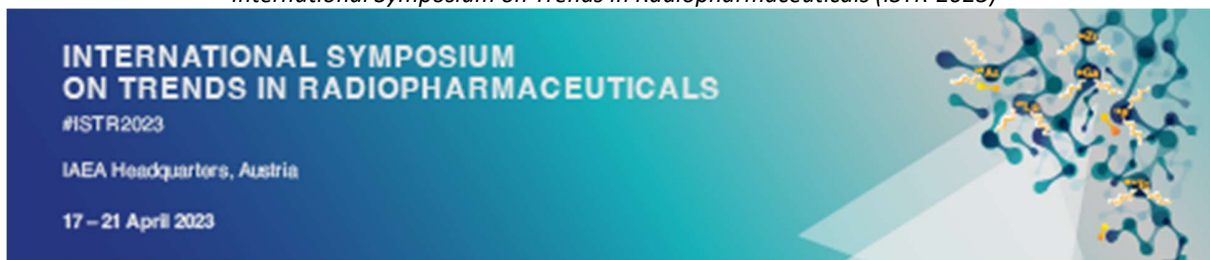
**IAEA-CN-310/148**

## **Chemical Purity Evaluation Method of the Hynic-Psma Lyophilized Kit by High Performance Liquid Chromatography**

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Prostate cancer is a disease with an increasing incidence in Chile, and is responsible for around 2,000 deaths each year. In Latin America, there are around 214,000 oncological causes in men and it corresponds to the first cause of death, in our country, it is the second cause of death. This figure increases its relevance when considering that with current tools the diagnosis is made in advanced stages of the disease, where metastatic processes are already triggered. For this reason, it is of special importance to develop and implement methods that provide an early diagnosis, in the early stages of the disease. In line with the Health Goals of the Decade (improve health, reduce inequalities in health, ensure the quality of health interventions), Molecular imaging is a technology that provides enormous benefits for early diagnosis and monitoring of cancer in general. In this context, this strategy contributes to the National Cancer Plan and its 2018-2028 Action Plan, promulgated in 2018 and whose objective is to reduce both incidence and mortality attributable to the disease, through strategies and actions that facilitate promotion, prevention, early diagnosis, treatment, palliative care and follow-up of patients, to improve their survival, quality of life and that of their families and communities. Molecular imaging (MI) is a type of medical procedure that provides visualization, characterization and measurement of biological processes at the molecular and cellular level in living systems. Nuclear medicine is a branch of IM that, Through the use of radiopharmaceuticals, it allows medical specialists to observe and measure functional, metabolic, chemical and biological processes within the body to diagnose and/or treat malignant tumors and other diseases. Two techniques stand out, Single Photon Emission Tomography (SPECT) and Positron Emission Tomography (PET). The first uses radioisotopes such as  $^{99m}\text{Tc}$  and is the most widely used IM technology, due to the greater number of public hospitals that have a SPECT camera. The development of new drugs for molecular SPECT imaging of prostate disorders may indeed provide a significant improvement to the care of many patients in the public care system. Prostate Specific Membrane Antigen (PSMA) is a transmembrane protein present in all prostate tissues and PSMA expression has been shown to be increased in patients with dedifferentiated, metastatic, or hormone-refractory tumors. Moreover, the level of PSMA overexpression has a prognostic value for the evolution of the disease, therefore the detection of PSMA by molecular imaging using radioactive  $^{99m}\text{Tc}$  results in a powerful diagnostic tool. A radiopharmaceutical is a medicinal product that is usually administered intravenously to the patient: this drug is the result of the union of 2 elements: a minimum of one



radioisotope (RI) which, with its radioactive nature, defines the character and diagnostic use of the radiopharmaceutical, and a Chemical Carrier (CQ) that plays an important role in the selective transport of the radionuclide to a specific biological target. The radioisotope used in the formation of the radiopharmaceutical will define with which imaging technology the diagnosis will be made, if  $^{68}\text{Ga}$  or  $^{18}\text{F}$  is used, PET will be used and if  $^{99\text{m}}\text{Tc}$  is used, SPECT will be used. Prostate Specific Membrane Antigen (PSMA) is a transmembrane protein present in all prostate tissues and it has been shown that PSMA expression is increased in patients with dedifferentiated, metastatic, or hormone-refractory tumors. Furthermore, the level of PSMA overexpression has a prognostic value for the evolution of the disease, therefore the detection of PSMA by molecular imaging using radioactive  $^{99\text{m}}\text{Tc}$  results in a powerful diagnostic tool. The structure of the HYNIC-iPSMA peptide is labeled (metal complex formation) with the radioisotope  $^{99\text{m}}\text{TcO}_4$ . The lyophilized formulation considers the compounds EDDA (ethylenediaminediacetic acid) and tricine (N-[Tris-(hydroxymethyl)-methyl]-glycine as coligants), its function is to stabilize the metal complex, tin chloride is also used, which works as a reducing agent of  $^{99\text{m}}\text{Tc}$ , in order to keep it in the oxidation state (+4), which allows the formation of the complex.

The objective of this work is to present a method of evaluation of the chemical purity for the HYNIC-iPSMA peptide as raw material, and in its lyophilized pharmaceutical form, for which two calibration curves were made, one to determine the chemical purity of the HYNIC-iPSMA peptide raw material, and two, to determine the chemical purity of the HYNIC-iPSMA peptide dosage form, by reconstituting the lyophilized reagent kit without radioactive material. Therefore, the quantification of the chemical purity of the pharmaceutical form of HYNIC-iPSMA was achieved using high performance liquid chromatography (HPLC). The method developed in this work is suitable for quantifying the active ingredient in a lyophilized sample of the pharmaceutical form of the HYNIC-iPSMA peptide. The method complies with the suitability parameters and validation requirements studied. During the development of this work it was observed that temperature is a parameter that must be controlled in order to achieve repeatable results. It is then determined that, The optimal storage temperature of the lyophilisate is between 2-8 °C, the temperature range that a pharmaceutical product should be in under refrigeration conditions. The developed chromatographic method offers substantial improvements regarding the analysis time and sensitivity of the method, since it is possible to obtain an analysis time of 8 minutes and it is possible to determine that the most adequate length to be able to quantify it is at 225 nm. Because the lyophilized pharmaceutical product decomposes due to the effect of temperature, according to the labeling procedure with the  $^{99\text{m}}\text{Tc}$  radioisotope described above, the loss due to degradation and therefore its effect on the complexation reaction must be considered. Analysis of retention times of the analyte achieve its unequivocal identification. The average range of time in which the chromatographic peak is detected is between 5.0 to 5.8 minutes.





**IAEA-CN-310/149**

## **Radioisotopes from Argentina to the World: Overview of INVAP'S Participation in Past and Current Radiochemical Projects**

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INVAP, a State company founded in 1976, was established by connecting basic research with industry and thus reaching the forefront in areas such as nuclear technology, defence, aerospace, environment and medicine. For more than 45 years developing nuclear technology in the world, INVAP has participated in nuclear projects attending to the needs of clients and basing its work on its management, design, construction and service provision capabilities in nuclear facilities, responding to each challenge with responsibility, quality and high performance. Within the nuclear area, INVAP participates in projects such as radioisotope production plants, radiopharmaceutical production plants, nuclear medicine centers and measurement systems for radioisotope emissions, among others. Here we provide a general description of the past, present and future milestones of radiochemistry and radiopharmacy in Argentina developed by INVAP to encourage future generations to be incorporated in the nuclear field. The applications of radioisotopes and radiopharmaceuticals in nuclear medicine are growing very fast throughout the world, generating the need to increase the incorporation of professionals in this field in society. Faced with this need, INVAP promotes the expansion of knowledge and the advancement and development of new technologies; which allows us to position ourselves as a strategic and leader company in the world market for the design and construction of radioisotope and radiopharmaceutical facilities. Molybdenum-99 production plants in Egypt and India; research reactors in Australia, Peru, Algeria, Argentina, Brazil and the Netherlands; nuclear medicine centers for radiopharmaceuticals production ( $^{18}\text{F}$ -FDG,  $^{11}\text{C}$ -Choline,  $^{13}\text{N}$  $\text{H}_3$ ) in Argentina and Bolivia, are some of the projects in which INVAP has successfully worked. The INVAP model is key to rethink an Argentine insertion into the international economy, promoting economic development and the expansion of technological and technical capabilities.





**IAEA-CN-310/150**

**Radioactive Gold Nanoparticles Modified with Doxorubicin and Trastuzumab (DOX-PEG-198AuNPs-PEG-Tmab) for Targeted Radionuclide Therapy of HER2-Positive Cancers**

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The aim of this study is to synthesize a novel radiobioconjugate containing simultaneously  $\beta$ -emitter -  $^{198}\text{Au}$  ( $^{198}\text{AuNPs}$ ), chemotherapeutic agent doxorubicin (DOX) and the guiding vector trastuzumab (Tmab). The size and shape of synthesized AuNPs, next their modification of the surface were confirmed by TEM (Transmission Electron Microscopy), DLS (Dynamic Light Scattering) and UV-Vis methods. Biological studies such as binding specificity, receptor internalization, cytotoxicity (MTS and apoptosis assays, spheroids), cell cycle and confocal microscopy were performed on SKOV-3 (HER2+) and MDA-MB-231 (HER2-) cancer cell lines. Obtained in vitro results showed that multimodal radiobioconjugate displays high affinity and cytotoxicity to cancer cells overexpressing HER2 receptors. Furthermore, biodistribution and therapeutic efficacy experiments performed on mice revealed high tumor uptake after intratumorally injection and reduction of tumor mass.

DOX-PEG- $^{198}\text{AuNPs}$ -PEG-Tmab radiobioconjugate exhibits very good properties for the treatment of HER2-positive cancers by intratumoral or post-resection injection.

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**IAEA-CN-310/151**

### **Current Situation and Perspectives of the Radioisotopes Production for Nuclear Medicine Purposes in Ezeiza Atomic Centre**

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The aim of this work is to show the current situation and future perspectives of the radioisotopes production for nuclear medicine purposes at the facilities located at the Ezeiza Atomic Center (CAE).

The RA-3 reactor, in operation since 1967, has a current power of 10MW. Irradiated targets are purified at Fission Products Production and Radioisotope Production Plant, currently producing Mo-99 and I-131 (fission) in the pharmaceutical forms of solution and capsules. Sm-153-EDTMP injections for therapeutic use are also produced and eventually 51-Cr and 32-P.

Since Mo-99 is the radioisotope of greatest application in nuclear medicine because the 80% of medical practices use its decay product, Tc-99m, added to the aging of the current reactors that produce it, the RA-10 reactor, under construction since 2016, will cover 15% of world demand, in addition to self-sufficiency of radioisotopes for the country, duplicating the present weekly production.

Moreover, since 1994, there is one of the 6 cyclotrons in Argentina, with energy of up to 42MeV and currents of 100uA, presently under maintenance, in which <sup>18</sup>F-FDG was produced for national distribution. Future perspectives include the return to this radiopharmaceutical production and the feasibility of producing <sup>67</sup>Ga and <sup>123</sup>I are being evaluated.



**IAEA-CN-310/152**

### **Traceability for Nuclear Medicine: The Status of Primary Radioactivity Standards**

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The medical use of radionuclides depends on the accurate measurement of activity (Bq) for regulatory compliance, patient safety, and effective treatment or image quality. In turn, these measurements rely on the realization of primary standards of activity by national metrology institutes (NMIs), with uncertainties that are fit for purpose. The current status of primary standards of activity for radionuclides used in medical imaging and therapy applications was reviewed. Results from international key comparisons are used to verify that standards for a variety of radionuclides are consistent and can conform with practitioners' expectations.

Through an analysis of international comparison data, it has been demonstrated that NMIs are able to produce primary standards for many of the isotopes currently used in nuclear medicine (e.g.,  $^{99m}\text{Tc}$ ,  $^{123}\text{I}$ ,  $^{111}\text{In}$ ,  $^{18}\text{F}$ ,  $^{64}\text{Cu}$ ,  $^{131}\text{I}$  and  $^{177}\text{Lu}$ ). The recent publication of three comparison results for the  $\alpha$ -therapy radionuclide  $^{223}\text{Ra}$  highlighted a gap in the availability of comparison exercises that the metrology community must address to establish better traceability for emerging medical isotopes. This need is notably the case for  $\beta$ -therapy radionuclides (e.g.,  $^{89}\text{Sr}$  and  $^{90}\text{Y}$ ),  $\alpha$ -therapy radionuclides (e.g.,  $^{225}\text{Ac}$  and  $^{211}\text{At}$ ), the promising Theranostic Tb isotopes, Auger therapy radionuclides (e.g.,  $^{165}\text{Er}$  and  $^{135}\text{La}$ ) and radionuclides used in in vitro diagnosis (e.g.,  $^{125}\text{I}$ ,  $^{35}\text{S}$  and  $^{32}\text{P}$ ).

The development of the extension of the BIPM's international reference transfer instrument (ESIR) will help to fill this gap in international comparisons, improve the metrological traceability of these isotopes and ultimately benefit nuclear medicine.



**IAEA-CN-310/153**

### **Comparison of Three Different Alternatives for Labelling PSMA under GMP Conditions**

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For the positron emission tomography (PET) imaging of prostate cancer, radiotracers targeting the prostate-specific membrane antigen (PSMA) are nowadays used in clinical practice. This radiopharmaceutical combines the inhibitor Glu-NH-CO-NH-Lys with different radionuclides ( $[^{68}\text{Ga}]\text{Ga}$ ,  $[^{18}\text{F}]\text{F}$ ) enabling specific imaging of tumor cells expressing PSMA.

Two of the most used ligands are PSMA-11 labelled with  $[^{68}\text{Ga}]\text{Ga}$  and PSMA-1007 labeled with  $[^{18}\text{F}]\text{F}$ . In recent years it is also possible to use PSMA-11 labeled by complexes with  $[^{18}\text{F}]\text{AlF}_2$ . The objective of this work is to compare advantages and disadvantages the three options for labelling PSMA derivatives under GMP conditions.

Labelling with  $[^{68}\text{Ga}]\text{Ga}$  turns out to be the simplest alternative, since it does not depend on the infrastructure of a cyclotron and is robust with a reasonable cost, but for few patients per synthesis. Of all the alternatives, the most economical is the  $[^{18}\text{F}]\text{AlF}_2$ -PSMA-11. This has the disadvantage that the synthesis is not robust and has less stability "in vivo" due to defluorination.

The  $[^{18}\text{F}]\text{F}$ -PSMA-1007 is a good alternative, which allows the performance of a large number of studies by labelling, presenting the disadvantage of high cost of supplies. The synthesis is robust and the compound obtained has good stability.

In conclusion, these results suggest that all alternatives are good option to meet clinical demand for PSMA. Each Center needs to decide the best option, depending on the patient demand and the available resources.



## IAEA-CN-310/154

### Automated Synthesis of [ $^{18}\text{F}$ ]Favipiravir on a Synthra RNplus Research Platform

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Favipiravir (T705, 6-fluoro-3-hydroxypyrazine-2-carboxamide) is a pyrazine analog that has demonstrated potent antiviral activity. The mechanism of its actions is thought to be related to the selective inhibition of viral RNA-dependent RNA polymerase.

The objective of this study was the optimization of the labelling procedure of Favipiravir with [ $^{18}\text{F}$ ]F on a Synthra RNplus research platform for its evaluation.

The synthesis was performed in an automated module (Synthra RNplus Research), based on what was reported by Bocan T. et al.[1] Radiochemical purity was determined by HPLC (Luna-PFE(2)-150x4.6mm, 5 $\mu\text{m}$ , Phenomenex) and the stability in the labeling medium was evaluated by HPLC and fluorescence in order to increase the detection limit of the product in the final formulation.

The optimized conditions for labeling were: 10 mg of precursor (6-chloro-3-hydroxypyrazine-2-carboxamide) in 300  $\mu\text{L}$  dry DMSO. The reaction mixture was heated at 130  $^{\circ}\text{C}$  during 10 minute. Purification was optimized using semi-preparative HPLC (Luna-PFE(2)-250x10mm, 5 $\mu\text{m}$ , Phenomenex) 5 % ethanol in 50 mM  $\text{H}_3\text{PO}_4$ , 4 mL/min.

The radiopharmaceutical remained stable in the formulation for at least 4 hours, and the mass of Favipiravir in the marker could be determined by fluorescence (1.9  $\mu\text{M}$ ), which allowed the detection limit of the cold mass to be extended in the final formulation.

The process was optimized in an automated synthesis platform, allowing in the future applying this methodology in the evaluation of future derivatives of Favipiravir.



**IAEA-CN-310/155**

**COVID-19 Lock-Downs As Management Opportunities in Radio-Pharmaceuticals Utilisation in Nuclear Medicine in Peru**

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During COVID 19 lock-down there were several meetings in Peru, to assure and reassure infection control, in Nuclear Medicine facilities, as a part of hospital and clinics group management. Classical safety radiation protection rules were useful for overcoming radio-pharmaceuticals and isotopes utilisation, as well as improving a secure relationship of health workers with Nuclear Medicine patients. There was a shortage of radio-pharmaceuticals, which are produced in Peru, for some weeks, mainly at the beginning of the lock-downs. Physicians and other professionals in Nuclear Medicine, performing in normal times diagnostic and therapeutic roles, switched to revise their duties and normalised work procedures, to have a glorious future after the situation returned to normal. Time and efforts have been surprisingly better than was expected, and there have been teaching facilities for resolving difficulties. Similarly, there was more teamwork to solve problems that seemed difficult to overcome and knowledge was conveyed to all team members in Nuclear Medicine. Nowadays, work has returned to a new normality, with improved procedures on the field.





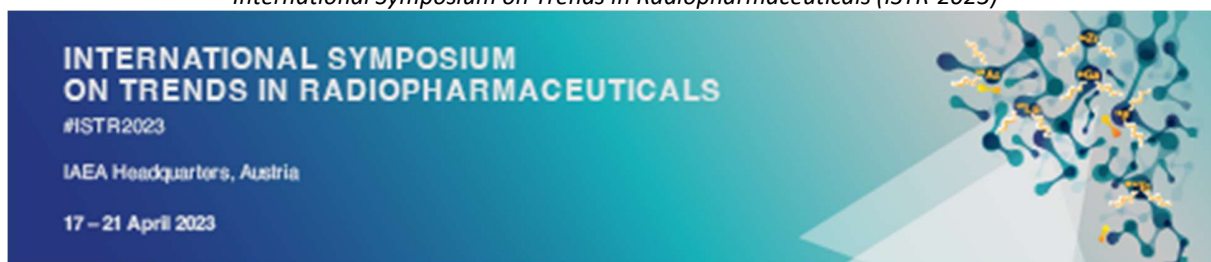
**IAEA-CN-310/156**

**Development of a Simple, Robust, and High-Yielding Manual Production of [<sup>177</sup>Lu]Lu-PSMA I&T Using Carrier-Added Lutetium-177 in Indonesia**

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[<sup>177</sup>Lu]Lu-PSMA I&T has shown great potential for theranostic application of prostate cancer (PCa), and therefore there is a growing interest in the clinical studies of this promising radioligand in several countries in the world. However, the clinical application of [<sup>177</sup>Lu]Lu-PSMA I&T in Indonesia has not been reported. Therefore, we aimed to develop a simple, robust, and high-yielding production procedure of [<sup>177</sup>Lu]Lu-PSMA I&T using carrier-added <sup>177</sup>Lu produced by our nuclear research reactor. We optimized the production methods such as the TLC system for quality control, the required [PSMA I&T]/<sup>177</sup>Lu ratios, pH, temperature, and incubation time. The stability and lipophilicity of [<sup>177</sup>Lu]Lu-PSMA I&T were also investigated. The radiochemical yield and the radiochemical purity of [<sup>177</sup>Lu]Lu-PSMA I&T were estimated by instant thin layer chromatography silica gel (ITLC-SG) with saline as a solvent. The optimized labelling condition was achieved by reacting a four-fold molar excess of the ligand with <sup>177</sup>Lu at 90 °C, pH ~5 for 10 min, resulting in a moderate specific activity of 17-20 GBq/μmol. The radiopharmaceutical [<sup>177</sup>Lu]Lu-PSMA I&T was obtained with a high radiochemical yield and a high radiochemical purity of > 98% (both radio-TLC and radio-HPLC). The addition of ethanol as a stabilization agent retained a high radiochemical purity (>97%) of [<sup>177</sup>Lu]Lu-PSMA I&T at both room temperature (22.5 °C) and refrigerator temperature (4-8 °C) for four days. [<sup>177</sup>Lu]Lu-PSMA-I&T exhibited high stability (>95%) after four days in saline and after two days in human serum in vitro. The lipophilicity determined by the shake-flask method in the n-octanol/PBS system resulted in a log-P value of  $-3,37 \pm 0,03$ , indicating high hydrophilicity of [<sup>177</sup>Lu]Lu-PSMA I&T. Overall, this study carried out emphasizes the developed simple, robust, and high-yielding formulation of [<sup>177</sup>Lu]Lu-PSMA-I&T can be prepared using carrier added <sup>177</sup>Lu available in Indonesia.



**IAEA-CN-310/157**

**$^{64}\text{Cu}/^{103}\text{Pd}$ -GluCAB: An In Vivo Albumin-Binding Theranostic Radiopharmaceutical for Dual Active and Passive Targeting of Breast Cancer**

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A new proposed radiopharmaceutical,  $^{64}\text{Cu}/^{103}\text{Pd}$ -GluCAB1, developed by Necsa for targeted cancer diagnosis comprises a glucose-functionalised macrocycle with a maleimide moiety that binds in vivo to circulating albumin<sup>2</sup>. The cleavable linker will then release the metabolite for internalisation or cell binding for short range emission inside the tumour. This aims to make use of the “enhanced permeability and retention (EPR) effect” and glucose metabolism in the same entity making use of the proven success of the EPR effect but avoiding the off target radiation in organs such as liver and spleen.

GluCAB precursors, comprising of the novel chelator TE1PA3 (a monopicolinate cyclam), can be radiolabeled with  $^{64}\text{Cu}$  and  $^{109}\text{Pd}$  in 0.01M PBS (pH 7.4) at 40°C and purified on a C-18 SPE. Other nuclides that can be used with GluCAB are  $^{103}\text{Pd}$  and  $^{67}\text{Cu}$ .

To date the radiolabeling has been optimized for  $^{64}\text{Cu}$  and in vivo preclinical studies (microPET/CT) with  $^{64}\text{Cu}$ -GluCAB have proven the concept of in vivo albumin binding and passive tumour localization.



**IAEA-CN-310/161**

### **The Third Generation of Radioembolization Microspheres ——<sup>90</sup>Y Carbon Microspheres**

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<sup>90</sup>Y microspheres are internal radiation therapy agents. At present, two types of <sup>90</sup>Y microsphere products (SIR-Spheres® and TheraSphere®) have appeared on the market globally. <sup>90</sup>Y carbon microspheres, independently developed in China, show good clinical potential. The particle size is between 20 and 45µm and the average particle size is 32.5µm. The production process of it does not rely on nuclear reactors for irradiation. There are about 1100Bq <sup>90</sup>Y loaded on each microsphere, and the leaching rate of <sup>90</sup>Y is far less than 0.1%, it can avoid the poor therapeutic effect caused by insufficient radioactive doses and the number of microspheres.

In the pharmacodynamic test of the rabbit VX2 hepatocellular carcinoma model, <sup>90</sup>Y carbon microspheres were perfused by hepatic artery interventions, and the results showed that the tumor volume inhibition rates were 73.6%, 69.9%, and 61.0% for the three dose groups starting from day 8 of dosing to the end of the experiment, and the tumor weight inhibition rates were 87%, 77%, and 75%, respectively, showing a certain dose-effect relationship. Meanwhile, <sup>90</sup>Y carbon microspheres were perfused into Beagle dogs through hepatic artery intervention. SPECT images were clear and no obvious extrahepatic shunt was found, and the leaching rate of <sup>90</sup>Y in blood, urine, and feces was 0.05 ‰, 0.2 ‰, and 0.004 ‰. The study on delayed radiotoxicity showed that only the target organ (liver) had significant radiation damage at the dose of 100MBq/kg and no unexpected toxic reaction was observed.



**IAEA-CN-310/163**

### **Optimization of $^{177}\text{Lu}$ Radiolabeling of DOTA-TOC Conjugate Using Box-Behnken Design**

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Lutetium-177-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid-tyr3-octreotide ( $^{177}\text{Lu}$ Lu-DOTA-TOC) is a promising therapeutic peptide receptor radionuclide therapy (PRRT) radioligand for treatment of neuroendocrine tumors. The research aimed to optimize the reaction conditions of the radiolabeling of DOTA-TOC conjugate with carrier added (c.a)  $^{177}\text{Lu}$  radionuclide. A Box-Behnken design with response surface methodology (RSM) was used to optimize the effect of four independent variables (the concentration of DOTA-TOC, pH of reaction, reaction time, and temperature of reaction) on one dependent variable (RCY of  $^{177}\text{Lu}$ Lu-DOTA-TOC). The radiochemical yield (RCY) of  $^{177}\text{Lu}$ Lu-DOTA-TOC radioligand was estimated by radio-TLC analysis. The optimized reaction condition resulting from RSM analysis was used to determine the minimum DOTA-TOC/ $^{177}\text{Lu}$  molar ratio needed to afford this radioligand in high RCY for the production of therapeutic formulation of  $^{177}\text{Lu}$ Lu-DOTA-TOC with a minimum amount of ligand. The analysis of variance (ANOVA) showed that the linear model of analysis was significant suggesting that the model was fit. One of the suggested reaction conditions for the target RCY (99%) with a desirability function of 1 was selected as the optimal radiolabeling condition. The optimum conditions of DOTA-TOC-labeled with  $^{177}\text{Lu}$  were found to be 16 nmol DOTA-TOC concentration, pH 4, 18 min, and 85 °C. The preparation of  $^{177}\text{Lu}$ Lu-DOTA-TOC can still achieve a high RCY (~95%) with a molar ratio DOTA-TOC/ $^{177}\text{Lu}$  of 6. This study suggested that the Box-Behnken-RSM approach was useful to obtain the optimum radiolabeling condition of  $^{177}\text{Lu}$ Lu-DOTA-TOC.



**IAEA-CN-310/164**

## **Current Status of Non-clinical Research on Radiopharmaceuticals in China**

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In 2020, China Institute for Radiation Protection (CIRP) was approved by the National Medical Products Administration (NMPA) for radiopharmaceuticals, filling the gap in non-clinical safety research on radiopharmaceuticals in China. Meanwhile, NMPA has successively issued the Technical Guidelines for Clinical Evaluation of Diagnostic Radiopharmaceuticals and the Technical Guidelines for Non-clinical Research of Diagnostic Radiopharmaceuticals, to promote and standardize the research, development, and clinical research of diagnostic radiopharmaceuticals in China. In 2022, the Guideline on Clinical Evaluation for Therapeutic radiopharmaceuticals (Draft) starts to conduct public consultation.

In 2021, eight national administrations including the China Atomic Energy Authority jointly issued the Mid and Long-term Development Plan (2021–2035) for Medical Isotopes. From 2020 to 2022, CIRP undertook and completed the nonclinical evaluation of four drugs, which were officially approved for clinical tests, including imaging agents in oncology, immunePET imaging of PD-L1 and hepatocellular carcinoma by TARE. CIRP launched the construction of the "International System for the nonclinical research and transformation of radiopharmaceuticals", aiming to establish an international technical service platform, promoting the nonclinical research and transformation of Chinese radiopharmaceuticals, and integrating them with international standards. Fig1. The capabilities of integrated technical service for radiopharmaceuticals



IAEA-CN-310/165

### **Synthesis and Biological Evaluation of 1-[2-(Cyclopentadienyltricarbonyltechnetium-99m)-N-Vanillyferrocenecarboxamide for Tumor Imaging**

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The high incidence and mortality of cancer and several receptors related tumors motivates efforts to develop innovative imaging probes to effectively diagnose, evaluate the extent of the tumor, and predict the efficacy of treatments while concurrently and selectively delivering anticancer agents to the cancer tissues. We choose capsaicin belonging to the capsaicinoides family having a structure comprising vanillylamine and fatty acids with an amine function. Capsaicin targets the TRPV-1 receptor and it is involved in several pathologies. Since capsaicin is a small molecule, it can be used for a good candidate for radiotracer. Technetium-99m ( $^{99m}\text{Tc}$ ) is one of the most common radiotracers for imaging. In an effort to develop new compounds, vanillyferrocenecarboxamide 1, was synthesized. This type of ferrocenyl compound is suitable for use as a precursor in the synthesis of the technetium analogus, 1-[2-(cyclopentadienyltricarbonyltechnetium-99m)-Nvanillyferrocenecarboxamide 2. We have found good conditions for the double ligand transfer reaction involving 1,  $[\text{}^{99m}\text{TcO}_4]^-$  and  $\text{Mn}(\text{CO})_5\text{Br}$  to produce 2 in 95% yield. For identification of the technetium compound, a rhenium analog was used for comparison using the HPLC technique. Compound 2 has a high radiochemical stability. The biodistribution studies were carried out according to the relevant national regulation, using wistar male mice weighing between 20 and 30 g. Purified compound 2 was injected via the tail vein. The dose employed was 10  $\mu\text{Ci}$  per animal (in 100 mL volume). At the specified time points postinjection of the 2 groups of three animals each were sacrificed by heart puncture; tissues of interest were removed and weighed; and radioactivity was counted. The injected dose (ID) was calculated by comparison with dose standards prepared from the injected solution of appropriate counting rates. and the data were expressed as percentage of ID per gram of tissue (% ID/g of tissue). Biodistribution studies showed a fast kidney excretion, low brain uptake and a retention in the testis. In summary, our study report the radiolabeling of N-vanillyferrocenecarboxamide with technetium 99m in one step. This radio-complex was obtained with high yields and high chemical proprieties. A biodistribution study was also performed to demonstrate the feasibility of using 2 as a potential agent for imaging tumor.





**IAEA-CN-310/166**

**47Sc Production: Comparison of the NatV(P,X) and 48Ti(P,X) Routes from the Dosimetric Point of View**

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The radionuclide  $^{47}\text{Sc}$  is a promising candidate for the development of theranostic radiopharmaceuticals, although its availability is currently low. Yields of  $^{47}\text{Sc}$  produced through proton irradiation of both natV and  $^{48}\text{Ti}$  targets at energies  $E_P \leq 40$  MeV were compared in this work. The co-production of other Sc radioisotopes and their contribution to the dose increment (DI) to the patient<sup>1</sup>, by considering a DOTA-folate conjugate ( $^{47}\text{Sc}$ -cm10)<sup>2</sup> as an example of radiopharmaceutical, were also evaluated.

About natV target, both  $^{48}\text{Sc}$  and  $^{46}\text{Sc}$  are co-produced, causing a decrease of the Radio Nuclidic Purity (RNP) over time and an increase of the dose to the patient. For  $E_P \leq 35$  MeV and 24 h irradiation, the RNP is  $>99\%$  and the DI is  $<10\%$  up to  $t_{\text{max}}=60$  h after the End of Bombardment (EOB). Increasing the irradiation time to 80 h, the  $^{47}\text{Sc}$  yield becomes almost a factor 3 higher, however  $t_{\text{max}}$  reduces to 30 h.

About  $^{48}\text{Ti}$  target,  $^{46}\text{Sc}$ ,  $^{44\text{m}}\text{Sc}$ ,  $^{44\text{g}}\text{Sc}$  and  $^{43}\text{Sc}$  contaminants are produced and, in all the considered scenarios, the RNP is initially very low. For  $E_P \leq 30$  MeV, the RNP increases, up to achieving 99% about 1500 h (almost 20 half-time of  $^{47}\text{Sc}$ ) after the EOB.

In conclusion, despite the  $^{47}\text{Sc}$  yield obtained by irradiation of  $^{48}\text{Ti}$  is larger when compared to the use of natV targets, its RNP is not suitable for medical applications.



**IAEA-CN-310/167**

## **Cellular and Multicellular Dosimetry of two Copper Radioisotopes: $^{67}\text{Cu}$ and $^{64}\text{Cu}$**

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Radiopharmaceuticals are usually distributed nonuniformly inside tissues, since only a fraction of the cells are actually labeled. Labeled and unlabeled cells often receive different absorbed doses depending on the distribution pattern at the cellular and subcellular level and the characteristics of the emitted radiations. Both  $^{67}\text{Cu}$  and  $^{64}\text{Cu}$  radionuclides have nuclear decay features which make them suitable for diagnostic and therapeutic applications in nuclear medicine. However,  $^{64}\text{Cu}$ -based therapy is commonly considered advantageous if the radionuclide is incorporated inside cell nuclei, as its Auger electron emission component may cause a very high level of DNA damage.

In this work, the MIRDCell software<sup>1</sup> was used to assess the doses due to radioactive decays of a uniform distribution of  $^{67}\text{Cu}$  and  $^{64}\text{Cu}$  in tumour models represented as isolated spheres of water density. Besides, the dependence of the dose to cell nuclei on the subcellular distribution of radionuclides, cluster cell dimension and percentage of labeled cells were also investigated by modelling these spheres as cluster of cells. The results of this study demonstrate that, if  $^{xx}\text{Cu}$  is localized into the cell nuclei, the absorbed dose in isolated single tumor cells is larger for  $^{64}\text{Cu}$  compared to  $^{67}\text{Cu}$ , but this advantage is lost in a cell cluster simulating a micro-metastasis.



**IAEA-CN-310/169**

**Registered Radiopharmaceuticals, Trends in Clinical Trials, the Role of Rosatom State Corporation**

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A tremendous growth of target therapy radiopharmaceuticals on clinical trials requires more isotopes. Isotope products are mainly manufactured by national corporations. Rosatom State Corporation has the largest capacity in the world, exploiting 8 reactors. To use Rosatom`s facilities effectively and to make them available worldwide it is essentially important to have a proper view upon isotopes and molecules on multinational clinical trials, radiopharmaceuticals indications, doses, time terms, infrastructure conditions and other information that may influence current and future demand for isotope products. This presentation is an attempt to summarize what is highly needed worldwide and what role may particular Rosatom`s plants play currently and potentially.



**IAEA-CN-310/170**

### **Women's Role in Radiopharmaceuticals Development and Production in Argentina**

Analia Soldati

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Argentina has a long tradition in peaceful uses of nuclear energy and its applications. The subject of radiopharmaceuticals for the diagnosis or treatment of human health diseases has been constantly growing since the 1950s, and during these years women who work in physics, chemistry, engineering, biology and medicine have been participating in education, research, development, production, control and even policy jobs, supporting the advances of the National Atomic Energy Commission (CNEA) laboratories, different universities, the Nuclear Medicine Departments of many Hospitals and even the argentinean Nuclear Protection Agency (ARN).

Nowadays, Argentina counts with 6 federal and 4 private centers of nuclear medicine with ARN clasified “class one” cyclotron-radiopharmacy installations, and distributed in all the territory, where radiopharmaceuticals are being developed and/or produced by a licensed team.

In this work, we explored quantitatively and qualitatively the role and situation of women in the workforce of the national radiopharmaceutical world using the personal interview method and literature research.

We relieve the number or women hired, the position occupied, the participation in national and international I+D and cooperation projects, the teaching and consulting activities, the highest study level, the familiar situation, the influence of maternity, and other items, and finally we postulate the trends and necessities for equal opportunities in this branch.



**IAEA-CN-310/172**

## **Radioiodinated Anti-HER2 Monoclonal Antibodies as Potential Therapeutic Radiopharmaceuticals**

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Human epidermal growth factor receptor type 2 (HER2) is overexpressed in various cancers, resulting in aggressive phenotype with poor prognosis. Developed therapeutic monoclonal antibodies (mAbs) targeting HER2-receptor could be useful for Targeted Radionuclide Therapy (TRT). Iodine has a number of radionuclides suitable for SPECT ( $^{123}\text{I}$ ) or PET ( $^{124}\text{I}$ ) imaging and radiotherapy ( $^{123}\text{I}$ ,  $^{125}\text{I}$ ,  $^{131}\text{I}$ ).

The aim of this study was to optimize radiolabeling conditions of anti-HER2 mAbs (trastuzumab and pertuzumab) with  $^{125}\text{I}/^{131}\text{I}$ , determine radiochemical purity of final products, binding affinity, specificity, internalization properties and cytotoxicity evaluation.

MABs were radiolabeled with  $^{125}\text{I}/^{131}\text{I}$  via Iodogen and purified on SEC PD-10 columns. Biological properties were evaluated on HER2-positive SKOV-3 and HER2-negative MDA-MB-231 cell lines. Various doses of  $^{125}\text{I}/^{131}\text{I}$ -mAbs were used to determine the EC<sub>50</sub> and D<sub>0</sub> values. Radiolabeling took ca. 10 min with yield of 90-99% and radiochemical purity above 98%. The  $^{125}\text{I}/^{131}\text{I}$ -mAbs retained their high affinity and specificity towards HER2-receptor as confirmed by negligible binding on SKOV-3 cells. They showed also cytotoxic effect, in an HER2-mediated manner, extent of which was mediated by both the added radioactivity and incubation time.

This study shows that  $^{125}\text{I}/^{131}\text{I}$ -mAbs are promising radioconjugates for TRT, especially the highly internalizing trastuzumab labeled with Auger's electrons emitter  $^{125}\text{I}$ .



### IAEA-CN-310/173

#### **[11C]KEN a Potencial GSK-3 $\beta$ Imaging Agent in the Alzheimer's Disease.**

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The phosphotransferase glycogen synthase kinase 3-beta (GSK-3beta) is an interesting molecular target in Alzheimer's disease. The objective of this research was the design and development of a [11C]C radiotracer derived from kenapullone (9-Bromo-7,12-dihydroindolo[3,2-d][1]benzazepin-6(5H)-one) a , GSK3-beta inhibitor (IC<sub>50</sub>=23nM).

[11C]KEN was synthesized by N-methylation on the indolic ring of kenapullone with [11C]CH<sub>3</sub>I in a TracerLAB FXc-pro (GE) research platform. The labeling reaction was optimized using 5-bromoindole due to the high cost of kenapullone. The parameters for optimization were: i)base (NaOH, Li<sub>2</sub>CO<sub>3</sub>, K<sub>2</sub>CO<sub>3</sub>), iii) temperature (65-135°C), iv)time (1-6minutes) and v) mass of 5-bromoindole (2.5-15 $\mu$ moles). Once the parameters were optimized, kenapullone was labeled under the optimized conditions.

The parameters that had the greatest impact on the reaction yield were base and temperature. The best conditions for labeling with [11C]C were: a temperature of 95°C in 0.4ml of dry DMF for 4min using 4mg of Cs<sub>2</sub>CO<sub>3</sub> and 15 $\mu$ mol 5-bromoindole, obtaining a yield of 56%ndc . Under these conditions the labeling of kenapullone resulted in a yield of 40%ndc and a RCP>90%.

In conclusion the [11C]KEN was obtained with adequate RCP and good stability. Further studies are being performed to assess the potentiality of [11C]KEN as GSK-3 $\beta$  imaging agent in the AD.





**IAEA-CN-310/177**

### **Synthesis and Evaluation of <sup>99m</sup>Tc-Lactoferrin for Detection of Staphylococcus Aureus Infections**

mouldi saidi, Alifa kanoun, Issam Ben Salem

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Human and camel lactoferrin an iron-binding protein (known to defend against viruses and bacteria) were labeled with technetium-99m with the aim of the development of a new radiotracers for infection imaging using a simple technique that yielded a labeling efficiency of 98% and stable complexes over time. The radiochemical purity of the labeled compounds was evaluated by ITLC and HPLC. The proteins were investigated for targeting infections in experimental animals. Biodistribution studies of those labeled proteins in different organs and in mice infected with Staphylococcus aureus at the femoral muscle were investigated. A high concentration of <sup>99m</sup>Tc-labelled molecules in the site of infection was observed.

Test ratios of 3.43 and 3.71 were obtained after 60 min for the camel and the human Lactoferrin, respectively. These values were compared to each other and to those reported in the literature, leading us to conclude that the <sup>99m</sup>Tc- labeled lactoferrin could be a promising radiotracers for the diagnosis of infection sites



**IAEA-CN-310/178**

### **Development of 3d-Printed Mice Phantom for Micropet System Calibration**

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Small animal micro-positron emission tomography (MicroPET) is of great importance for the development of new radiopharmaceuticals for molecular diagnosis and therapy and thus for potential clinical applications. The calibration procedure of a MicroPET system is essential for small animal imaging due to the image resolution and spatial geometry. It requires several steps and materials, and most importantly, a suitable phantom. The aim of this study was to develop a 3D printed phantom of a male nude mouse of 28 g, based on the tomographic image database of the Digimouse® project by Stout et al. (2002) and Dogdas et al. (2007) (Mendes et al., 2017). The 3D-printed mouse phantom (DM \_ BRA) consists of a cast with a 2 mm thick outer layer and a hollow interior filled with an  $^{18}\text{F}$ -FDG solution with known  $^{18}\text{F}$  activity. The phantom was positioned and several images were taken over a period of time after the  $^{18}\text{F}$ -FDG solution had decayed, and the number CPS /ml was determined to correlate with the activity concentration in MBq/ml. A curve of counting efficiency as a function of activity was obtained for the MicroPET system at the Radiopharmaceuticals Research and Production Unit (UPPR/CDTN/CNEN) in Brazil.



**IAEA-CN-310/179**

### **The Status and Prospects of Radiopharmaceutical Industry in Russia**

Oleg Mansurov, Irina Svyato

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The presentation provides the ongoing status and prospects of radiopharmaceutical industry in Russia. At present Russia supplies isotope products to more than 50 countries, including ones for medical purposes. The present list of produced radiopharmaceuticals is limited to basic products for diagnosis (C-14, Tc-99m, I-131) and therapy (I-131, Sm-153) purposes. The construction of a new large radiopharmaceutical plant (plant square - 28000 m<sup>2</sup>; technology lines - 21) in 2025 in Obninsk will substantially increase the nomenclature of radiopharmaceuticals up to 25 drug forms. The plant established according to cGMP regulations will produce a variety of diagnostics and therapy radiopharmaceuticals based on Lu-177, Ra-223, Pb-212, Y-90, Bi-213, Sr-89, Ac-225, Ga-68, Th-227, Rb-82, etc. The presentation gives statistical and analytical information about the current practice of radiopharmaceutical application related to diagnostics and treatment of different nosologies of oncology. It also outlines the ongoing efforts on expansion of the use of radiopharmaceuticals in the country (infrastructure development, specialized personnel development, etc.). An overview of ongoing R&D activities in the field of innovative radiopharmaceuticals that take place in the Russian nuclear research organizations is also provided.



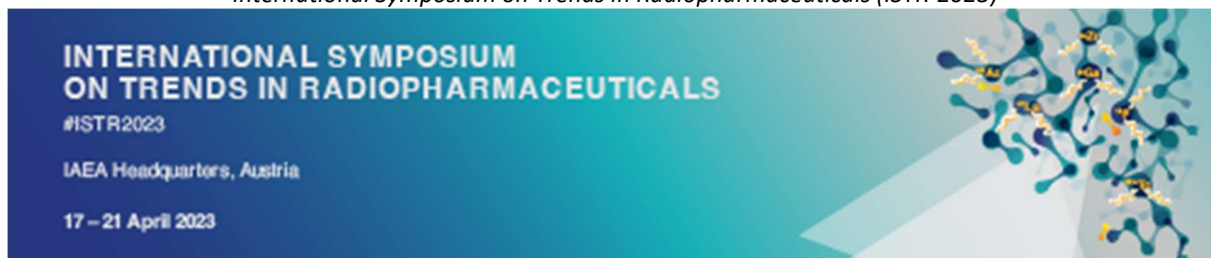
**IAEA-CN-310/180**

**The Development of New Radiopharmaceuticals Based on Nanoantibodies and Alternative Scaffold Proteins: Current Challenges and Prospects**

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Theranostics is the term used to describe the combination of using one radioactive drug to identify (diagnose) and a second radioactive drug based on the same carrier molecule to deliver therapy to treat main tumor and metastatic tumors. One of the most promising vectors for delivering radionuclides to the tumor are VHH fragments of single-domain monoclonal antibodies (nanobodies) and various alternative scaffold proteins. The report analyzes the current state of diagnosis and treatment of oncological diseases using labeled nanobodies and scaffolds, prospects for their use and limitations. In addition, the author presents his own experience in the development of radiopharmaceutical drugs based on nanoantibodies (including bispecific ones), as well as scaffolds labeled  $^{99m}\text{Tc}$ ,  $^{68}\text{Ga}$ ,  $^{64}\text{Cu}$ ,  $^{225}\text{Ac}$ ,  $^{227}\text{Th}$ ,  $^{177}\text{Lu}$ , for theranostics of oncologic diseases.



**IAEA-CN-310/181**

**Synthesis of Gold Nanoparticles Labeled with Auger Electron Emitters:  $^{197}\text{Hg}/^{197\text{m}}\text{Hg}$  As Potential Therapeutic Radiopharmaceuticals**

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Mercury radionuclides  $^{197}\text{Hg}$  and  $^{197\text{m}}\text{Hg}$  can find applications in Auger electron therapy due to their high efficacy of Auger electron (AE) and conversion electron (CE) emission. [1] To obtain stable binding of mercury radionuclides and the highest specific activity of synthesized compounds, we propose the application of gold nanoparticles (AuNPs) as carriers for  $^{197}/^{197\text{m}}\text{Hg}$ .

The  $^{197}\text{Hg}$  and  $^{197\text{m}}\text{Hg}$  radionuclides were produced in the cyclotron of the Triangle Universities Nuclear Laboratory (TUNL, USA) through  $^{197}\text{Au}(d,2n)^{197}/^{197\text{m}}\text{Hg}$  reaction and the thermal neutron irradiation in Maria nuclear reactor (NCBJ, Poland) through  $^{196}\text{Hg}(n,\gamma)^{197}/^{197\text{m}}\text{Hg}$  reaction. The theoretical and experimental thick-target yields for the accelerator production were calculated, and the method of radionuclides separation from target material based on LN-Resin was developed. We found that both tested methods proved to be efficient for the production of  $^{197}/^{197\text{m}}\text{Hg}$  with activities sufficient for therapeutic application.

Radionuclides were successfully attached to 5 nm AuNPs nanoparticles by amalgamation on their surface ( $\text{Au}_3\text{Hg}$ ) and coated with polyethylene glycol (PEG) - 5000 g/mol (1:95 AuNPs:PEG). In the final step, thiol-PEG-trastuzumab was attached to AuNPs (1:5 AuNPs:PEG-trastuzumab).

In order to check the therapeutic potential of the radiobioconjugate, in vitro studies were performed.



### **IAEA-CN-310/183**

#### **Establishment of the Nuclear Medicine Research and Innovation Center for the Development of Emerging PET Radiopharmaceuticals**

Ivy Angelica Nunez, Adelina Bulos, Joanna Michelle Chua-Aniago, Janice Mallillin, Carlo Arcilla

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In the Philippines, Cancer is one of the top non-communicable diseases with a mortality rate of 60%. To increase early diagnosis and cancer detection among Filipinos, the Philippine Nuclear Research Institute of the Department of Science and Technology initiated the establishment of a medical cyclotron facility and PET/CT imaging center to produce the most commonly used tracer, <sup>18</sup>F-FDG with the aim of expanding production to non-FDG tracers that are being locally used for research and other clinical applications.

The facility is envisioned to reduce the cost of using cyclotron-based radiopharmaceuticals and tracers with the intention to make it available to lower-income patients in the country. Currently, only privately held facilities are capable of producing cyclotron-based radiopharmaceuticals making PET/CT procedures limited and expensive. With the facility, research and development of emerging PET radiopharmaceuticals are also planned for local production.

The poster presentation will showcase the current developments in the establishment of the Nuclear Medicine Research and Innovation Center (NMRIC). Its perspective, design of laboratories and its GMP compliance, programs, and activities towards its completion and eventual operation for supplying PET radiopharmaceuticals for cancer diagnosis and treatment.





**IAEA-CN-310/184**

## **Recent Radiopharmaceutical Utilization Profiles in the Philippines**

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Philippine Nuclear Research Institute (PNRI), Commonwealth Avenue, P.O. Box 213, Quezon City, Philippines

One of the key requirements of nuclear medicine procedures is the use of radioisotopes and radiopharmaceuticals. Radiopharmaceuticals generally consist of two components, a radioactive element (radionuclide), that permits external scan, linked to a non-radioactive element, a biologically active molecule, drug or cell (red and white blood cells labeled with a radionuclide, for example) that acts as a carrier or ligand, responsible for conducting the radionuclide to a specific organ.

Radiopharmaceuticals are used both in diagnostic imaging and radiotherapy, the general purpose of which is to assist in diagnoses of organs and treatments of pathological conditions, such as cancer and other non-communicable diseases. In the imaging modality, radiopharmaceuticals are administered via oral, intravenous, or by inhalation to enable visualization with their radioactive tracers of various organs, such as kidneys, lungs, thyroid and heart functions, bone metabolism and blood circulation. In therapeutic modality, aiming to treat cancer or over functioning thyroid gland, a high dose of radiation is delivered through specific radiopharmaceuticals targeting the diseased organ.

Most of the radiopharmaceutical requirements of nuclear medicine centers in the Philippines are currently all imported. And there is also an observation on the increasing rate of establishment of new nuclear medicine centers.

The poster presentation will deal mainly with the recent profiles of the radiopharmaceuticals commonly used across the country by region. Studies will be done on the collated available data through the years to include the pandemic period. From then conclusions and recommendations can be inferred to promote enhanced nuclear medicine applications in the country.



IAEA-CN-310/186

## Optimization of In-house Formulation of $^{177}\text{Lu}$ -CHX-A''-DTPA-Trastuzumab for Diagnostic and Therapeutic Doses: An Institutional Review

Bhakti Shetye

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Radioimmunotherapy has played a pivotal role in diagnosis and treatment of various types of cancers. Trastuzumab (Herceptin®) selectively binds with high affinity to the extracellular domain of the human epidermal growth factor receptor protein (HER2) and is used in the treatment of HER2+ metastatic breast cancer. Trastuzumab labelled with Lu-177 acts as a useful radioimmunotherapeutic agent as its low activity dose can be used for assessment of individual patient dosimetry which will be further used for planning of the therapeutic dose. The objective of this study was to prepare diagnostic and therapeutic doses of  $^{177}\text{Lu}$ -CHX-A''-DTPA-Trastuzumab with optimum labeling efficiency and assess its pharmacokinetic behavior.

Trastuzumab conjugates were prepared at a molar ratio of 1:10 (antibody: BFCA) (1) wherein p-SCN-Bn-CHX-A''-DTPA was used as the chelator. Reconstituted trastuzumab (22mg/ml) was conjugated with p-SCN-Bn-CHX-A''-DTPA by incubating the mixture at 25°C for 2hrs followed by 24 hrs incubation at 4°C at pH 9.0. Unconjugated CHX-A''-DTPA was removed by buffer exchange with 0.1M sodium acetate (pH= 6.5). Radiolabelling of the conjugate with  $^{177}\text{LuCl}_3$  was performed at room temperature for 15 min. Purification of labelled product was carried out using PD-10 desalting column with 0.05M phosphate buffer (pH=7.4) as the eluant. Ascorbic acid was added to the product to prevent radiolysis. Sterile filtration using 0.22 $\mu$  filter ensured the sterility of the product. Characterization of the product was determined by SE-HPLC with TSK gel column using 0.05M phosphate buffer (pH= 6.8) containing 0.05% sodium azide as eluant and by TLC carried out using Whatman paper no 3 as stationary phase and 10 mM sodium citrate as a mobile phase.

In our institute, 22 diagnostic doses of 10-12 mCi each and 12 therapeutic doses of 90-100 mCi  $^{177}\text{Lu}$ -CHX-A''-DTPA-Trastuzumab were prepared. The % labeling efficiency, specific activity (mg/mCi) and the radioactive concentration (RAC in mCi/mL) of the formulation were calculated. The radiochemical purity of the product as determined by HPLC and TLC was > 99 %. HPLC chromatogram of  $^{177}\text{Lu}$ -CHX-A''-DTPA-Trastuzumab showed retention time of 10.4 min. TLC of labelled product remained at the point of spotting (Rf= 0). Measured specific activity was 10.33  $\pm$  2.2mCi/mg. The in-house preparation of both diagnostic and therapeutic doses of  $^{177}\text{Lu}$ -CHX-A''-DTPA-Trastuzumab was optimized which showed good radiochemical purity. Initial patient studies have been performed which showed promising results. Thus, the in-house preparation of  $^{177}\text{Lu}$ -CHX-A''-DTPA-Trastuzumab can be used as an effective thernostic radiopharmaceutical for treatment of breast cancer.



**IAEA-CN-310/187**

### **Acquiring GMP Status for Tc-99m Facility in the Philippines: Opportunities, Challenges and Lessons Learned**

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The Philippines will soon have the capability to locally prepare and produce the most commonly used medical radioisotope with the setting-up of Molybdenum-99/Technetium-99m generator production facility at the Department of Science and Technology – Philippine Nuclear Research Institute (DOST-PNRI). Currently, government/private hospitals import Technetium-99m (Tc-99m) generators from overseas. When the facility is fully operational, it will be able to supply the local Technetium-99m requirements of the nuclear medicine centers in the country. There are about 73 hospitals in the country with nuclear medicine facilities, 69 facilities of which are equipped with gamma cameras. The recent annual importation of Tc-99m is about 27,000 Giga Becquerel (GBq) for 2018 and 18,500 GBq for 2019 and 6,466 GBq for 2020. The local availability of Technetium-99m will mean (1) wider and more accessible usage of this radioisotope for nuclear medicine procedures (2) research on Technetium-99m labelling of molecules and new pharmaceuticals will be enhanced and (3) other research studies such as radiotracer applications in industry and other research fields can be undertaken.

With the facility established and ready for operations, one major challenge in achieving operational capabilities is obtaining a license to operate with the cGMP compliance which can be obtained from the local Food and Drugs Authority (FDA). Recent submission of primary requirements for licensing showed the need to comply in the following main areas: personnel, premises, equipment and processes, sterility assurance and maintenance program for critical equipment.

The poster presentation will deal on the challenges and opportunities involved in acquiring GMP status, as well as the lessons learnt in the whole process of GMP regulatory compliance.



**IAEA-CN-310/188**

**Assessment of Cell Damage Produced by  $^{161}\text{Tb}$ -/ $^{177}\text{Lu}$ -Somatostatin Analog Radiopharmaceuticals**

Laura Melendez-Alafort, Erika AZORIN-VEGA, GUILLERMINA FERRO-FLORES, Cristina Bolzati, Antonio Rosato, LAURA DE NARDO

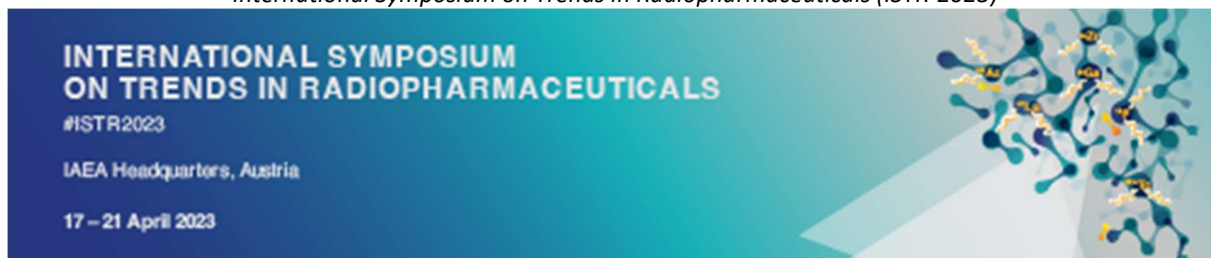
Istituto Oncologico Veneto, IOV-RCCS - Via Gattamelata 64, Padova, Italy

The use of  $^{161}\text{Tb}$  has been proposed for targeted radionuclide therapy (TRT) because its decay properties are quite similar to those of  $^{177}\text{Lu}$ , which is currently the most used radionuclide in TRT.  $^{161}\text{Tb}$  emits low-energy photons that are useful for SPECT imaging and relatively low-energy  $\beta^-$ -particles. However, unlike  $^{177}\text{Lu}$ ,  $^{161}\text{Tb}$  emits a significant number of internal conversion electrons (IE) and Auger electrons (AE) with energies  $\leq 40$  keV, which could be an advantage to improve the therapeutic efficacy. Moreover, in vitro and in vivo characteristics of 2 somatostatin (SST) analogs labeled with both  $^{161}\text{Tb}$  and  $^{177}\text{Lu}$  using DOTA as chelating agent demonstrated that both radionuclides produce stable complexes with very similar biodistribution and pharmacokinetics properties.

In this research, the biological damage produced to clusters of AR42J cells by three different SST analog radiopharmaceuticals (RFs) labeled with  $^{161}\text{Tb}$  or  $^{177}\text{Lu}$  located in different regions within the cells was assessed. For this purpose, the cellular dosimetry and cell surviving fraction assessments using the MIRDcell code were performed.

The results demonstrated that the mean cell absorbed dose is not sufficient to predict cell survival, in this case the most important factors are the localization of the RFs at cellular level and the pattern distribution of the dose within the different cell compartments.

In conclusion, when  $^{161}\text{Tb}$ -SST radiopharmaceuticals are internalized in the cells, the emitted IE and AE contribute significantly to the dose absorbed by the cell nucleus. Consequently, the therapeutic efficacy of  $^{161}\text{Tb}$ -RFs is higher compared to  $^{177}\text{Lu}$ -RFs.



**IAEA-CN-310/189**

**Preclinical dosimetric studies of  $^{177}\text{Lu}$ -scFvD2B,  $^{177}\text{Lu}$ -PSMA-617 and  $^{177}\text{Lu}$ -iPSMA**

Laura Melendez-Alafort, GUILLERMINA FERRO-FLORES, Blanca Eli Ocampo-García, Clara Santos-Cuevas, Sofia Turato, Giulio Fracasso, Cristina Bolzati, Antonio Rosato, LAURA DE NARDO

Istituto Oncologico Veneto, IOV-RCCS - Via Gattamelata, 64, 35128 Padova PD, Italy

Targeted radionuclide therapy (TRT) combine selective uptake and high internalization in tumor cells with minimal risk to healthy tissues. Consequently, internal dosimetry has become a very important tool for evaluating the risks and benefits of new TRT agents.

The aim of this study is to estimate the tumor-absorbed doses produced by a single chain(scFv)-based construct,  $^{177}\text{Lu}$ -scFvD2B, and to compare it with those produced by two low molecular weight (LMW) agents currently used in prostate cancer therapy,  $^{177}\text{Lu}$ -PSMA-617 and  $^{177}\text{Lu}$ -iPSMA.

The three radiopharmaceuticals (RFs) were prepared and their radiochemical purity determined. Biodistribution studies of each RF were then carried out in healthy mice to calculate the number of disintegrations in the main organs per unit of administered activity. Organs absorbed dose were then calculated with OLINDA/EXM 2.1.1 for each  $^{177}\text{Lu}$ -RF using both adult male and mouse phantoms. Tumor-absorbed dose was calculated for different tumor size using tumor uptake values, obtained from 3D SPECT image reconstruction of mice bearing LNCaP micro-pulmonary tumors treated with the  $^{177}\text{Lu}$ -agents.

All  $^{177}\text{Lu}$ -agents were obtained in high yield (>98%). Dosimetric studies with mouse and human phantoms demonstrated that organ absorbed doses of  $^{177}\text{Lu}$ -scFvD2B were higher than those of  $^{177}\text{Lu}$ -LMW agents. However, tumor-absorbed doses of  $^{177}\text{Lu}$ -scFvD2B for all tumor sizes investigated were 2.8 to 3.0 times higher than those of  $^{177}\text{Lu}$ -iPSMA and  $^{177}\text{Lu}$ -PSMA-617, respectively.

In conclusion, this study demonstrated the potential of  $^{177}\text{Lu}$ -scFvD2B as a therapeutic agent for PSMA-expressing tumors, due to its higher tumor-absorbed dose compared to  $^{177}\text{Lu}$ -LMW agents.



**IAEA-CN-310/190**

## **A Comprehensive Platform for Management the Production and Distribution of Radiopharmaceuticals**

shayma mohammed, Adel Trabelsi, Moez Trabelsi

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Work practices in the radiopharmacy should be consistent with standard operating procedures, all professional activities must be documented and made available to those working in radiopharmacy to ensure that practices are harmonized and standards maintained. Despite this, all of these tasks are performed manually or semi-automatically.

Developing a comprehensive platform to ensure a rigorous management system that links the management system of nuclear medicine to the management system of nuclear radiopharmacy in accordance with the recommendations of International Agency of Energy Atomic would organize the work of management system and minimize the manual human handling that has proven to be the main source of error in this area.

The platform consists of 11 modules (Order, Central Pharmacy, Financial, General Management, Production, Stock, Quality Control, Transport, Release, Statistic and Database). It can be used by 15 classes of actors.

The automated system presents accessibility, security, facility and traceability, approximately, makes all the management automatic provides a good codification and a better user experience with a modern and rich graphical interface.





IAEA-CN-310/191

**Targeting Pancreatic Ductal Adenocarcinomas (PDAC) with Neuroendocrine Differentiation (NED) Subgroup of Tumours with Combination of  $^{177}\text{Lu}$ -DOTATATE and Dihydroxy Stilbene(DHS) Combination: Mechanistic Insights**

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The existence of adenocarcinomas with neuroendocrine differentiation (NED) provides the possibility of treating this subgroup of tumours with PRRT alone or in combination. Despite the huge benefits of PRRT in NET patients salient questions pertaining to its molecular mechanism of action remain largely unknown. In the current investigation, we proposed to elucidate the mechanism of action of  $^{177}\text{Lu}$ -DOTATATE (Lu-DT) in PDAC and possible improvement of PRRT outcome in combination with Dihydroxystilbene (DHS).

Lu-DT and DHS combination therapy showed that colony forming ability of both MIA-PaCa-2 and PANC-1 gradually reduced with increasing dose of Lu-DT (0.25-1 MBq/ml) with no colony noticed beyond 5 MBq/ml dose. Interestingly, clonogenic results showed that DHS effectively radiosensitized both PDAC cells in a concentration dependent manner. The radio sensitizing effect of DHS was more robust at later time points as revealed by flow cytometry based sub-G1 assay. DHS augmented Lu-DT induced DSBs in PDAC cells. Lu-DT induces cell cycle arrest in G2-phase in MIA-PaCa-2 cells. Furthermore, combination treatment led to enhanced accumulation of ER in PDAC Cells suggesting their role in induction of ER stress. DHS abrogates Lu-DT induced reticulophagy, contributing to DHS mediated radiosensitization. In summary, the in vitro results of this study displays huge potentiality of combination therapy of  $^{177}\text{Lu}$ -DOTATATE and Dihydroxy stilbene in treating NED subgroup of PDAC cells.



**IAEA-CN-310/192**

## **Development of Solid Target Technologies for $^{225}\text{Ac}$ Production with Proton Bombardment**

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Due to its clinical significance, targeted alpha therapy (TAT) has attracted a lot of attention. Actinium-225 ( $^{225}\text{Ac}$ ,  $\alpha = 100\%$ ,  $T_{1/2} = 9.92$  days) is a promising radionuclide applicable to TAT. However, its production on a wide scale is in the development stage, while the global demand has increased. Alternative production routes are therefore widely desired. This work is showing a production feasibility of  $^{225}\text{Ac}$  via the nuclear reaction  $^{226}\text{Ra}(p,2n)^{225}\text{Ac}$  using a solid target technology on a low-energy medical cyclotron.

A Monte Carlo analysis has been performed for a customized  $30^\circ$  angled ALCEO solid target system, bombarding with a low-energy medical cyclotron at  $100 \mu\text{A}$  for 10 hours a special sealed shuttle with 124mg electroplated  $^{226}\text{Ra}$  on a platinum substrate. Barium electroplating (purity 99,999%) have been performed ( $N = 20$ ) to simulate the feasibility of the  $^{226}\text{Ra}$  one.

According to the Monte Carlo analysis, the bombarded sealed shuttle shown no detachment/damaging of the electroplated Ra. More than 200 radioisotopes will be produced during the nuclear bombardment, but only few with a reliable amount, and anyway easily to purify with commercial cartridges. The expected production yield is 7,4 mCi/h (EOB) @ 100uA, with yield per mass fraction of 0,0596 (mCi h<sup>-1</sup> 100  $\mu\text{A}$ -1 mg<sup>-1</sup>). Barium electroplating results smooth and repetible; the sealed shuttle anyway will avoid any cyclotron contamination problems during the bombardment.

This work has shown the possibility to provide on the market a reliable and automated solid target system to produce  $^{225}\text{Ac}$  via the nuclear reaction  $^{226}\text{Ra}(p,2n)^{225}\text{Ac}$  bombarding electroplated radium.



**IAEA-CN-310/193**

## **Radioisotope Separation of Platinum Group Elements for Potential Applications in Targeted Cancer Therapy**

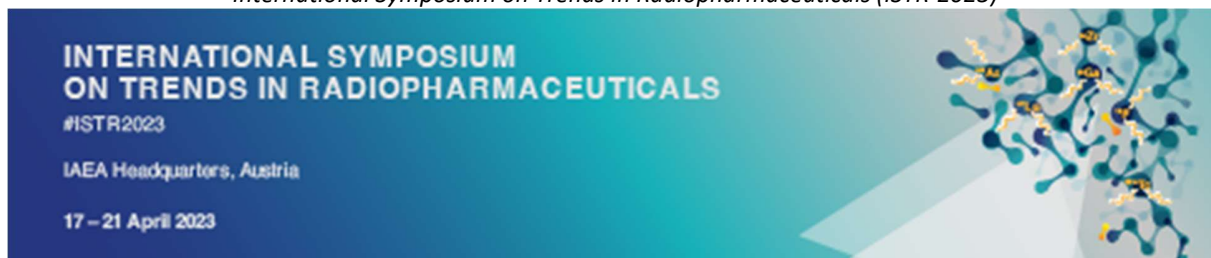
Zoltán Szűcs, Aicha Nour Laouameria, Hunyadi Mátyás

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Radionuclides offer an increasing potential for a wide range of endotherapeutic application, which is an effective and safe tool if their decay properties and biochemical functionality are appropriately chosen. The radioisotope  $^{103}\text{Pd}$  emits Auger electrons during its decay. The radiobiological effect of Auger electrons is so useful due to their high LET value (Linear energy transfer). Therefore, the targeted radionuclide therapy in oncology is increasing interest in such isotopes. However, its application to date has been severely limited by the extremely cumbersome and costly wet chemical process used to extract it, electrochemical dissolution in concentrated hydrochloric acid, remaining  $\text{RhCl}_3$  as waste, which is unsuitable for re-irradiation, and this justifies the demand on alternative technology.

The aim objective of this study is the design and the construction of radionuclide separation equipment for platinum group metals (PGM), especially  $^{103}\text{Pd}$ . The dry distillation method (DDM) is proposed to be employed. If differences between the isothermal vapor pressures of the radionuclide element and the target element are sufficiently large and positive, the effective separation and carrier-free collection of the radionuclides becomes possible. Considerable vapor pressures for PGM can only be achieved at elevated temperatures, practically above  $1600\text{ }^\circ\text{C}$ . In this temperature region the diffusion and out-gassing rate of radionuclides from the solid matrix of the target material are enhanced, hence the expected duration and expenses of the extraction process can be suppressed to an acceptable level. To our best knowledge, no scientific report is available on DDM separation of  $^{103}\text{Pd}$ , and related preparation of radiopharmaceuticals has not been applied in practice so far.

This presumably forms a good development basis for a prototype device, which is expected to be competitive and beneficiary for a scaling-up of radionuclide production for radio-therapeutic applications. We aspire to develop a simple, chemical-free, new separation method. Additionally, the very expensive rhodium metal will remain in the form of metal at the end of the process making it recyclable.



**IAEA-CN-310/194**

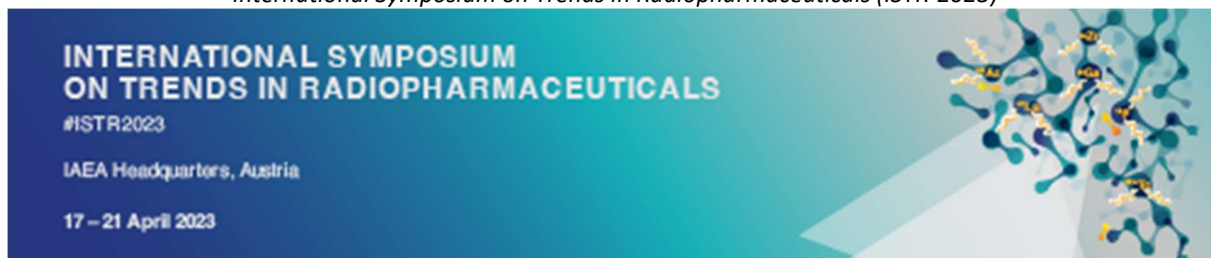
### **Synthera+ Platform Application of $^{68}\text{Ga}$ , Produced from $^{68}\text{Zn}$ Using HCl Medium**

Mátyás Fodor, Zoltán Szűcs

University of Debrecen, Egyetem ter 1, Debrecen, Hungary

Our concept is to produce  $^{68}\text{Ga}$  by the (p,n) reaction of  $^{68}\text{Zn}$  in hydrochloric-acid solution in a liquid target, via cyclotron. The target body is already ready, and initial irradiation tests with distilled water were carried out to monitor the pressure increase, which was found to be within safety limits. Before attempting the conference, we aim to finish irradiating  $^{68}\text{Zn}$  enriched  $\text{ZnCl}_2$  hydrochloric acid solutions, and separate the obtained  $[\text{}^{68}\text{Ga}]\text{Ga}$ -chloro complex from the bulk  $\text{Zn}^{2+}$  ions, and evaluate its radiochemical purity.

The produced radioisotope will be transferred to the iba Synthera+ panel, where the separation will happen. The radiochemical purity of the obtained product will be evaluated on a HPLC with UV-vis and gamma-spectrometer detectors.



**IAEA-CN-310/195**

### **Production of Sc Radioisotopes by Proton-Induced Reaction on CaO Target**

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A majority of medically important radioisotopes are created in neutron-induced reactions (reactor-based). Currently, alternative methods of production are being intensively investigated. The studies on alternative methods were prompted by unplanned reactor shutdowns several years ago, which resulted in a shortage of isotopes (i.e.,  $^{99}\text{Mo}/^{99}\text{Tc}$ ), which are used in medical applications. These studies are also boosted by the advancement of diagnostic techniques and the search for longer-lived isotopes for PET scanning. Hence, accelerators could be good candidates for the purpose of production.

Scandium radionuclides have recently gained a great deal of attention because they allow for personalized adjustment of radiation characteristics to improve the efficiency of medical care or therapeutic benefit. Scandium radionuclides scandium-43/44 ( $^{43/44}\text{Sc}$ ) as positron emitters and scandium-47 ( $^{47}\text{Sc}$ ) as beta-emitters appear to fit perfectly into the concept of theranostic pair. Proton irradiation of a calcium oxide target at a cyclotron can produce it. The production of  $^{46,48}\text{Sc}$  impurities hinders the purity of  $^{47}\text{Sc}$ , which is highly dependent on the energy of protons impinging on the target and the thickness of the target material. An accurate understanding of the production cross-sections is required for this purpose.

In this presentation we will discuss the results of the production of different Sc radioisotopes in natural CaO target by p-induced reactions up to 60 MeV.



IAEA-CN-310/196

## Evaluation of Human Hepatoma Cells Targeting of Biocompatible and Peptide-Functionalised Polymer Nanoparticles Encapsulating an Imaging Agent

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Nanomedicine, the application of nanotechnologies to the medical domain, is a fast-growing research field, especially the production of nanoparticles enabling encapsulation then controlled and targeted release of molecules of interest, such as a cytotoxic drug. Diagnostic could also benefit from the use of such nanovectors containing one or more imaging agent(s) (fluorescent dye, contrast agent, radionuclide) to image a tumour. Among the aliphatic polyesters' family, poly(malic acid) (PMLA) and its derivatives have raised a growing interest in the biomedical field because of their properties of biocompatibility and biodegradability and potential applications in drug delivery. In addition to these remarkable properties, a whole family of PMLA derivatives can be obtained by modifying the synthesis of the monomers and the reactions of the homopolymerisation and copolymerisation of these monomers. We have recently developed PMLA-based nanovectors, taking advantage of the exceptional properties of such polymers. They have been functionalised with hepatoma-targeting peptides, and a  $^{99m}\text{Tc}$ -based radiotracer for SPECT imaging and/or fluorescent probe for optical imaging have been encapsulated. Benzyl polymalate and its derivatives (PEGylated and/or peptide-modified) were prepared according to the methods previously described. The nanoparticles, incorporating a lipophilic imaging agent (DiD-Oil,  $^{99m}\text{Tc}$ -SSS, or both), have been formulated with the nanoprecipitation method. Encapsulation efficiency has been measured after purification with size-exclusion chromatography on Sephadex PD-10 columns. The resulting nanoparticles were characterised by DLS and TEM. In vitro studies have been performed on HepaRG hepatoma cells, using flow cytometry to quantify internalisation. Prepared nanoparticles were monodisperse and stable, with a spherical morphology. Encapsulation of fluorescent DiD-Oil and lipophilic  $^{99m}\text{Tc}$ -SSS radiotracer did not affect significantly the properties of the peptide-functionalised nanoparticles. Fluorescent nanoparticles have thus been used as a surrogate for radiolabelled ones for subsequent in vitro studies. Cell internalisation was strongly dependent on the peptide sequence of presence/absence of PEG.

We have developed a family of nanoparticles based on degradable, biocompatible and functionalisable polymers, enabling the binding of specific targeting agents and incorporating an imaging agent, either for optical or scintigraphic imaging. These objects deserve further investigation to gain a deeper understanding on their properties and in vivo behaviour. Encapsulation of a therapeutic radiotracer is also planned.





**IAEA-CN-310/197**

### **Copper-Mediated Radioiodination of Novel Prosthetic Groups**

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Boron reagents are widely used in production of radiopharmaceuticals to achieve the regio-selective labelling with various radiohalogens. In radioiodine chemistry boron reagents can be used for both electrophilic and nucleophilic reactions. The nucleophilic approach utilizes Cu(II) complexes to catalyse the reaction. Such strategy was proven to be effective for labelling of aryl-boronic esters containing electron-donating and electron-withdrawing groups.

**Objective:** The aim of this study was to radiolabel new prosthetic groups using copper-mediated iododeboronation method. Radiolabelled prosthetic groups will be further used for protein labelling via disulfide rebridging as a part of a different project.

Two new prosthetic groups were radiolabelled with iodine-131 using the copper-mediated iododeboronation approach. [<sup>131</sup>I]NaI was added to the solution of boronic-ester precursor with Cu(OCOCF<sub>3</sub>)<sub>2</sub> and 1,10-phenantroline in methanol/water mixture. Reaction was carried out for 20 min at 80°C.

Radio-HPLC and radio-TLC analyses confirmed that both prosthetic groups were successfully labelled with iodine-131 using the described method.

The preliminary results using the copper-mediated iododeboronation method for radiolabelling are promising. Further work will concentrate on the optimisation of reaction conditions, including comparison of different copper complexes. The boronic-ester will be also tested in the electrophilic labelling strategy.

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**IAEA-CN-310/199**

### **Radioiodination of Novel Prosthetic Groups for Disulfide Rebridging**

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Disulfide rebridging is a new strategy for coupling of prosthetic groups with biomolecules. It allows site-selective labelling with minimal modification of tertiary structure of biomolecules and it was successfully used with  $^{18}\text{F}$ ,  $^{64}\text{Cu}$  and  $^{89}\text{Zr}$ .

The aim of this study was to design and synthesize new prosthetic groups and couple them to octreotide via disulfide rebridging.

Prosthetic groups were labelled with  $^{131}\text{I}$  from corresponding stannylated precursors via electrophilic substitution or from boronic esters via copper-mediated nucleophilic approach. In electrophilic synthesis  $^{131}\text{I}[\text{NaI}]$  was added to solution of oxidant (Chloramine-T or NCS) and stannylated precursors, reaction was done at room temperature for 10 min. In nucleophilic approach,  $^{131}\text{I}[\text{NaI}]$  was added to a solution of boronic ester precursor,  $\text{Cu}(\text{O}(\text{C}(\text{O})\text{CF}_3)_2)$  and 1,10-phenanthroline and the reaction was heated for 20 min at  $80^\circ\text{C}$ .

Radio-HPLC and radio-TLC confirmed that both labelling strategies resulted in the formation of desired products. Preliminary analyses suggest that the nucleophilic strategy gave higher radiochemical yield than the electrophilic one.

The new  $^{131}\text{I}$ -labelled prosthetic groups for disulfide rebridging were prepared with two different methods. Current work concentrates on the conjugation of pre-labelled prosthetic group to octreotide followed by in vitro evaluation.

We acknowledge support from the European Union Horizon 2020 research and innovation program under grant agreement no. 857470 and from the European Regional Development Fund via the Foundation for Polish Science International Research Agenda PLUS program grant No. MAB PLUS/2018/8.



IAEA-CN-310/200

## LAT1 Inhibitory Potency of ADFB-Based Cancer Theranostic Radiopharmaceutical Designs: A Molecular Docking Simulation

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L-type amino acid transporter-1 (LAT1) is a valid molecular target on cancer cell membranes. Although JPH203 is considered the most potent LAT1 inhibitor, its structure precludes JPH203 from being developed into a theranostic radiopharmaceutical. ADPB ((S)-2-amino-4-(3,5-dichlorophenyl) butanoic acid) has a relatively similar LAT1 inhibitory potency to JPH203 yet has a smaller and simple structure, allowing versatile bioconjugation. We performed molecular docking simulations to investigate whether ADPB-based theranostic radiopharmaceutical designs might have a better LAT1 inhibitory potency than JPH203-based ones. Eight ADPB-based and 24 JPH203-based theranostic radiopharmaceutical designs were computationally docked into LAT1 in Molecular Operating Environment (MOE) 2020 software. The 3D structure of human LAT1 was downloaded from RCSB PDB (ID: 7DSQ). The 3D theranostic radiopharmaceutical designs (each contains ADPB or JPH203, a chelate (DOTA, NOTA, or NODAGA) with or without a linker (Ahx, 6-aminohexanoic acid), and a radiometal ( $^{68}\text{Ga}$  or  $^{177}\text{Lu}$ )) were built and optimized in MOE 2020. A set of known LAT1 ligands ( $n = 16$ , with in vitro  $\text{pIC}_{50}$  data) were also drawn and then were first docked into LAT1 to help select the most suitable scoring function (whose docking scores (S, kcal/mol) showed the highest correlation to in vitro  $\text{pIC}_{50}$  data). The selected scoring function was applied to dock all testing compounds into LAT1 3D structure. Docking scores were converted into estimated  $\text{pIC}_{50}$  using the linear regression formula from the correlation analysis. The LAT1 inhibitory potency (estimated  $\text{pIC}_{50}$ ) of ADPB-based and JPH203-based theranostic radiopharmaceutical designs was compared with that of JPH203 (in vitro  $\text{pIC}_{50}$  7.22) and ADPB (in vitro  $\text{pIC}_{50}$  6.19). Atomic interaction between an ADPB-based radiopharmaceutical design and amino acid sequences on the LAT1 binding pocket was visualized and analyzed from the obtained 3D docking poses. An additional linker improved LAT1 inhibitory potency of DOTA-contained ADPB-based theranostic radiopharmaceutical designs. Among eight ADPB-based theranostic radiopharmaceutical designs, the estimated  $\text{pIC}_{50}$  of  $^{68}\text{Ga}$ -NODAGA-Ahx-ADPB ( $6.87 \pm 0.31$ ) and  $^{68}\text{Ga}$ -DOTA-Ahx-ADPB ( $6.47 \pm 0.27$ ) exceeded the  $\text{pIC}_{50}$  value of native ADPB, but still tenth molar order lower than the  $\text{pIC}_{50}$  of JPH203. Of note,  $^{177}\text{Lu}$ -DOTA-Ahx-ADPB and  $^{177}\text{Lu}$ -DOTA-ADPB possess the estimated  $\text{pIC}_{50}$  much higher than the common ligand-protein binding affinity (extremely rarely above picomolar order), thus deemed a further experimental confirmation. In addition,  $^{177}\text{Lu}$ -DOTA-Ahx-ADPB and  $^{177}\text{Lu}$ -DOTA-ADPB have strong atomic interactions with key amino acids on the LAT1 binding pocket, particularly PHE252, ASN258, and TYR259, while  $^{68}\text{Ga}$ -NODAGA-Ahx-ADPB and  $^{68}\text{Ga}$ -DOTA-Ahx-ADPB have at least one interaction with PHE252, the LAT1 proximal gating residue. DOTA-Ahx-ADPB and NODAGA-Ahx-ADPB can be further developed as theranostic radiopharmaceutical kits.



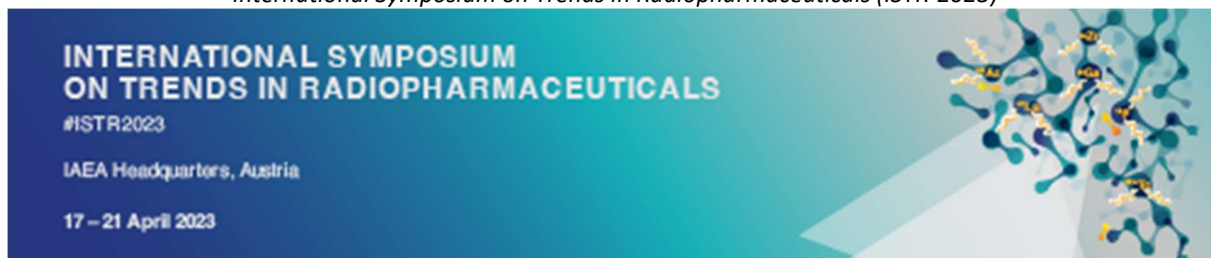
## IAEA-CN-310/201

### Ws-[<sup>99m</sup>Tc(N)(PNP3OH)]<sup>2+</sup>: A Water Soluble Synthone for the Labelling of Protein Scaffolds

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The labeling of bioactive molecules with a water-soluble [<sup>99m</sup>Tc][Tc(N)(PNP)]-synthon is reported. The method, which takes advantage of the reactivity properties of the new [<sup>99m</sup>Tc][Tc(N)(PNP3OH)]<sup>2+</sup>-framework[PNP3OH=N,N-bis(di-droxymethylenphosphinoethyl) methoxyethylamine] was efficiently exploited to tag different chelators containing [S<sup>^</sup>S]<sup>2-</sup>, [S<sup>^</sup>O]<sup>2-</sup> or [S<sup>^</sup>NH<sub>2</sub>]<sup>-</sup> donor sets (YZ-*l*) as bifunctional chelating agents. The relevance of ws-[<sup>99m</sup>Tc(N)(PNP3OH)]<sup>2+</sup>-synthon for the labeling of protein scaffolds was evaluated by choosing apomyoglobin (apoMb) as a model protein, which was first derivatized by a site-specific enzymatic reaction catalyzed by transglutaminase with the H-Cys-Gly-Lys-Gly-OH tetra-peptide (H3Cys~apoMb) in order to insert a reactive N-terminal Cys for <sup>99m</sup>Tc chelation. Radiosyntheses were performed under physiological conditions at room temperature within 30 min. They were reproducible, highly specific, and quantitative. The final complexes are hydrophilic and stable. The biological behavior of selected [<sup>99m</sup>Tc][Tc(N)(YZ-*l*)(PNP3OH)] complexes were considered. Biodistributions show favorable pharmacokinetics within 60 min after injection and predominant elimination through the renal-urinary tract. These data suggest a role for [<sup>99m</sup>Tc][Tc(N)(PNP)]-technology in the labeling of temperature-sensitive biomolecules for SPECT imaging.



**IAEA-CN-310/202**

### **Targeting SOX9 Signaling Pathway for Colorectal Cancer Stem Cell Inhibition using Bi-213 labelled Evodiamine: An In-silico Study**

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Radiopharmaceuticals have become one of the primary options for cancer therapy by targeting specific genes or proteins. The alpha-emitting radionuclide is gaining significant interest, particularly Bismuth-213 (Bi-213). A novel potential protein target is SOX9 which is known to play an essential role in cancer metastases. This study will focus on the computational research of labelling Bi-213 with Evodiamine, a naturally derived compound capable of causing the downregulation of SOX9. The proposed Evodiamine-DOTA-Bismuth (EvoBi) complex structure was optimised using the density functional theory (DFT) method with a def2-TZVPP basis set with Orca software as a platform. The optimised complex structure was simulated to determine its binding energy with the high mobility group (HMG) domain of the SOX9 target receptor using Autodock 4. In addition, various colorectal cell lines were screened to determine SOX9 expression using DepMap R-Package RStudio® and continued to assess the cytotoxicity of Evodiamine using CLC Pred. The study results find that the self-consistent field was convergence at minimum energy of -73,072.79 eV. In contrast, the calculated binding energy of EvoBi with HMG SOX9 was lower than non-modified evodiamine (-6.79 and -5.74 kcal.mol<sup>-1</sup>, respectively), indicating EvoBi has stronger interactions with HMG SOX9. Meanwhile, the SOX9 genetic dependency based on the evaluation shows that highly expressed in colorectal, gastric and pancreatic cancer with 5-8 TPM. This was also continued by evaluating the cytotoxicity effect of Evodiamine, where a high cytotoxicity effect was identified in HCT116 cells with Pa (0.867) and Pi (0.005), which indicated that the compound was active in killing cancer cells. This study's results show that the Evodiamine-DOTA-Bismuth complex has the potential to be used as a radiopharmaceutical therapy for cancer stem cells and metastatic processes.





IAEA-CN-310/203

### Impact of Different $[^{99m}\text{Tc}][\text{Tc}(\text{N})\text{PNP}]$ -Scaffolds on the Labeling of the RgdFk Peptide and the Biological Properties of the Obtained Radiocompounds

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An interesting platform to label biomolecules is the  $[^{99m}\text{Tc}][\text{Tc}(\text{N})(\text{PNP})]$ -system (PNP = bisphosphinoamine). Here we present a comparison of the reactivity of three different  $[\text{Tc}(\text{N})(\text{PNP})]$ -synthons, as well as their impact on the stability and biological properties of the corresponding  $[^{99m}\text{Tc}][\text{Tc}(\text{N})(\text{PNP})]$ -labeled RGDfK pentapeptide. Conjugation of the RGDfK with Cys was followed by labeling with the  $[^{99m}\text{Tc}][\text{Tc}(\text{N})(\text{PNP})]$ -synthons. Evaluation of the radiocompounds for their lipophilicity, stability and in vitro/in vivo targeting properties was then performed. All compounds were easily obtained in very high radiochemical yield ( $\geq 95\%$ ), but only the use of PNP3OH allows to obtain the corresponding  $[^{99m}\text{Tc}][\text{Tc}(\text{N})(\text{PNP3OH})(\text{RGDfK})]^+$  at room temperature. The different synthons influence mainly the in vitro cell binding and in vivo performances of the radioconjugates. Different pharmacokinetics in healthy rats and tumor accumulation in mice xenografts were observed as a function of lipophilicity and sterical hindrance of the  $[^{99m}\text{Tc}][\text{Tc}(\text{N})(\text{PNP})]$ -framework. In particular  $[^{99m}\text{Tc}][\text{Tc}(\text{N})(\text{PNP3OH})(\text{RGDfK})]^+$  and  $[^{99m}\text{Tc}][\text{Tc}(\text{N})(\text{PNP3})(\text{RGDfK})]^+$  are better performing than the  $[^{99m}\text{Tc}][\text{Tc}(\text{N})(\text{PNP43})(\text{RGDfK})]^+$ ; consequently, they are more suitable for further radiopharmaceutical purposes. In general, the good labeling properties of the less lipophilic and water soluble  $[^{99m}\text{Tc}][\text{Tc}(\text{N})(\text{PNP3OH})]^-$  synthon are exploitable to the labeling of temperature-sensitive biomolecules.





**IAEA-CN-310/205**

### **[<sup>99m</sup>Tc][Tc(CO)<sub>3</sub>]-Labeling of ScfvD2b-Hystag for SPECT Imaging of PSMA in Prostate Cancer**

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The single chain variable fragment scFvD2B is specific to the extracellular domain of prostate specific membrane antigen (PSMA), overexpressed in prostate cancer (PCa). It is stable, quickly and efficiently accumulates in PCa tumors, and rapidly clears from non-target organs. These features make it exploitable as molecular vector for target specific radiocompounds with moderately short-lived radionuclides (e.g. <sup>99m</sup>Tc), significantly limiting the patient absorbed dose. Therefore, a C-terminal hexahistidine-tagged scFvD2B (scFvD2B-HisTag) was labeled with the [<sup>99m</sup>Tc(CO)<sub>3</sub>]<sup>+</sup>-framework, in order to achieve a PCa SPECT imaging radioimmunoconjugate. Radiolabeling was performed by incubation of 100-150 μg scFvD2B-HisTag with [<sup>99m</sup>Tc][Tc(CO)<sub>3</sub>(OH<sub>2</sub>)<sub>3</sub>]<sup>+</sup> (obtained through the IsoLink® kit), at 37°C for 2 hours in a final volume of 250 μL. RCY was in the range 28-43%; after size exclusion chromatography, the RCP was 98%. The labeling of scFvD2B-no Tag under same conditions gave no results.

Purified [<sup>99m</sup>Tc][Tc(CO)<sub>3</sub>]-scFvD2B-HisTag was stable in PBS, human serum, and toward transchelations. Cellular uptake and internalization were assessed in PSMA(+) (LNCaP and PC3-PIP) and PSMA(-) (PC3) lines, giving encouraging results. Blocking experiments with excess scFvD2B-HisTag confirmed the receptor-specificity of [<sup>99m</sup>Tc][Tc(CO)<sub>3</sub>]-scFvD2B-HisTag.



**IAEA-CN-310/206**

### **Design, Synthesis and Preliminary Evaluation of a $^{68}\text{Ga}$ -Labeled Thia Fatty Acid Derivative Towards PET Imaging of Myocardial Metabolic Abnormalities**

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Radiolabeled fatty acid derivatives have been utilized as early prognostic markers for timely clinical intervention in ischemic disease states. Towards this, a fatty acid derivative with sulfur heteroatom in the chain for improved pharmacokinetics and bearing NOTA as BFCA for efficient  $^{68}\text{Ga}$ -labeling was synthesized and preliminary biological evaluation of  $^{68}\text{Ga}$ -labeled formulation was carried out.

A multistep synthesis scheme starting from 11-bromoundecanoic acid was followed for the preparation of 11-(3-aminopropylthio)undecanoic acid which was subsequently conjugated with p-SCN-benzyl-NOTA to give the final ligand. This was radiolabeled with [ $^{68}\text{Ga}$ ]GaCl<sub>3</sub> at pH ~4.0 and tested for biological efficacy by performing biodistribution studies in normal fasted female swiss mice (n = 3) taking four time points (2, 5, 10 & 30 min).

The ligand was synthesized in moderate yield (~60%) and was radiolabeled with  $^{68}\text{Ga}$  in high yield (>90%) and high radiochemical purity (>95%), as ascertained by radio-TLC. Biodistribution study of the tracer revealed satisfactory initial myocardial uptake of ~1% at 5 min post-injection which also showed significant retention (~0.5%) up to 30 min. However, the heart/liver, heart/lung and heart/blood ratios were <1 at all time points.

A new NOTA-coupled thia fatty acid derivative was successfully synthesized and radiolabeled with  $^{68}\text{Ga}$ . Preliminary biological evaluation of the radiotracer showed prominent heart uptake but the target to non-target ratios were sub-optimal. Further studies are underway to understand the true efficacy of the design.



IAEA-CN-310/207

### **Applying the Reduce, Reuse, and Recycle Principle in the User-Friendly Sterility Testing Method for Injectable Radiopharmaceuticals**

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The world is facing a plastic pollution crisis that is overflowing landfills, polluting waterways, and exacerbating the effects of climate change. It is estimated that eight million metric tons of plastic waste flows into our oceans each year. BRIT produces and supplies various diagnostic and therapeutic radiopharmaceuticals. Sterility Testing (ST) is a mandatory test for release of injectable radiopharmaceuticals. A simple vacuum-based manifold system was successfully tested by us to circumvent problems posed by conventional ST. A sterile PVC tubing assembly with polycarbonate adaptors and polyethylene Luer caps is a requirement for this method and a minimum of six assemblies are required for every batch of radiopharmaceutical tested. This assembly is routinely used in house as consumables for production of  $^{68}\text{Ga}$  based radiopharmaceuticals and was hence available as spent waste. Being single-use plastics, these contribute significantly to the plastic pollution crisis. In this preliminary study, it was attempted to recycle these assemblies, with a view to reduce and reuse plastic waste as well as cost-containment of the ST. The spent PVC tubing assemblies were left to decay for a period of not less than 20 half-lives ( $^{68}\text{Ga}$   $t_{1/2} = 68$  min) followed by clearance by Health Physicist. Subsequently, these were rinsed several times with sterile Water for Injection using the manifold system, dried, individually packed and sealed in polypropylene packs and sterilised in house (RPP, BRIT) using 25kGy (2.5Mrad) dose of gamma rays from a  $^{60}\text{Co}$  source (650 kCi). The radiation absorbed dose was evaluated potentiometrically using 15mM ceric-cerrous dosimeter. The Sterility Testing using these recycled assemblies included the radiopharmaceuticals:  $^{153}\text{Sm}$ -EDTMP,  $^{177}\text{Lu}$ -EDTMP,  $^{177}\text{Lu}$ -DOTA TATE,  $^{131}\text{I}$ -mIBG and  $^{99\text{m}}\text{TcO}_4$  eluates from  $^{90}\text{Mo}$ - $^{99\text{m}}\text{Tc}$  generators [04 batches each, RAC  $\sim 20\text{mCi/mL}$  (740MBq/mL) per vial]. Sterile saline was used to inoculate the ST media and used as controls. All the injectable radiopharmaceutical products tested passed ST as indicated by absence of microbial growth on completion of the test. There was no alteration in the functioning of the recycled plastic assemblies in terms of smooth transfer of products/controls during ST as well as the integrity of the sterile packaging. This preliminary work proves the potential of reuse of the PVC tubing assemblies as accessories for the user-friendly vacuum-based manifold system of Sterility Testing. Apart from cost-containment, the in house recycling of these materials by gamma sterilisation, presents a green solution to the reduction of environmental waste.



**IAEA-CN-310/208**

### **Bacterial Endotoxin Testing of Injectable Radiopharmaceuticals: Vendor Qualification**

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Diagnostic and therapeutic injectable radiopharmaceuticals are regularly supplied by BRIT and it is mandatory to perform Bacterial Endotoxin Test (BET) before release of these products. We describe here the comparison of the currently used BET by gel clot method using Limulus Amoebocyte Lysate (LAL) reagents procured from two different manufacturers. The tests were carried out as per protocols based on visual observation of the gel clot formed and also included, in one case, an option of Kinetic Turbidimetric Assay (KTA) using the same reagents in a portable, turbidimetric analysis system which includes pre-installed BET compliant software. This system offers the advantage of BET by gel clot, turbidimetric as well as chromogenic method. The gelation time is calculated based on light intensity transmitted at 430nm which gradually decreases as the reaction proceeds and stops on completion of reaction. BET was carried out in accordance with the Indian Pharmacopeia. The Control Standard Endotoxin was reconstituted to obtain a dilution of 0.5 EU/mL and used in conjunction with the matching LAL of sensitivity 0.125 EU/mL. The radiopharmaceuticals tested were diluted suitably as per the MVD (Ref: 1) and included  $^{131}\text{I}$ -mIBG injection,  $\text{Na}^{99\text{m}}\text{TcO}_4$  eluates from  $^{90}\text{Mo}$ - $^{99\text{m}}\text{Tc}$  generator and cold kits for preparation of  $^{99\text{m}}\text{Tc}$ -phytate, DTPA and EC injections. At the end of incubation period ( $37\pm 1^\circ\text{C}$ ,  $60\pm 2$  mins), the tube was inverted by  $180^\circ$  to visually detect gel clot formation. The results were compared with negative and positive water control tests and product control tests. The former contained endotoxin-free water and the latter contained the radiopharmaceutical product in the absence and presence of standard endotoxin, respectively. In case of KTA, a standard curve using Endotoxin standards (1, 0.1 and 0.01 EU/mL) was generated and reaction times noted. The gel-clot assay using the same reagents was co-related to the value obtained in KTA by inverting the assay tube to  $180^\circ$  and visually inspecting the integrity of the gel clot after completion of the incubation period. Gel clot formation was observed, as expected, in all positive control tubes thus verifying the suitability of the test protocols. The quality of the gel clots was found to be poor as they were fragile and had a tendency to dissolve easily when compared to the robust gel clots obtained by the kits currently in use. The KTA results corroborated well with the corresponding gel clot method using the same reagents and the positive product controls showed endotoxin recovery within the acceptable range (Endotoxin Spike Recovery Limit: 50-200%). All the kits tested yielded valid results and although the gel clots formed were comparatively inferior, they were found adequate for the intended purpose. The KTA assay proved far superior in terms of offering precise quantification by kinetic methods, speedy and objective results and cost-effectiveness due to multi-utility of reagents used and is worthy of further study. This preliminary vendor qualification exercise thus provided a viable alternative to our existing method and also contributes to the cGMP objective of our QC/ QA Departments.



IAEA-CN-310/209

## Cationic Modification of C-18 Reverse Phase HPLC Column for Quality Control Analysis of $^{131}\text{I}$ -Sodium Iodide Solution

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Radioiodines like  $^{131}\text{I}$ -,  $^{124}\text{I}$ ,  $^{125}\text{I}$  are integral part of diagnostic and/or therapeutic nuclear medicine.  $^{131}\text{I}$  Iodate ( $\text{IO}_3^-$ ) is a possible radiochemical impurity which can present itself during Quality Control Testing of  $^{131}\text{I}$  NaI solution. Radiochemical Purity (RCP) of  $^{131}\text{I}$  NaI is routinely performed as described in Indian Pharmacopeia by paper chromatography using 70% MeOH as developing solvent. In our earlier work we have successfully demonstrated the utility cationic Column modification using n-octylamine to determine radiochemical purity  $^{131}\text{I}$ - sodium iodide solution. In India Sodium Thiosulfate is added as stabilizer for  $^{131}\text{I}$ -NaI solution to the concentration of 25 to 100mg/37GBq. Thiosulfate concentration is routinely estimated by iodimetric titration with Iodine solution. However, these methods involve handling of substantial amount of radio-iodine which is a radiological safety issue. The aim of present work is to demonstrate a new instrument based method using High Performance Liquid Chromatography (HPLC) which employs cationic modification of C-18 reverse Phase column for determination of Radiochemical purity analysis as well as to estimate the concentration of thiosulfate anion in a single injection thus limiting exposure to radio-iodine. The column was equilibrated with mobile phase for 45 minutes. Potassium iodide, potassium iodate, Sodium thiosulfate procured from reputed manufacturers were used as cold standards for HPLC analysis. Standardization with respect to modifier concentration and polarity of mobile phase were carried out.  $^{131}\text{I}$  NaI solution for therapeutic use (sample) was diluted with 0.1mg/ml KI and 0.2mg/ml  $\text{KIO}_3$  prior to chromatography. Different concentrations of Sodium Thiosulfates were used to obtain a calibration curve to estimate thiosulfate concentration. Thiosulfate concentrations were obtained in amount per milliliter and were converted to mg/GBq after estimating the radioactivity concentrations. The results of Radiochemical purity and thiosulfate estimation were compared with that obtained by standardized method (Paper chromatography and iodimetric titration). It was found that  $\text{I}^-$  has a retention time of about 12 minutes while  $\text{IO}_3^-$  elutes out at 4 minutes and these match with the retention times of corresponding cold moieties. The retention time of thiosulfate anion is around 35.4 minutes. There is a large difference in retention times of  $\text{I}^-$  &  $\text{IO}_3^-$  and Thiosulfate anions. This difference was favorably exploited for quality control analysis of  $^{131}\text{I}$ - Sodium Iodide solution. The thiosulfate concentrations observed were correlating with that of standard method. However, due to detector response at higher concentration, there is need to dilute the sample. Quality control testing is important requirement in the production process of Radiopharmaceuticals. Reverse phase Column modification using suitable anionic or cationic modifiers have been described for a number of compounds. Here we have been successful in demonstrating the utility Column modification using n-octylamine to convert it in an anion exchange column for the analysis of  $^{131}\text{I}$ - sodium iodide solution. Normally, sodium thiosulphate in the range of 25-100mg/Ci is added to  $^{131}\text{I}$ -sodium iodide solution as a stabilizing agent. This method has potential to be applied in regular Quality Control analysis for determination of radiochemical purity as well as thiosulphate content in a single injection obviating the need to handle radio-iodine for extended period of time.





**IAEA-CN-310/211**

### **Evaluation of Two Defensins Short Analogues As Potential Radiotracers for Detection of Infection Foci**

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The EcgDf1, a 47 amino acid defensin, was identified from the transcriptome of a Uruguayan native plant, *Erythrina crista-galli*, “Ceibo” tree. With the aim to develop new radiopharmaceuticals for detection of hidden infections, our group has been working on the characterization of different short analogues of this peptide radiolabeled with different strategies. EcgDf21 (NH<sub>2</sub>-ERFTGGHCRGFRRRCFCTKHC-COOH), was derivatized in the amino-terminal group with HYNIC for the radiolabeled with <sup>99m</sup>Tc and tricine for completed the coordination sphere. EcgDf11 (NH<sub>2</sub>-KGHCRGFRRRC-COOH) with involves the active site of the peptide was derivatized in the lysine group with the bifunctional chelating agent NOTA and radiolabelled with <sup>68</sup>Ga. Labelling conditions were optimized and physicochemical characteristics of the different complexes were evaluated. Both complexes were stable in milieu, human plasma and against competitive ligands at least for 3 hours and show an intermediate plasma protein binding as well. Complementary, in vitro binding assays to microorganisms cultures were performed, showing that [<sup>99m</sup>Tc]Tc-HYNIC-EcgDf21 has a specific binding of 45% to *C. albicans*, *A. niger* and *S. aureus*. Biodistributions and image acquisition in mice revealed clear discrimination between lesion and healthy tissues (T/NT~3). Similar studies are currently being performed for [<sup>68</sup>Ga]Ga-NOTA-EcgDf11.





**IAEA-CN-310/212**

### **Production of Radioisotopes at the Medical Cyclotron Facilities in Bangladesh: Experiences & Perspectives**

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A cyclotron is a particle accelerator which employs electromagnetic fields to accelerate charged particles with extremely high energy and speeds. It is used for producing radioisotopes for radiopharmaceuticals which are used to diagnose and treat cancer. In Bangladesh, the first medical cyclotron was installed in a private hospital named United Hospital, Dhaka at 2011. This one is the only cyclotron (9.6 MeV energy from GE) which supplied the PET tracers to all PET-CT centres in country since 2011 to 2020. Considering the necessity of a cyclotron, the government took the initiative to establish a cyclotron facility at the National Institute of Nuclear Medicine & Allied Science (NINMAS) under Bangladesh Atomic Energy Commission (BAEC). After completion of all purchase procedure, an 18/9 MeV cyclotron from IBA was installed on 2020. Radioisotopes such as F-18, C-11, N-13 and O-15 can be produced with this cyclotron consisting with eight target ports. Four target ports have been chosen for the F-18, one for C-11, one for N-13, one for O-15 and one for solid target. This cyclotron is also capable for producing Ga-67, Ga-68, I-124, I-123, In-111, Tc-99m, Cu-64 and Zr-89 radioisotopes. Presently the cyclotron has been exclusively used for the production of F-18 for  $^{18}\text{F}$ -FDG PET imaging. For 60-minute bombardment time at cyclotron, 40 to 50 microamp beam current is employed to produce F-18 with an amount of 2500 to 3500 mCi. After synthesis of FDG, the yields of  $^{18}\text{F}$ -FDG were found around 40-50%. In the past year, we supplied around 52 Ci of  $^{18}\text{F}$ -FDG to six PET-CT centers. Considering the demand of PET-CT scan and the necessity to expand the facilities all over the country, the government has taken the initiative to establish another three cyclotron facilities at different area of the country. It is expected that within one year these facilities will be established.



**IAEA-CN-310/213**

**Optimization of F-18 radioisotope production with 18 MeV Cyclotron at the National Institute of Nuclear Medicine and Allied Sciences, Bangladesh**

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A cyclotron is used for producing radioisotopes for radiopharmaceuticals which are extremely used for diagnosing and treating cancer. An 18/9 MeV Cyclotron (18 MeV for proton and 9 MeV for deuteron, Model: Cyclone 18/9, IBA) was installed at the National Institute of Nuclear Medicine and Allied Science (NINMAS) under Bangladesh Atomic Energy Commission (BAEC). Several number of radioisotopes such as F-18, C-11, N-13 and O-15 can be produced with this cyclotron. Solid target option is also accessible in this cyclotron. It is capable for producing Ga-67, Ga-68, I-124, I-123, In-111, Tc-99m, Cu-64, and Zr-89 radioisotopes. At present, 18F-FDG are being produced in a regular basis for PET imaging. 40 to 50 micro amp beam current is employed for 60-minute bombardment to produce F-18 with a quantity of 2500 to 3500 mCi. The production amount of F-18 varies due to the using of variable production parameters. Parameters used in the production are limited to physical factors such as target material, target volume, collimator, stripper foil, and ion source. As a result, the yield of F-18 is considered to be the most important aspect in providing sufficient activity. For this, it is very essential to find the best operating parameters that minimizes both production time and cost. In order to produce an optimal F-18 production, all parameters such as Dee voltage, vacuum level, beam current, irradiation time, amount of enriched O-18 water, target pressure and others were extremely taken into account and found the optimum operating values.



**IAEA-CN-310/215**

### **Development of Radiopharmaceutical for Lung Cancer Therapy using Curcumin and Scandium Radiotracer**

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Curcumin (CUR), a polyphenol compound widely used as a food ingredient, is a prominent natural product with potential clinical effects including anticancer properties. However, the main problem recognized in utilization of curcumin as therapeutic agent is its limited bioavailability. Metal-CUR complex formation could increase bioavailability and potential anticancer activity of CUR. This study aims to synthesize the scandium curcumin complex (Sc-CUR), determine the interaction of Sc-CUR with lung cancer related EGFR receptors and its biodistribution profile in normal mice. Sc-CUR was synthesized by mixing CUR and [<sup>46</sup>Sc]ScCl<sub>3</sub> with the addition of pH 4 acetate buffer with heating at 90°C for 30 minutes. Radio-TLC analysis of [<sup>46</sup>Sc]Sc-CUR showed 92.50% yield of direct complexation reaction between Sc and CUR with 1:2 (Sc:CUR) optimum molar ratio. Affinity of Sc-CUR with EGFR tyrosine kinase was lowest in docking study using autodock 4.2 compared to CUR and EGFR inhibitor Gefitinib (-9.17, -7.92 and -7.65 kcal.mol<sup>-1</sup> respectively). The downstream signaling cascades and malignant cell proliferation could be inhibited. Biodistribution study of [<sup>46</sup>Sc]Sc-CUR in BALB/c normal mice showed highest accumulation in lung (70.48% ID.g<sup>-1</sup>) 30 minutes p.i. According to the result of this study, Sc-CUR has a potential to be developed as radiopharmaceutical for lung cancer therapy.



**IAEA-CN-310/216**

### **Dual-targeted $^{111}\text{In}$ -radiocomplexes for Auger Therapy of Prostate Cancer**

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The radiobiological effects induced by AE emitters might include hardly repairable and lethal DNA damage in the targeted tumor cells, if the AEs are emitted in close proximity to a radiosensitive cellular target, such as the nuclear DNA or the mitochondria. Having this in mind, we have focused on dual-targeted  $^{111}\text{In}$ -complexes carrying a PSMA inhibitor and a triphenyl phosphonium (TPP) group to promote a selective uptake by Pca cells and their accumulation in the mitochondria. In this communication, we describe novel DOTA-based chelators functionalized with PSMA-617 and TPP derivatives and their respective natIn and  $^{111}\text{In}$  complexes. The  $^{111}\text{In}$  complexes were obtained in high radiochemical yield and purity at high specific activity and their chemical identity was ascertained by HPLC comparison with the cold congeners. Their preclinical evaluation included cellular uptake and internalization and PSMA-blocking studies in different cell lines (LNCaP, PC3 PIP and PC3 Flu), subcellular localization experiments and the evaluation of radiobiological effects based on the clonogenic survival assay. MicroSPECT imaging studies in PSMA-positive and PSMA-negative Pca xenografts were also performed to assess the specific tumor-targeting ability of the different radioconjugates.



**IAEA-CN-310/217**

### **Gold Nanoparticles for Image-Guided delivery of Pt(IV) Prodrugs to Gastrin-Releasing Peptide Receptor Positive Cancers**

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Gold nanoparticles (AuNPs) have proven to be remarkable tools for drug delivery and theranostics of cancer. Furthermore, Pt(IV) prodrugs are interesting alternatives to the common Pt(II) complexes used for chemotherapy. Aiming an image-guided nanoplatform to selectively deliver Pt(IV) prodrugs to gastrin releasing peptide receptor (GRPR) expressing tumors, small core AuNPs carrying a thiolated DOTA derivative, a GRPR-targeting bombesin analog and a Pt(IV) prodrug were synthesized. In the GRPR+ prostate cancer PC3 cells, the best performing AuNP-BBN-Pt nanoparticles displayed an IC50 value lower than cisplatin in the same cells. While did not show any cytotoxic effect in the non-tumoral RWPE-1 prostate cells indicating higher selective index towards cancer cells than cisplatin. The AuNPs were successfully labeled with  $^{67}\text{Ga}$  and displayed high uptake and rate of internalization in PC3 cells. Biodistribution of  $^{67}\text{Ga}$ -AuNP-BBN-Pt in a PC3 tumor-bearing mice after intratumoral administration showed prolonged radioactivity and Pt retention, high in vivo stability and 20% of the injected platinum remaining in the tumor after 72 h post-injection. Moreover, microSPECT imaging studies confirmed the uptake and considerable retention of the  $^{67}\text{Ga}$ -labeled AuNPs in the tumors. These results suggests the potential of these targeted AuNPs loaded with Pt(IV) prodrugs for prostate cancer theranostics.

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**IAEA-CN-310/219**

## **Radiopharmaceuticals Development – Bench to Clinic**

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In the years following Henri Becquerel's and Marie Curie's discovery of radioactivity in 1890, there has been an exponential rise in the development of radiopharmaceuticals for clinical use. Nuclear medicine journey began in the 90s when radium was used for treating TB skin lesions, tumors, and a variety of other illnesses. Later, the discovery of technetium-99m and radioisotopes of iodine (I-125 and I-131) opened new horizons for radiopharmaceuticals development. A new era of radiopharmaceuticals development opened up after technetium-99m and radioisotopes of iodine (I-125 and I-131) were discovered. It paved the way for the decades-long development of modern-day radiopharmaceuticals.

Over 10,000 hospitals worldwide utilize radioactive isotopes produced by cyclotrons / generators (F-18, C-11, Ga-68, Tc-99m). Technetium-99 (Tc-99) accounts for about 80% of all nuclear medicine procedures, with some 40 million procedures per year, making it the most used radioisotope. According to the statistics, there is a constant increase of over 10% in the use of radiopharmaceuticals in clinical diagnosis every year.

There has been an increased interest in cyclotron radioisotopes over the past two decades owing to their potential clinical applications in diagnostic medicine (Ga-68, Cu-64, O-15, Sc-44) as well as therapeutic medicine (At-211, Ac-225). As part of the development flow, the first and foremost step is the production and the purification of cyclotron-based radioisotopes. From halogens (F-18, I-125/131) to gases (C-11) to radiometals (Ga-68, Cu-64, In-111, Lu-177, Ac-225, At-211), cyclotron production and radiochemistry techniques differ considerably.

Moreover, for clinical translation, certain quality assurance criteria must be met according to the US Pharmacopeia established by the U.S. Food and Drug Administration (FDA). In order to conduct clinical trials with a new radiopharmaceutical, the filing of an Investigational New Drug (IND) application is vital. The IND application primarily includes a section on manufacturing, a section on toxicology / pharmacology, as well as a section about clinical protocols (with consent forms). Thus, starting from lab-bench to clinical translation, the development of a new radiopharmaceutical requires a timeline that spans over a decade.





**IAEA-CN-310/220**

### **NROC: Opportunities and Perspectives of Radiopharmaceuticals**

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At the moment, NM in the Republic of Kazakhstan is developing at a rapid pace. Discussion of the issues of development of which are held at the state level. Only recently, at the end of 2021, the first department of radionuclide therapy with 15 metabolic therapy room was opened, and next year a new center with 8 metabolic therapy room will open, while 2 NM centers openly declare their intention to expand in this direction.

Theranostics. The development of theranostics is one of the main tasks of the state in the field of NM development. NROC has every opportunity to implement and take the status of the leading NM center in the Republic of Kazakhstan. We see the first stage of our development in the introduction of theranostic pairs based on the isotopes  $^{99m}\text{Tc}$  and  $^{177}\text{Lu}$ ,  $^{61}\text{Cu}$  and  $^{177}\text{Lu}$ ,  $^{68}\text{Ga}$  and  $^{177}\text{Lu}$ .



IAEA-CN-310/222

### **Comparative Evaluation of Renal Functions Using $^{68}\text{Ga}$ -DOTATATE and Conventional Nuclear Imaging Modalities in Patients Being Planned for Peptide Receptor Radionuclide Therapy (PRRT)**

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$^{68}\text{Ga}$ -DOTATATE PET imaging is being used for diagnosing and staging of Neuroendocrine tumors (NET) for more than a decade. Pretherapy evaluation includes renal function assessment with conventional nuclear imaging such as  $^{99\text{m}}\text{Tc}$ -DTPA,  $^{99\text{m}}\text{Tc}$ -EC scans etc. since renal dysfunction limits the dose and cycles of PRRT that can be administered. It has been seen that  $^{68}\text{Ga}$ -DOTATATE shows high grade localization in the normal renal cortex, which raises a possibility of estimating qualitative and quantitative (split function) renal function in these patients in a single study.

The purpose of this study was to demonstrate efficacy of the  $^{68}\text{Ga}$ -DOTATATE PET imaging to estimate split renal function in patients being planned for PRRT and correlate it with similar parameters obtained from  $^{99\text{m}}\text{Tc}$ -DTPA and  $^{99\text{m}}\text{Tc}$ -EC imaging.

In house  $^{68}\text{Ga}$ -DOTATATE and  $^{99\text{m}}\text{Tc}$  based renal compounds were labeled using good manufacturing practices (cGRPP) before being cleared for patient use. 5 male (age range: 38-70 year) and 5 female (age range: 25-71 year) treatment naive patients who were being planned for PRRT underwent  $^{99\text{m}}\text{Tc}$ -DTPA,  $^{99\text{m}}\text{Tc}$ -EC and  $^{68}\text{Ga}$ -DOTATATE imaging as per the institution protocol. PET images of kidneys were obtained after 60 min using Philips Gemini TF 16 slice PET/CT scanner. ROIs were drawn around each renal cortex and background corrected counts were obtained to calculate the split function of each kidney. The values so obtained were compared with parameters obtained from conventional renal scintigraphy by using appropriate statistical tools.

Correlation ( $r = 0.82$  with  $^{99\text{m}}\text{Tc}$ -EC and  $r = 0.85$  with  $^{99\text{m}}\text{Tc}$ -DTPA) was found between the renal parameters obtained from  $^{68}\text{Ga}$ -DOTATATE (PET) and conventional scintigraphy. Renal function assessment with  $^{68}\text{Ga}$  needs to be evaluated further in more number of patients to validate our findings.



**IAEA-CN-310/223**

**An Automated Module for Easy and Facile Separation of No Carrier Added Lutetium-177 from Irradiated Enriched Ytterbium-176 Targets**

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Lu-177 is a proven radioisotope for targeted radionuclide therapy (TRT) owing to its favorable nuclear decay and complexation chemistry. While carrier-added and no carrier added (n.c.a) Lu-177 are employed for TRT, it is desirable to use n.c.a. Lu-177 for maximum therapeutic benefit. The Eichrom process is well established to produce n.c.a Lu-177 [1]. This work is aimed to establish the viability of the Eichrom process for the production of multi-Curie quantities of n.c.a. Lu-177 using an indigenously designed automated module.

Isolation of n.c.a Lu-177 utilizing the Eichrom method was established by processing Yb-176 enriched Yb<sub>2</sub>O<sub>3</sub> targets (40-100 mg) irradiated in Dhruva Reactor. The quality of n.c.a Lu-177 was verified by labeling DOTA-TATE and PSMA-617. Subsequently, an automated module for isolation of n.c.a Lu-177 was designed, installed, and cold commissioning was completed.

An HMI-controlled, remote-operated, metal-free, nitrogen-driven module having separate loading, washing, and elution modes was designed and installed in-house after optimizing process parameters. The module is housed inside a 50 mm lead-shielded tong box and mounted on a movable trolley allowing easy replacement of columns. The schematic of the module and real-view images are shown below. The module decreased the processing time from ~ 2 days to less than 8 hours.



**IAEA-CN-310/224**

**Regulatory Requirements and Economic Feasibility for Developing a Mobile SPECT/CT Unit with Radiopharmacy Facilities**

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Brazil has been facing great challenges related to the public health care system, not being able to manage the high national demand for diagnostic imaging tests, therefore avoiding the possibility of an early diagnosis for oncological and cardiovascular diseases. An important medical specialty for providing an early and accurate diagnosis is Nuclear Medicine. Early diagnosis is crucial for health professionals to make decisions that enable more effective treatments and improve the chances of cure.

Due to the irreversible damages caused to patient's health resulting of delay in diagnosis, this research project carried out at Nuclear and Energy Research Institute (IPEN/CNEN), together private companies and associated institutions, focus on regulatory requirements and economic feasibility for developing a mobile unit with hybrid Single Photon Emission Computed Tomography/Computed Tomography (SPECT/CT) equipment and radiopharmaceuticals facilities for radiolabeling reagents kits with technetium-99m.

A mobile SPECT/CT unit with adequate radiopharmacy facilities will be an excellent innovative solution to support Brazilian public hospitals to address the demand for diagnostic imaging tests. This mobile unit could provide health care in isolated areas or even big cities where there are shortage of health resources and high mortality rate for cancer and heart disease.



**IAEA-CN-310/225**

### **Preliminary Evaluation of Technetium-99m-Labeled Cefepime Using Tricine As Co-Ligand As a Potential Radiopharmaceutical for Localization of Infectious Sites**

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In developing countries, microbial actions are causing several infectious diseases associated with morbidity. So the identification of infection site at primarily stage of the disease is crucial for successful treatment. Radiolabeled antibiotics are promising radiopharmaceuticals for the precise diagnosis and detection of infectious lesions. The purpose of this study is to make a preliminary evaluation of technetium-99m-labeled cefepime as a potential radiopharmaceuticals for the early detection of infectious sites.

Cefepime was labeled with  $^{99m}\text{Tc}$  using tricine as co-ligand and stannous chloride dihydrate as reducing agent. The influence of various parameters such as amount of tricine, reducing agent, pH value, and reaction time on labeling process was studied. The radiochemical purity was determined with the help of instant thin layer chromatography (ITLC).  $^{99m}\text{Tc}$ - Cefepime was prepared by mixing Cefepim 1 mg, stannous chloride ( $25\mu\text{g}$  to  $100\mu\text{g}$ ), tricine ( $100\mu\text{g}$  to  $500\mu\text{g}$ ) and sodium pertechnetate ( $370\text{ MBq}$ ). The pH was adjusted using HCl or NaOH at various pH values (4-8).

The Radiochemical purity was carried out by using ITLC-SG. To determine the pertechnetate content of the preparations, one strip was developed using acetone as the mobile phase. To determine the colloid content in the preparations, the second ITLC strip was developed using acetonitrile /water (50 :50) as the mobile phase. The stability of the  $^{99m}\text{Tc}$ -cefepime was studied at room temperature and human blood serum using ITLC-SG. After optimizing the conditions, the maximum labeling efficiency was achieved when 1 mg of cefepime was labeled with 10–20 mCi sodium pertechnetate in the presence of  $500\mu\text{g}$  of tricine and  $25\mu\text{g}$  of  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ . The optimum Ph was 8 and reaction time was 30 min. It was also observed that the complex was stable for more than 90% up to 3h. The complex was significantly stable in vitro in serum at  $37^\circ\text{C}$  within 1h after reconstitution. The Preliminary evaluation of technetium-99m-labeled cefepime show that labeling in the presence of co-ligand tricine and reducing agent  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$  in basic medium is quick, stable, and efficient at room temperature and human blood serum. Technetium-99m-cefepime may further be used in precinical and clinical to diagnose sites of infections due to its broad spectrum including Gram-positive bacteria, Gram-negative bacteria and some anaerobes.



**IAEA-CN-310/226**

### **Occupational Radiation Dose Management in a Medical Cyclotron Facility**

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We operate an 11 MeV Siemens Eclipse medical cyclotron and produce about 555 GBq (15 Ci) of  $^{18}\text{F}$  per day to manufacture various PET radiopharmaceuticals. The potential radiation exposures are high in such as facility. For example, 37 MBq (1 mCi)  $^{18}\text{F}$  source at one cm will have 50 mSv/h. In addition to having heavily shielded hot cells, multiple other precautions need to be taken in a cyclotron centre to reduce the exposure to radiation workers. This paper describes how the radiation exposure had been brought to very low levels by efficient work practices and other precautions taken at sight. For analysis purpose, the radiation workers in the facility were grouped into three based on their job nature, which are cyclotron operators, radiochemists, and radioactivity transport drivers. Besides TLD, electronic pocket dosimeters were also provided to the workers to monitor daily radiation dose for collecting data on radiation exposure due to each operation. The RSO of the centre is responsible to monitor the operations and take appropriate steps to ensure ALARA dose. The average annual whole-body dose to the cyclotron operators and radiochemists were less than 0.25 mSv. The annual wrist dose of cyclotron operators and radiochemists were less than 3 mSv. The radiation dose to drivers carrying radioactivity to different hospitals received less than 4 mSv per annum. Additional lead shielding was provided in the vehicles to reduce the dose to the drivers as they carry radioactive packages over longer distances. Implementation of strict radiation safety protocols, regular training to the staff and good manpower management helped to reduce the annual occupational doses to far lower than the ICRP limits.





**IAEA-CN-310/227**

### **Radioactive Waste Management in Medical Cyclotron Facility**

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Solid, liquid and gaseous forms of radioactive wastes are generated during the operation of a medical cyclotron for production of radiopharmaceuticals. The main objective of this study is to evolve guidelines on the management of these radioactive wastes ensuring protection to the occupational workers and general public. In our centre we have Siemens Eclipse HP cyclotron having dual proton beam with maximum current of 120 mA. The cyclotron is operated on 5-6 days in a week mainly producing FDG. It is also used for production of other  $^{18}\text{F}$  radiopharmaceuticals on demand. Radioactive waste management here is planned based on the quantities produced and the half-life of the radionuclide. Considerable amount of short lived gaseous waste is released inside the hot cell during synthesis. The practice in most countries is to release the waste to atmosphere after filtration through HEPA and charcoal filter. However, as per regulatory requirements in India, the radioactive gaseous waste is collected, compressed and stored for complete decay prior to release. In our facility we have a series of four 350 litres capacity storage tanks which hold the gases at 16 bar pressure. These storage tanks are situated inside the cyclotron vault. Typical surface exposure after synthesis of about 275 GBq  $^{18}\text{F}$  is  $\sim 200 \mu\text{Sv}$ . After decay of 16 hours, the gas is released to the atmosphere through the stack at about 35 metres above ground level. Two continuous stack monitors having scintillation and GM detectors are installed to measure the exposure rate. Short lived radioactive liquid waste is generated mainly in the synthesis module, which is collected and stored inside the hot cell and is disposed after complete decay. The  $\text{H}_2^{18}\text{O}$  water recovered after irradiation contains long lived radioactivity. In our facility enriched water is not reused. However, this is a valuable material and it can be reused after purification or sent back to the enrichment plant. The solid cartridges used for purification is stored for decay in shielded modules waiting for disposal. Solid wastes are also generated during synthesis. Short lived solid waste include QMA cartridge, purification column, tubes, cassettes, needles and syringes. These are stored within the hot cells for 18-20 hours and then kept in waste storage room for a few days and disposed as regular waste after monitoring. Haver foil, hex grid, target body, target carousel, carbon foil are long lived solid waste generated from the periodic maintenance of cyclotron target system. These parts have long lived radionuclides formed due to neutron irradiation. Dedicated 100 mm lead shielded containers are used for storing the above parts and will be disposed after 15-20 years as normal waste once the radioactivity level is within permissible limit.

In conclusion, the management of radioactive waste in a cyclotron facility must be well planned at the project stage and managed in a systematic manner during the operation of the cyclotron. Sufficient shielded facilities must be planned forefront for the storage of long lived solid wastes generated during the operation of the machine.



**IAEA-CN-310/228**

### **Overview of STAX Infrastructure Development and Current Detector Installations**

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The Source Term Analysis of Xenon (STAX) project has been installing stack detectors at participating fission-based medical isotope production facilities for several years to measure radioxenon emissions. The objectives of this project are to investigate the effect of the global radioxenon background created from industrial releases on nuclear explosion monitoring; to better understand the amounts and isotopes of radioxenon released from participating medical isotope production facilities; and learn whether this information can be used to improve nuclear explosion monitoring, such as by the International Monitoring System for the Comprehensive Nuclear-Test-Ban Treaty. Data collected is being used to create an experimental infrastructure for sharing of radioxenon release data from isotope production facilities.

This is an overview of the STAX project and current detector system installations focusing on lessons learned from the system at the National Institute for Radioelements (IRE) in Fleurus, Belgium which has been operating and transferring collected data to the STAX repository for approximately five years. Information on the installed equipment, the data security and flow infrastructure, and calculations for determination of radioxenon releases from the facility will be discussed. Additionally, results from the STAX automated processing data quality investigation and a comparison of collected STAX data collected by IRE for regulatory reporting are shared.



## IAEA-CN-310/229

### **Production and Application of $^{177}\text{Lu}$ -PSMA and $^{225}\text{Ac}$ -PSMA in the Sustainable Innovation Model Through Balanced Scorecard (BSC)**

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$^{177}\text{Lu}$ -PSMA and  $^{225}\text{Ac}$ -PSMA appear in the theranostic concept, with astonishing results in prostate cancer patients, who did not respond to conventional therapies. In Europe, these treatments are used successfully. However, in Brazil, 30% of patients do not respond well to new radiopharmaceuticals, requiring broader studies.

The "Multicenter program using PSMA radioligands for diagnosis and therapy of patients with prostate cancer", in which this research project is inserted, in partnership among the Nuclear and Energy Research Institute (IPEN-CNEN), a private company and associated institutions, aims to expand the therapeutic alternatives for patients with cancer unresponsive to the treatments available in the public health network in the State of São Paulo.

IPEN-CNEN will produce the radiopharmaceuticals that will be distributed to Public Hospitals responsible for the selection, treatment and follow-up of patients with metastatic castration-resistant prostate cancer (mCPRC), and for the genetic and molecular characterization of patients unresponsive to treatment.

The present research will study the technical and economic feasibility in the production and application of these radiopharmaceuticals, with clinical studies in patients with mCPRC, applying the Balanced Scorecard (BSC) management tool, measuring its performance by indicators aiming at a strategic and efficient management, with the possibility of their marketing.



**IAEA-CN-310/230**

### **Occupational Radiation Protection of Undertakers and Crematorium Staff in Case of a Patient Death Shortly After Radionuclide Therapy**

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At the request of the French nuclear safety authority (ASN), the French Institute for radiation protection and nuclear safety (IRSN) performed a study about occupational radiation protection issues in the case where a patient dies shortly after radionuclide therapy with new radiopharmaceuticals.

IRSN reviewed European recommendations about death and cremation. These European data were completed with some recommendations made outside Europe (USA, Canada) and data from international organisations (International Commission on Radiological Protection, International Atomic Energy Agency).

For 4 most promising new therapeutic radionuclides identified in a previous IRSN study [1] – Lu-177, Ra-223, Ho-166, Ac-225 - the doses that could be received by undertakers (during transport before burial and embalming) and crematorium staff were assessed using simple models, realistic scenarios and conservative hypotheses. For instance, for transport and embalming, the times of presence near the body, namely at 50 cm, were 1 and 2 hours, respectively.

For Ra-223 and Ac-225, the assessed doses for undertakers are negligible, thus the immediate transport/embalming of the body is possible. For Lu-177 and Ho-166, a few days delay after the death is necessary before transport/embalming to comply with regulatory dose constraints, without exceeding the French legal delay limits for taking care of the body.

For cremation, the assessed doses were usually under 1 mSv per cremation.

In light of the assessed occupational doses, practical radiation protection proposals for French authority, undertakers, and crematorium staff were established in case of death shortly after radionuclide therapy.



**IAEA-CN-310/231**

**Experiences from Radiometal Production and Purification on a TR-24 Cyclotron at Edmonton's Medical Isotope and Cyclotron Facility**

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Edmonton's Medical Isotope and Cyclotron facility has produced multiple diagnostic imaging isotopes on its 24 MeV TR-24 cyclotron, starting with Tc-99m from Mo-100 target material in 2014, and more recently Ga-68, La-133/135, Pb-203, Cu-64, and Zr-89. To produce these radionuclides, we designed and implemented an adaptable and turnkey radionuclide production process, spanning cyclotron targetry and automated radionuclide separation and purification. Our approach involved a sealed solid target design, which permits irradiating multiple target materials (including those that are sensitive and toxic) with minimal target modifications, a convenient and simple target retrieval procedure, and a standardized automated target dissolution purification process on a NEPTIS automated synthesis unit which is compatible with a wide variety of separation chemistries. Radionuclides produced using our process possess a high radiochemical purity, have radiolabeled chelators and small molecules with high molar activities, and have been used for preclinical cell uptake and animal PET imaging studies, and a SPECT imaging clinical trial. We present our recent experiences with cyclotron production of Ga-68, La-133/135, Pb-203, Cu-64, and Zr-89, and automated chemical purification techniques.



**IAEA-CN-310/232**

### **Development and Validation of Manual Radiochemical Purity Test for Ga68- Labelled Radiopharmaceuticals**

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The production of  $^{68}\text{Ga}$  radiopharmaceuticals, whether manually or through an automated procedure, is critical for clinical practice. The goal of this research was to validate manual quality control for Ga-68 DOTATOC and Ga68-PSMA 11.

From March 2022 to July 2022, we conducted a retrospective study to test the Ga68-DOTOATOC and Ga68-PSMA11 antibodies in 219 consecutive patients. After purification with a C18 cartridge, Ga68-labeled radiopharmaceuticals were studied for quality control factors such as radiochemical purity using instant thin-layer chromatography (ITLC). ITLC silica gel sheets were used as the stationary phase, distilled water as the mobile phase, and radiodetection was performed after cutting the sheets in two parts (lower 1/3 and upper 2/3).

The prepared material's radiochemical purity was >99%, and the labeled Ga68 was stable for more than 2 hours; however, it was used in patients immediately after preparation. There were no adverse reactions in any of the patients, and the image qualities were consistent with previous reports. The percentage of error was 0.7% of the total prepared Ga68-labeled radiopharmaceuticals, which was attributed to human errors during preparation.

In our experience, manual synthesis performs reliably with a low failure rate. Our system produced Ga-68 DOTATOC and Ga68-PSMA11 with high labeling efficiency and purity (the radiochemical purity of the labelled Ga68 was determined to be >99%). This system, when combined with the recommended  $(^{68}\text{Ge})/(^{68}\text{Ga})$  generator, is ideal for use in hospital-based radiopharmacy.





IAEA-CN-310/233

### **The Large-Scale Production of Technetium-99m (Tc-99m) from Natural Molybdenum Is a Challenge for Diagnostic Radionuclides**

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The large-scale production of Technetium-99m (Tc-99m) from natural Molybdenum is a challenge for diagnostic radionuclides. About 900 grams of natural Molybdenum Oxide are needed to produce 10 TBq of Tc-99m, using Indonesia multi-purpose reactor G.A, Siwabessy, with  $1.5 \times 10^{14} \text{ cm}^{-2} \cdot \text{s}^{-1}$  neutron flux and 100 h irradiation. A large amount of irradiation targets can be shrunk by high-density sample preparation. The separation of Tc-99m from the Mo(Mo-99) solution is the most crucial issue. Activated carbon (AC) is a powerful adsorbent material for separation and purification due to its surface porosity and dynamics. Heptamolybdate ion ( $\text{MoO}_4^{2-}$ ) has low interaction with the carbon; conversely, pertechnetate ion ( $\text{TcO}_4^-$ ) strongly adsorbed. According to the previous report, this AC method is able to extract and separate high-purity Tc-99m from Mo-99 solution of  $1 \times 10^{12} \text{ Bq}$  level in a short time. The cold experiment was conducted by passing 104 mL of molybdate solution (211 mg nat-Mo/mL) in various pH containing 422  $\mu\text{g}$  of Rhenium for representing Technetium, through the 4.5 g of AC. ICP-MS measured the total molybdenum trapped and eluted from the column is an average of 92.0  $\mu\text{g}/\text{gram}$  carbon or 0,0018% of the initial molybdenum. The adsorption capacity for 1 gram of AC is 74.4  $\mu\text{g}$ , 72.0  $\mu\text{g}$ , and 20  $\mu\text{g}$  of Rhenium in the pH range 7-8, 10-11, and 12-13, respectively. The adsorbed Rhenium multiplied by Tc-99m specific activity (193.8 GBq/ $\mu\text{g}$ ) is equal to 14,43 TBq, 13.96 TBq, and 3.88 TBq. Experiments using radiotracers Mo-99 and Tc-99m showed the consistency of AC in separating the parent and daughter radionuclides. Hope in the future, the production of Tc-99m with high activity using natural molybdenum can be applied as raw material for injectable diagnosis radiopharmaceuticals.



**IAEA-CN-310/234**

### **Computational Study of Infrared (IR) Spectrum: Spectrum Comparison of Radiopharmaceutical Structure, their Daughter Structure, and Stable Structure**

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One method to control the quality of radiopharmaceuticals use an infrared spectrometer. The instrument uses the principle of vibration of 2 near atoms where the mass and distance of the atoms have a crucial role. Radiopharmaceuticals are drug compounds that have been labeled with radioisotopes. Radioisotopes have a different mass from their stable atom, after decaying the mass of the daughter atom generally is different from that of the parent atom. It mass difference was predicted to affect the IR spectrum result which is possible to make a noise in the QC process. thus, the quantum computing method can be used to predict it. Prediction of the IR spectrum was conducted using metaGGA-DFT method the TPSH and diffused-double zeta basis-set the ma-def2-SVP. The studied structures were Ga-DOTA which was commonly used for diagnostics and Ac-Macropa for Targeted alpha therapy (TAT). The complex structure of the Ga-DOTA in stable condition and the radioisotope  $^{68}\text{Ga}$  has a similar IR spectrum. The decayed form of Zn-DOTA has a shifted IR spectrum. the alpha-based radiopharmaceuticals,  $^{225}\text{Ac}$ -Macropa has a similar spectrum with  $^{227}\text{Ac}$  impurity that cannot be distinguished with the IR spectroscopy.  $^{226}\text{Ra}$  that residue from production process has a shifted IR spectrum with  $^{225}\text{Ac}$ .  $^{221}\text{Fr}$  that daughter atom from  $^{225}\text{Ac}$  was obtained IR-spectrum shifted, but this radioisotope will immediately decay and chemically will be separated from the macropa chelator because it was not stable. Furthermore, the IR spectrum obtained can be a guide if an impurity with a similar spectrum is found in the QC process of Ga-DOTA and Ac-Macropa-based radiopharmaceuticals.



**IAEA-CN-310/235**

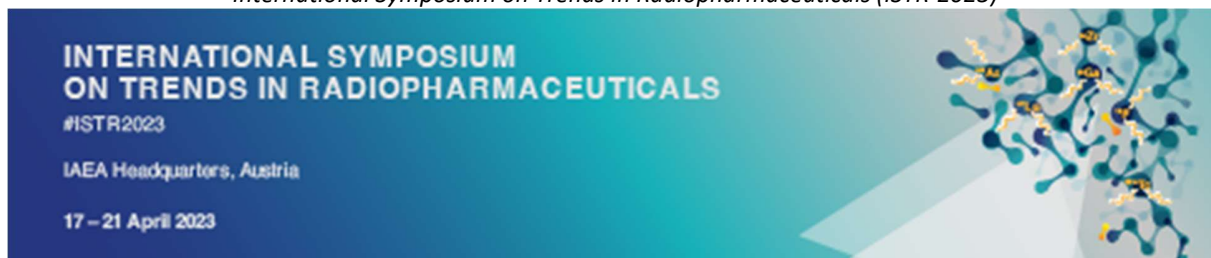
## **The Need for Radio Isotopes Production in Sub Sahara Africa for Qualitative Health Care Delivery and Cancer Treatment for Sustainable Development: Case Study Nigeria**

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Radioisotopes are used in variety of ways in industries to improve productivity and measurement. In agriculture to improve yields, food storage and preservation. In medicine for both therapeutic and diagnostic cancer treatment. There is inadequate supply of radioisotopes in Nigeria and Sub-Saharan Africa due to shortages of supply of radioisotopes. Nigeria with a population of over 200,000,000 inhabitants are the highest users of radio isotopes in the region which are also used in the oil and gas sector for nuclear well logging activities, and Industrial applications i.e. radiotracers for non destructive tests. Radioisotopes used for medical applications are of greater concern because of its limited supply for treatment of cancer patients however, some of the major constrains for the market are shorter half- life of radioisotopes, high capital investment, regulatory guidelines and reimbursement issues<sup>1</sup>, there are also shortages of facilities and radiopharmaceuticals, patients have to wait for several months to get treatment despite shortages of facilities radio pharmaceuticals takes longer than expected time to arrive, most radiopharmaceuticals used in Nigeria are imported from the Republic of South Africa and other Countries. There are sometimes delays in clearing the imported radiopharmaceuticals at the point of entry by customs officials are some of the challenges facing Nigeria and the region. The global market for Radioisotopes is estimated to be valued as 10.81 billion in 2016 and is expected to reach 19.43 billion by the end of 2021. During this period of forecast the market is expected to grow at a CAGR of 12.45%<sup>2</sup>. There would be significant demand for Sub Saharan Africa in the forecast. The aim of the study is to examine the need for the production of radio isotopes in Nigeria to prevent the current shortages as an investment opportunity for the Government and Investors in health care delivery and in nuclear and radiation technology for sustainable development in Nigeria and Sub-Saharan Africa. This result would determine the need for investing in radioisotopes production in Nigeria and advice on how to overcome the existing shortage of radioisotopes in Nigeria.

This Paper would also examine the reason for the delays in granting import license for radioisotopes to Nigeria; examine the cause of delays in clearing radioisotopes at the airports and seaports, feasibility of producing radioisotopes in Nigeria. This paper would conclude by recommending solutions to prevent the delays and advising the Governments and Investors on the possibilities of investing in Isotope production in Nigeria which would supply the entire Sub Saharan Africa.



**IAEA-CN-310/236**

**Direct Production of Ga-68 in 30 MeV DAE Medical Cyclotron and Subsequent Synthesis of <sup>68</sup>Ga-PSMA-11 Radiopharmaceutical Using Indigenously Developed Semi-Automated Module**

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Gallium-68 (<sup>68</sup>Ga,  $t_{1/2} = 67.8$  min) possesses substantial potential in nuclear medicine being extensively used in labelling of biomolecules like somatostatin and PSMA inhibitor analogues. <sup>68</sup>Ga is generally produced from <sup>68</sup>Ge/<sup>68</sup>Ga generators. An alternative method to produce <sup>68</sup>Ga directly is by using enriched <sup>68</sup>Zn via the <sup>68</sup>Zn(p,n)<sup>68</sup>Ga nuclear reaction.

Gallium-68 is produced from in-house developed enriched Zinc-68 electroplated target. A semi-automated production of Gallium-68 as <sup>68</sup>GaCl<sub>3</sub> radiochemical, using a suitably modified operating procedure compared to the IBA certified Ga-67 synthesis module, and subsequent synthesis of <sup>68</sup>Ga-PSMA-11 radiopharmaceutical as a sterile, pyrogen free, isotonic aqueous solution used for prostate cancer PET/CT imaging has been reported. The production of [<sup>68</sup>Ga]Ga-PSMA-11 has been carried out in a semi-automated radiochemistry module under an aseptic environment. Physico-chemical and biological quality control of [<sup>68</sup>Ga]Ga-PSMA-11 were optimized and they are in accordance with Indian Pharmacopeia. The clinical efficacy of [<sup>68</sup>Ga]Ga-PSMA-11 in PET-CT studies reinforces the quality of the product to be used as a pharmaceutical grade diagnostic radiopharmaceutical.



**IAEA-CN-310/237**

### **Pursuing the Theragnostics Principle at Paul Scherrer Institute**

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The concept of “theragnostics” in nuclear medicine involves the diagnosis and treatment of a patient using a radionuclide of the same element, to ensure what you image is what you treat. The concept is currently being followed by means of diagnosis with  $^{68}\text{Ga}$ , followed by radionuclide therapy using  $^{177}\text{Lu}$ .

Researchers at Paul Scherrer Institute are pursuing the idea utilizing the same element, but different radioisotopes thereof for diagnosis and therapy. Over the last decade, much research has been performed with radioisotopes of scandium and terbium radioisotopes. The radiotheragnostics principle was demonstrated with the use of cyclotron-produced  $^{44}\text{Sc}$  (and later with  $^{43}\text{Sc}$ ) for tumour diagnosis, while  $^{47}\text{Sc}$  was produced for preclinical therapy studies. Four radioisotopes of terbium are deemed interesting for nuclear medical purposes:  $^{152}\text{Tb}$  and  $^{155}\text{Tb}$  can be used for diagnostic purposes via positron emission tomography (PET) and single photon emission computed tomography (SPECT), respectively, while  $^{149}\text{Tb}$  and  $^{161}\text{Tb}$  are interesting therapeutic radionuclides due to their  $\alpha$ - and  $\beta$ -emission, respectively.

The production and use of these radionuclides are discussed, along with their potential for clinical use in future. An outlook will include possibilities of producing novel radionuclides with new facilities/installations.



**IAEA-CN-310/238**

### **Production of the Theranostic Radioisotope $^{155}\text{Tb}$ in Biomedical Cyclotrons Using Enriched $^{155}\text{Gd}$ Targets**

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The gamma and Auger emitter  $^{155}\text{Tb}$  shows great prospects in theranostics for its potential applications in SPECT imaging and Auger therapy. Nevertheless, the supply of  $^{155}\text{Tb}$  is insufficient because it is mainly produced by spallation nuclear reaction and only a few facilities have production capability. Therefore, to increase its availability, this work proposes to use enriched gadolinium targets to produce  $^{155}\text{Tb}$  through deuteron-induced reaction  $^{155}\text{Gd}(d,n)^{155}\text{Tb}$ . The objectives of this work are to measure the cross sections of the reaction and to develop a method for mass production of  $^{155}\text{Tb}$ . For cross section measurements, thin targets have been manufactured through the co-electrodeposition method. Ten Ni- $^{155}\text{Gd}_2\text{O}_3$  composite targets have been prepared using 1.0 g of highly enriched (92.8%)  $^{155}\text{Gd}_2\text{O}_3$  powder. The thickness of each target is between 10  $\mu\text{m}$  and 20  $\mu\text{m}$ , and the  $^{155}\text{Gd}$  content is between 0.7 mg to 2.0 mg. These targets were irradiated at GIP ARRONAX cyclotron by deuteron beams with an energy ranging from 8 MeV to 30 MeV. Cross sections of  $^{155}\text{Tb}$  and other terbium impurities ( $^{153}\text{Tb}$ ,  $^{154}\text{Tb}$ , and  $^{156}\text{Tb}$ ) were measured with the stacked foils technique. The results generally agree with the TENDL calculation values. These measured results, as the first experimental cross section values of the reaction  $^{155}\text{Gd}(d,x)\text{Tb}$ , were used for estimating the production yield and purity. For mass production, thicker targets were prepared via the pelletizing method. A uniform and compact  $\text{Gd}_2\text{O}_3$  pellet with a thickness of 0.4 mm was manufactured using 0.6 g of enriched  $^{155}\text{Gd}_2\text{O}_3$  powder. This pellet was irradiated by deuteron beams with an incident energy of 15 MeV and an exit energy of 9 MeV. The production yield of  $^{155}\text{Tb}$  is  $10.2 \pm 0.7 \text{ MBq}/\mu\text{Ah}$  and its final purity is 89%. This experimental thick target production yield is consistent with the estimated value using the measured cross section data. Furthermore, the dissolution of the pellet and the recycling of  $\text{Gd}_2\text{O}_3$  powders have also been investigated in this work, the recovery rate reached 84%. In conclusion, from the cross section measurement to the mass production, and then to the recycling of target material, this work proposes a possible production route for Tb radioisotopes using low-and-medium-energy cyclotron facilities. Details of the targetry conception, irradiation device, and the cross section results will be introduced in the oral presentation.





**IAEA-CN-310/239**

### **Radiolabeling of Ciprofloxacin in the Detection of Orthopedic Infections**

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The aim of the study is detection and evaluation of the infective foci in orthopedic patients using own method of labelling of ciprofloxacin with Tc-99m (Institute for Nuclear Sciences, Vinča).

Total of 35 patients with clinical suspicion on orthopedic infection was investigated. In all the patients, whole body skeletal scintigraphy was performed. Ciprofloxacin chloride (3,5 mg) was mixed with 555 MBq of 99mTc in 3 ml of physiological solution and incubated for 20 min. After slow i.v. injection in a cubital vein, dynamic acquisition (1 f/min) was performed during first 60 min in the position of interest, followed by static acquisition (500 000 imp) of the whole body, anterior and posterior view after 1h and 4h in all patients. When necessary, additional scintigrams were acquired after 24h. In all the patients with negative or equivocal findings of planar scintigraphy, emission computerized tomography (SPECT) was performed (60 positions, 6 degrees). Interpretation was made by three independent observers. Additional data were provided using clinical finding, ultrasonography, radiography, computer tomography and magnetic resonance imaging, laboratory analyses, and surgical or microbiological confirmation of infection. In our study, the highest uptake of radiopharmaceutical was present in liver and urinary bladder, while there was no free pertechnetate in a thyroid gland.

There were 18 TP findings (4 with septic arthritis, 5 with osteomyelitis of femur, after fracture and osteosynthesis, 4 with flegmona of crural region and the foot caused by diabetes, and 5 with infection of the hip prosthesis), 12 TN (5 with osteoporosis, 5 with hip luxation and 2 with femoral fracture and osteomyelitis without infection), three FP (femoral osteomyelitis without infection and loosening of hip prosthesis without infection), while two FN (one due to TBC vertebral osteomyelitis, and the other with resistance to antibiotic therapy). The smallest lesion found was 15x20 mm. Scintigraphy after 4h reduced the number of FP findings from 7 to three, and increased the number of TP from 14 to 18, while scintigrams taken after 24 h did not influence the results of the study. Sensitivity was 90%, specificity 80%, positive predictive value 86%, negative predictive value 86% and accuracy 86%. In all 18 patients infection was caused by *Staphylococcus aureus*, in three associated with *Staphylococcus alpha haemolyticus*, *Pseudomonas* and *Acino bacter*). In one patient with FN finding, infection was caused by *Micobacterium tuberculosis*, and in the other resistant to antibiotic. According to our results, scintigraphy with radiolabeled ciprofloxacin is a useful method for detection and assessment of exact localization of orthopedic infections.



**IAEA-CN-310/240**

### **Radiobiological Effects of Radium-223 in 3D Cell Cultures of Metastatic Prostate Cancer**

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The clinical outcomes of Radium-223 dichloride solution ( $^{223}\text{RaCl}_2$ ) do not meet the initial expectations, mostly justified by the doubts about Ra-223 localization in the metastatic niche and how it interacts within the metastatic niche.

Analysing the radiobiological effects of radium-223 in 3D cell models of metastatic prostate cancer (mPCa) to better understand its mode of action among the constitutions of the metastatic niche as well as the molecular pathways involved in the radiobiological response.

Spheroids of PC3 cells were created and irradiated with increasing activities of  $^{223}\text{RaCl}_2$  (55-7040 kBq/kg) for 24 h. The spheroid's size and disintegration were followed for 8 days by optical microscopy and images were analyzed with ImageJ or AnaSP software. Cell viability, survival and types of death were evaluated 7 days post-irradiation.

It was observed a decrease in spheroid size, integrity and proliferation with increasing activities of  $^{223}\text{RaCl}_2$ , mainly for exposures to 5280 and 7040 kBq/kg. An increase in cell death with increasing activities, mostly by apoptosis, was also observed. We are also developing experiments in 3D heterotypic cultures to consider the role of angiogenesis, osteoblastic cycle, and immune system in  $^{223}\text{RaCl}_2$  therapeutic effects.



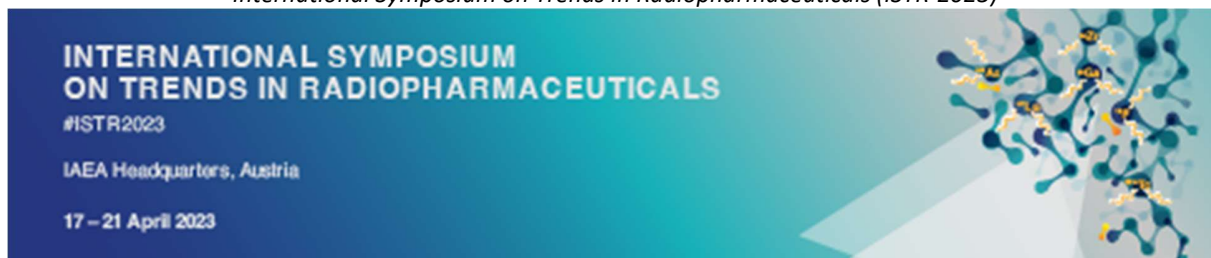
IAEA-CN-310/242

## Nimotuzumab Fragment-Based Radiopharmaceutical for Targeting EGFR-Overexpressing Tumor Cells

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Epidermal growth factor receptor (EGFR) is a receptor tyrosine kinase that is overexpressed in many cancers, including breast, glioma, ovarian, non-small-cell lung, head and neck squamous cell carcinoma, and prostate cancer. Several treatments have been developed to target these receptors. One of them is nimotuzumab, a monoclonal antibody (mAb) that binds to the extracellular domain of EGFR, then preventing its downstream signaling. This recombinant mAb showed optimal affinity and high specificity to EGFR. However, the penetration is slow and remains in the blood circulation for extended durations (from days to weeks) due to their high molecular weight (150 kDa). Reduction in the size of the mAb molecule is proposed as means to overcome these limitations. Since bivalent binding (binding with both antibody arms to two receptors) is essential for nimotuzumab, therefore, we modified the size of this mAb without disturbing its binding site. To date, there are still limited studies developing radiopharmaceuticals that use antibody fragments for cancer treatment. Therefore, this study aimed to examine the characteristic of nimotuzumab fragment-based radiopharmaceutical in cancer cells that overexpress EGFR. Pepsin is used to cleavage nimotuzumab molecules at the C-terminal side of the inter heavy-chain disulfides in the hinge region to form bivalent antigen-binding fragments [F(ab')<sub>2</sub>]. Our results found the optimum fragmentation time of nimotuzumab to produce fragments F(ab')<sub>2</sub> was 14 hours. The F(ab')<sub>2</sub>-nimotuzumab formed was then purified from its impurities which formed during the enzymatic cleavage process by using a PD-10 column (Sephadex G25). Furthermore, intact nimotuzumab and F(ab')<sub>2</sub> fragments were <sup>125</sup>I-labelled with the Na <sup>125</sup>I using the iodogen method to form <sup>125</sup>I-nimotuzumab and <sup>125</sup>I-F(ab')<sub>2</sub>-nimotuzumab. Then, <sup>125</sup>I-nimotuzumab and <sup>125</sup>I-F(ab')<sub>2</sub>-nimotuzumab were purified from free <sup>125</sup>I using a gel filtration column. Fractions that have high radioactivity were then tested for their radiochemical purity utilizing paper chromatography. The result demonstrated the radiochemical purity for <sup>125</sup>I-nimotuzumab and <sup>125</sup>I-F(ab')<sub>2</sub>-nimotuzumab are 98.27 % and 93.14 %, respectively. Moreover, to examine the binding profile of nimotuzumab after fragmentation and its effect on cell viability, we perform several in vitro studies (binding affinity with the cell-based competitive assay, uptake assay, specific internalization assay, and colorimetric assay for measuring cell metabolic activity) in EGFR-overexpressing cancer cells (A549 lung cancer). The emergence of new radiopharmaceuticals that can interact strongly with the receptors and rapidly reach the target cells is highly desirable to improve the treatment efficiency in cancer therapy.



**IAEA-CN-310/243**

### **Radiation Exposure for Pharmacists and Radiographers with $^{18}\text{F}$ -FDG in a PET/CT Centre**

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Physiological imaging modalities that combine positron emission tomography and computed tomography (PET/CT) are used in the diagnosis of severe diseases. PET radiopharmaceuticals introduce a risk of high occupational radiation exposure to staff handling them.  $^{18}\text{F}$ Fluorine-Fluorodeoxyglucose ( $^{18}\text{F}$ -FDG) is the most commonly used PET radiopharmaceutical.

To determine the radiation exposure of staff working at the PET/CT facility of an academic hospital in Gauteng.

The study was quantitative and descriptive. The radiation exposure data of participants were collected using electronic pocket dosimeters, ring dosimeters and thermoluminescent dosimeters. The participants' workflow was also tracked. The tasks that led to the highest radiation exposure were identified.

Occupational radiation exposure data of five radiographers and eight radiopharmacists were collected. Radiopharmacists' daily radiation exposure ranged between  $0.01\ \mu\text{Sv}$  and  $0.32\ \mu\text{Sv}$  while that of radiographers ranged between  $7.08\ \mu\text{Sv}$  and  $19.14\ \mu\text{Sv}$ .

Staff working at the PET/CT facility were not at risk of radiation exposure above the accepted annual limits, which are  $20\ \text{mSv}$  per annum, averaged over 5 years, and with no more than  $50\ \text{mSv}$  in one year.

There is a need for continuous training in radiation protection measures for all staff working in the PET/CT facility.



IAEA-CN-310/244

## Production of Pb-203 from Target Manufacturing to Chemical Separation Pb/Tl

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Pb-212 ( $t_{1/2} = 10.6$  h) and Pb-203 ( $t_{1/2} = 51.9$  h), can be used as a theranostic pair of isotopes for theranostic applications in nuclear medicine. Pb-212 can be obtained from ageing Th-232 and is used for alpha targeted therapy whereas Pb-203 can be produced by proton or deuteron irradiation of a thallium target and allows for single photon emission computed tomography (SPECT) thanks to its 279.2 keV (80.9%) photons. Current production of Pb-203 uses natural Tl bombarded by a proton beam. In this work, we consider alternative production routes using enriched Tl-205 and a deuteron beam in order to limit the level of Pb-201 ( $t_{1/2} = 9.33$ h) impurities and to avoid the production of Pb-200 ( $t_{1/2} = 21.5$ h). Starting from cross section measurements, we have defined optimal production parameters and yields. In parallel, we have developed a manufacturing process of the target by electroplating as well as a separation chemical process using a Pb resin from Triskem. This scheme will allow us to produce Pb-203 in the near future. The electrodeposition technique is used to prepare enriched Tl target for both cross section measurements and mass production. The temperature and pH of the solution are fixed respectively at 20°C and 8. The solution contains EDTA as complexing agent, hydrazine to prevent Tl<sup>+</sup> from oxidation to Tl<sup>3+</sup> and Brig-35 as surfactant. For the study of Pb-203 production cross sections and its impurities, thin deposits of Tl-205 (thicknesses ranging from 10  $\mu$ m and 15  $\mu$ m) with a circular shape (4 cm<sup>2</sup>) were made. Experiments were done with a deuteron beam whose energy is ranging from 22 MeV and 34 MeV. For the future routine production, a large deposit of enriched Tl is needed (14 cm<sup>2</sup> area) to reduce the heat deposition density. A 40  $\mu$ m thick was successfully obtained with a smooth deposit and good adhesion on gold backing. In parallel, we have studied the chemical separation of Pb/Tl using Pb-203 and Tl-202 ( $t_{1/2} = 12.31$  d) obtained by irradiation of thin deposits of natural Tl (20  $\mu$ m) with an intensity of 50 nA deuteron beam during 1 h beam. Large natural Tl targets were dissolved in 1 mol/L of hot nitric acid (70°C) and tracers were added to be able to follow the different species. The solution was first filtered to recover the precipitate of thallium nitrate, which is formed at ambient temperature. The solution was then poured in the column containing the Pb resin previously conditioned with 1 mol/L of HNO<sub>3</sub>. Tl was recovered by further eluting with 1 mol/L of nitric acid. For the elution of Pb, we studied two Methods: the first one corresponds to elution with 0.001 mol/L of nitric acid and the second one with ammonium acetate 1M at pH 7. The recovery of Pb is 83% and 88% respectively with less than 1% of the presence of the impurities of Tl in the solution containing Pb. Our results shows that future routine production of Pb-203 using enriched thallium target and deuteron beam is feasible and that the direct elution of Pb-203 with ammonium acetate 1M at pH 7 seems very promising. This work will be presented during the presentation.





**IAEA-CN-310/245**

## **Immunopet Imaging of Staphylococcal Infections in Osteomyelitis Mouse Model**

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*Staphylococcus aureus* is the most frequent cause of joint infections. The release of  $\alpha$ -toxin is one of the main virulent factors that enables bacterial colonization in human body. We present a specific anti  $\alpha$ -toxin antibody radiotracer for the selective detection of *S. aureus* infection by immunoPET/CT in an infective osteoarthritis mouse model.

Anti  $\alpha$ -Toxin Ab (150kDa, 1mg) was conjugated with p-SCN-Bz-DFO (30min, 37°C). Radiolabeling was performed in HEPES with 3mCi of  $[^{89}\text{Zr}]\text{Zr}(\text{ox})_2$  and 15mCi of  $[^{68}\text{Ga}]\text{GaCl}_3$  (1h, RT) (Figure 1A). Purity and in vitro stability in PBS were assessed by radio iTLC and HPLC (Figure 1B-C). Pharmacokinetic profile was evaluated in healthy animals 24h post-infection using  $[^{89}\text{Zr}]\text{ZrTox}$ . In vivo  $[^{89}\text{Zr}]\text{ZrTox}$  and  $[^{68}\text{Ga}]\text{GaTox}$  PET/CT imaging in an infective osteoarthritis mouse model were performed 48h post-infection.

Results/Discussion:  $[^{89}\text{Zr}]\text{ZrTox}$  and  $[^{68}\text{Ga}]\text{GaTox}$  were successfully synthesized with radio-chemical yields of  $60.8\pm 13.3\%$  and  $66.0\pm 8.3\%$ , purity  $> 95\%$  and specific activity of 10.4 and  $5.7\pm 0.91$  mCi/mg, respectively. Pharmacokinetic profile confirmed a blood half-life of 2.33 d, typical for 150 kDa antibodies (Figure 1D). Ex vivo biodistribution confirmed hepatobiliary metabolism, with main accumulation in liver (Figure 1C). In vivo PET/CT imaging of  $[^{89}\text{Zr}]\text{ZrTox}$  and  $[^{68}\text{Ga}]\text{GaTox}$  confirmed the uptake of both tracers in infected joints at initial infection stages (Figure 2).

We have successfully synthesized the immunotracers  $[^{89}\text{Zr}]\text{ZrTox}$  and  $[^{68}\text{Ga}]\text{GaTox}$  and confirmed their ability to in vivo detect active staphylococcal infections in an osteoarthritis model.





**IAEA-CN-310/246**

## **Heterodimer Peptide Based on RGD and NPY Analog for Breast Tumor Targeting**

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Heterodimer peptides targeting more than one receptor target can be advantageous as tumors can simultaneously express more than one receptor type. The design of heterodimer peptides can significantly increase the avidity and specificity of the contrast agent due to simultaneous binding to more than one type of receptor or at least one receptor independently, compared to their corresponding monospecific counterparts. A heterodimer molecule consisting of cyclic RGD and NPY analog motifs in a single probe is an attractive approach, as both receptors are overexpressed simultaneously in breast cancer. We hypothesize that a peptide ligand recognizing both  $\alpha\beta3$  integrin and NPY receptors will be advantageous because of its dual-receptor-targeting ability, which could enable the determination of disease location, monitoring of pathological and molecular changes associated with payload delivery, as well as a comprehensive view of the material behavior in vivo that can be utilized to guide therapeutic and diagnostic interventions. The HYNIC-cRGDfk-NPY peptide was radiolabeled with  $^{99m}\text{Tc}$  using tricine/EDDA as coligand. The cellular-specific binding of  $^{99m}\text{Tc}$ [HYNIC-cRGDfk-NPY] was evaluated on different cell lines as well as with a blocking experiment on MCF-7 and MDA-MB231 (human breast cancer cells). The proof-of-concept of tumor-targeting was performed through ex vivo biodistribution in normal mice, MCF-7 and MDA-MB231 tumor-bearing mice also in SPECT/CT images. By using tricine/EDDA as a coligand, labeling yield was more than 97%. The in vitro cell uptake test showed that this radiolabeled peptide had a good affinity to MDA-MB231 and MCF-7 cells. The in vivo results showed a tumor/muscle ratio of  $5.65 \pm 0.94$  for MCF-7 model, and  $7.78 \pm 3.20$  for MDA-MB231. Also, tumor uptake was reduced significantly from 9.30% to 4.41% (MCF-7) and from 4.93% to 2.3% (MDA-MB231) in blocking study whereas 500-fold molar excess of cold peptide was injected 30 min prior to the injection of related radioconjugated peptide suggesting the potential of heterobivalent radioligand  $^{99m}\text{Tc}$ -HYNIC-cRDGfk-NPY to target breast tumors targeting.



IAEA-CN-310/247

### **Quantitative Formulation of Non-Carrier Added Sodium Iodide (Na,<sup>131</sup>I) Aqueous Solutions with Sodium Thiosulfate Reducing Agent: Theoretical Determination of Initial Concentration and Modeling of the Radio-Chemical Decomposition Kinetics**

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Iodine-131 either directly as sodium iodide or in the form of iodine-131 radiolabeled compounds is one of the most widely used radioisotopes in Nuclear medicine for diagnosis and therapeutic purposes for a wide variety of disorders (hyperthyreosis, Thyroid carcinoma and other tumors tissues). The general production route of <sup>131</sup>I widely used is irradiation of uranium <sup>235</sup>U(n,f)→<sup>131</sup>I followed by complex radiochemical separation and purification processes to extract <sup>131</sup>I. <sup>131</sup>I may also be obtained by neutron irradiation of various chemical forms of tellurium target following neutron activation reaction <sup>130</sup>Te(n,g) <sup>131</sup>Te --β--><sup>131</sup>I followed by the relatively simple dry distillation technique based on the differences in the volatilization properties of iodine and tellurium target. In all production route, no carrier iodide can be added in such a manner that the final product is essentially carrier-free and contains only minute amount of naturally occurring <sup>127</sup>I or the almost Stable <sup>129</sup>I, as stated in the International and many others pharmacopoeias (BP, Eur. Pharm), Appropriate reducing agent is then added (mainly Sodium thiosulfate pentahydrate (STS) (Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>·5H<sub>2</sub>O) to prepare radiopharmaceuticals solutions and capsules by all manufacturers around the world and in a large variety of different concentrations depending on the sourcing route. As no stable carrier <sup>127</sup>I is used during production as prescribed by pharmacopoeias, the amount of radiogenic iodine produced should be known in each irradiation route. In this work we present theoretical calculations of the minimal quantity of sodium thiosulfate for Non-Carrier Added sodium iodide (Na,<sup>131</sup>I) aqueous solutions containing only radiogenic iodine obtained by neutron irradiation of tellurium dioxide (TeO<sub>2</sub>) target The radio-chemical decomposition kinetics of STS was investigated on the three consecutive batches produced for Drug Marketing Authorization purpose Testing radiation effects was performed using two different initial activities during pharmaceutical stability studies. Determination of sodium thiosulfate concentrations were conducted after analytical validation according to the ICH guidelines for method validation. Irradiation process was conducted on three batches and used a mean weight of 68,7 g (RSD 1.7%) of natural TeO<sub>2</sub> target material with a chemical purity of 97,5% ((Te=53,51g), 35 h intermittent irradiation (7h irradiation/17h sequential cooling/day for 5 days, final cooling time was 52h), at an average neutron flux of 3,3.10<sup>13</sup> n.cm<sup>-2</sup>.s<sup>-1</sup>. Isotopic Abundance α (molar fraction in %) and cross section of tellurium isotope used in theoretical calculations are as described and reported in the literature: <sup>130</sup>-Te is 34,48% (σ = 0.2 ± 0.1 barn); <sup>128</sup>-Te is 31.79% (σ = 0.155 ± 0.04 barn) and <sup>126</sup>-Te is 18,71% (σ = 0.9 ± 0.15 barn).



The Dry distillation process allowed us to recover an average of 1197 mCi of  $^{131}\text{I}$  (RSD=2%) from 3 batches, the average yield obtained was up to 95,5% (RSD=1,1%) of  $^{131}\text{I}$ , compared to theoretical calculation. The weight and the number of moles of  $^{131}\text{I}$  were calculated using equation relating radioactivity to the weight of  $^{131}\text{I}$  produced:  $A_c (\text{Bq}) = \lambda \cdot N = \lambda \cdot N_A \cdot W/M$ .

Calculation For 1 Ci is  $W(^{131}\text{I}) = 8,047 \cdot 10^{-6} \text{ g} = 0,0307 \times 10^{-6} \text{ moles of } ^{131}\text{I}_2 \text{ (Iodine)}$

However, Sodium thiosulfate reacts with all iodine in the preparations ( $^{131}\text{I} + ^{127}\text{I} + ^{129}\text{I}$ ) whose quantities were estimated by simplified Neutron activation equations following:

Weight of  $^{127}\text{I}$  produced  $W(^{127}\text{I}) = 1,3 \cdot 10^{-20} \cdot m(\text{Te}) \cdot \Phi \cdot t \text{ (g)}$

Weight of  $^{129}\text{I}$  produced  $W(^{129}\text{I}) = 3,6 \cdot 10^{-20} \cdot m(\text{Te}) \cdot \Phi \cdot t \text{ (g)}$

And the total Iodide number of moles of Iodide  $\text{I}_2$  for 1 Ci  $^{131}\text{I}$  produced was  $= 0,1708 \cdot 10^{-6} \text{ moles}$  with a ratio  $^{131}\text{I}/(^{127}\text{I} + ^{129}\text{I}) = 0,2192$ . Calculation of the Equivalent weight of sodium thiosulfate from Redox reactions involved in the in chemical process of trapping iodine in alkaline solutions gives the minimal quantity of  $0,0848 \mu\text{g}$  of  $(\text{Na}_2\text{S}_2\text{O}_3 \cdot 5\text{H}_2\text{O}) / \text{mCi}$  of  $^{131}\text{I}$ . This quantity is 943 times less than the quantity we already used in our produced batches, i.e.,  $0,08\text{mg/mCi}$  and has shown very well pharmaceutical stability behavior (pH, RCP, Iodide and Iodate Content). The radio-chemical decomposition kinetics of STS was investigated a low activity (10 mCi,  $[\text{STS}] = 6,45 \cdot 10^{-4} \text{ M}$ ) and a ten times higher activity and molarity in standardized volumes solutions (5 ml). In such concentration, STS undergoes chemical decomposition by oxidation and/or radiolysis process. Results showed that STS decomposition proceeds with good fitting according to Zero-Order kinetics. The Rate Constant  $d(\text{mol/l/day})$  were calculated, the Half-life :  $t_{1/2} = [\text{STS}]_0 / 2 \cdot k$  (9 days), shelf-life :  $t_{[\text{STS}]=0} = [A]_0 / k$  (18 days) and the Average Ratio  $k(100 \text{ mCi})/k(10 \text{ mCi}) = 10$  of the preparations were calculated.

It is necessary to optimize the quantitative formulation of the reducing agents used in iodine  $^{131}\text{I}$  radiopharmaceuticals by understanding the chemical and physical phenomena allowing the radioelement and the radiopharmaceutical to be obtained as well as by modeling of the kinetics of decomposition reaction that take place in the radiopharmaceutical preparation. This work makes it possible to define and justify the minimum necessary quantity of reducing agent to be used for the production of  $^{131}\text{I}$  radiopharmaceuticals from the neutron activation pathway. The kinetics of decomposition of thiosulfate at a rate of  $3 \cdot 10^{-4} \text{ mol/l/day}$  for 100mCi makes it easy to formulate a product according to the expiry dates set by each manufacturer without the need to use inappropriate quantities, while ensuring the quality and safety of the radiopharmaceutical product.



## **IAEA-CN-310/248**

### **New Regulatory Framework for Radioisotopes Production and Radiopharmacies in Brazil**

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In Brazil, as has been occurring worldwide, the number of procedures using radiopharmaceuticals is increasing. The production and selling of short half-life radioisotopes used to be a monopoly of the Brazilian Government. In 2006, a Constitutional Amendment revoked the state monopoly due to the need to use short half-life radioisotopes (less than 2 hours) in nuclear medicine centers very far from the government production facilities. In 2021, a new Constitutional Amendment revoked the monopoly for all radioisotopes. This work aims to present the current panorama of the production of radioisotopes and radiopharmacies in Brazil and the recent advances in the regulation of the sector. Currently, there are 17 radioisotope production facilities in Brazil, of which 3 are in the pre-operational, 13 are in operation, and 1 is in decommissioning stages. In turn, there are 5 centralized and industrial radiopharmacies under licensing in the country, being 1 in the pre-operational and 4 in operation. The licensing and control of radioisotope production facilities with cyclotron accelerators are subject to the CNEN's Standard of Safety and Radiological Protection Requirements in Radioisotope Production Facilities with Cyclotron Accelerators, published in October/2020. Similarly, the regulatory agency is in the final stages of elaboration and publication of the standard of Safety and Radiological Protection Requirements in Centralized and Industrial Radiopharmacies. The standards define safety requirements in the pre-operational, operational, and decommissioning stages. It also establishes safety systems, ventilation requirements, and constructive aspects such as the flow of materials and sources, among others. The absence of international guidelines for regulation is a challenge to the establishment of a regulatory framework. The expectation of new radiopharmacies highlights the need for a robust and agile legal framework for the licensing and control of the sector.



**IAEA-CN-310/249**

### **Rational Development of a Family of Estradiol-Derived [99mTc]Tc Complexes Using in Silico Tools**

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Our area has developed a family of [99mTc]Tc complexes derived from estradiol for breast cancer imaging using different metal oxidation states and chelating units, and studying their influence on the overall properties of the resulting products. A [99mTc]Tc(V) nitrido symmetric complex with two units of a estradiol derived dithiocarbamate as bidentate ligand, presented the best physicochemical and biological properties, comparable to [18F]F-FES.

In order to improve this complex, a library of 12 [99mTc]Tc(V) nitrido complexes was proposed, varying the linker between the biomolecule and the dithiocarbamate (chelating unit).

Molecular docking was performed using the MOE 2015.10 software. Library structures were drawn and minimized with the OPLS-AA force field. The selected target is the estrogen receptor using the 2JF9 deposition in the RCSB PDB. After treatment and molecular target minimization, three molecular dockings were run between the 12-complexes of the library and the estrogen receptor (Placement- Alpha triangle, rescoring 1-2 Affinity dG, retain 50.

5 complexes were found to have the highest receptor binding. Work will continue employing molecular dynamic simulations in order to evaluate the access of these 5 complexes to the receptor involved. The complexes with the best results will be synthesized and evaluated in the laboratory.





**IAEA-CN-310/250**

### **Current Status of Radiopharmacies in Countries Member of the Ibero-American Forum of Radiological and Nuclear Regulatory Bodies: Licensing and Safety Requirements**

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Centralized and industrial radiopharmacies are essential in radiopharmaceutical production and commercialization. The radiopharmacies provide access to different radiopharmaceuticals, in addition, to optimizing distribution logistics, enabling the sale of radiopharmaceuticals with different life averages, and guaranteeing the quality of the radiopharmaceutical during all the stages of the process. However, the risk associated with these facilities is relevant, being necessary for a consistent regulatory effort in terms of the preparation of guidelines and standards, safety assessment, and regulatory inspections. A current panorama of radiopharmacies and their licensing process in the countries member of the Forum Ibero-American Radiological and Nuclear Regulatory Bodies was prepared through a questionnaire and meetings held within the framework of the project focused on authorization requirements and procedures for the inspection of radiopharmacies. Among the countries, there are 78 radiopharmacies associated a cyclotrons facilities in operation and more 6 under construction. Also, there are 337 industrial or centralized radiopharmacies no associated cyclotron o reactor in operation, and more 4 under construction. Only 5 countries (Argentina, Brazil, Chile, EUA, and Peru) are producing radioisotopes with reactors, and 5 countries (Argentina, Brazil, Cuba, EUA, and Mexico) produce Mo99/Tc99m generators. Most countries don't have a specific standard for radiopharmacies and the absence of international guidelines about the criteria for licensing and inspection requirements for radiopharmacies is a challenge to the establishment of a regulatory framework. Due to this scenario, the forum, with IAEA's support, is developing a guideline to help the regulatory bodies in a field with a high growth perspective and few international recommendations. The guideline is based on that the characteristics of radiopharmacies can be very different, therefore, their design should take into account the risks associated with handling unsealed sources such as construction requirements, operations procedures, characteristics of radionuclides, safety systems, among others. The exchange of experience between countries is essential to establish a robust and agile regulatory framework.





IAEA-CN-310/252

## **Preclinical Validation of Freeze-Dried Kit of Albumin Nanoparticles Synthesized by a Radiolytic Method**

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Radiopharmaceutical kits containing human serum albumin nanoparticles (HSA-NP), which after radiolabeling with Sodium Pertechnetate solution ( $^{99m}\text{Tc}$ ) results in nanocolloids, are already commercialized by international companies. These kits are used to characterize the lymphatic system and, in particular, to detect sentinel lymph nodes in breast cancer and melanoma patients. Albumin has also recently been extensively utilized to form nanoparticles for drug delivery in cancer, i.e., Abraxane®, an FDA-approved nanomedicine consisting in paclitaxel encapsulated by albumin nanoparticles (130 nm), for metastatic breast cancer treatment (2005), lung cancer (2012), and metastatic pancreatic adenocarcinoma (2013). Well-established literature data, and experimental data obtained by our CRP research, demonstrate that albumin nanoparticles synthesized by gamma radiation have the potential to become a similar product to those available on the market. As the particle size distribution is well defined and parameters such as qualitative and quantitative composition are relevant and comparable to commercial ones. The albumin nanoparticles produced by radiation synthesis were lyophilized in a radiopharmaceutical kit containing HSA-NPs, Poloxamer 188, sodium phytate, tin chloride, glucose, and anhydrous disodium hydrogen phosphate. The OECD Guidelines for the Testing of Chemicals were performed to assure the safety of using the albumin nanoparticle freeze dried kits. The development of studies included: Genotoxicity tests (OECD 471: Bacterial Reverse Mutation Test, OECD 474: Mammalian Erythrocyte Micronucleus Test), Carcinogenicity tests (OECD 453: Combined Chronic Toxicity/Carcinogenicity Studies) and Acute Toxicity (OECD 420). In addition, biodistribution of  $^{99m}\text{Tc}$  radiolabeled albumin nanoparticle was performed in healthy mice. The results show that HSA-NP was not able to induce chromosomal breaks and/or chromosomal gain or loss under experimental conditions, indicating no genotoxic effect. Furthermore, it was considered non-mutagenic, as it did not induce mutations by shifting the reading frame or substitution of base pairs in the genome of the strains used (TA97a, TA98, TA100, TA102 and TA1535). The treated rats had weight gain and the blood counts showed no abnormalities, in the same way normal biochemical parameters were found indicating the nontoxicity of the product. Furthermore, the ex-vivo biodistribution study in normal mice showed rapid blood clearance with high hepatobiliary and low renal excretion, which is in agreement with literature studies and commercial products leaflets.



IAEA-CN-310/254

### **Cyclotron-Production of Mn-52 for PET/MRI Imaging**

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In the context of the LARAMED (LABoratory of RADIOisotopes for MEDicine) research program we developed the technology for cyclotron-driven Mn-52 radionuclide production, with applications in PET/MRI diagnostic techniques as the main goal. The final purpose is to use manganese complexes to obtain unprecedented molecular matching, using the paramagnetic properties of Mn(II) and the availability of radioactive manganese isotopes with suitable decay properties.

Mn- may be produced exploiting the Cr-52(p,n)Mn-52 nuclear reaction using protons (10-20 MeV). The targets were produced using the Spark Plasma Sintering (SPS) technique and cryomilling to reduce the powder granulometry size before sintering. After preliminary tests with Cr-nat material, the Cr-52 powder was used. The obtained pellet was bonded to Au+Nb backing materials, by SPS as well. Targets were irradiated using an ACSI-TR19/300 cyclotron. Ion exchange chromatography was used to separate Mn from Cr;  $\gamma$ -spectrometry analysis was applied to determine the % of Mn recovery and ICP-OES analysis to determine the amount of Cr in the final Mn-52 solution. A cassette-based automatic module with a solid target dissolution system was developed and applied with separation procedures.

Finally, labeling tests with cyclotron-produced Mn-52 with the ligand sodium 1,4-dioxo-8-azaspiro[4.5]decane-8-carbodithioate (DASD) and the ligand 1,4,8,11-tetraazacyclotetradecane (CYCLAM) are currently under processing.



**IAEA-CN-310/255**

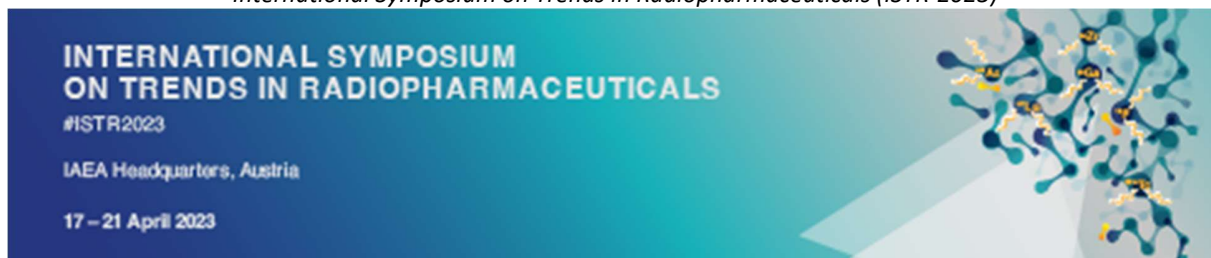
### **Advancement of Mn(II) Complexes for PET/MRI Imaging**

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The hybrid PET/MRI is a very powerful imaging technique in many clinical and preclinical applications since it combines MRI sequences with functional PET information in a single scan. The goal of our work is to develop a new class of Mn(II)-dithiocarbamates complexes to be potentially used as magnetic resonance imaging contrast media. We prepared Mn(II)-disubstituted symmetrical complexes containing dithiocarbamates under inert atmosphere and they proved to be the perfect candidates for our purpose because they showed high levels of paramagnetism, measured by a Superconducting Quantum Interference Device (SQUID) magnetometer (operating with a maximum applied field  $H = 50$  kOe).

Studies conducted to evaluate the properties of paramagnetic imaging in water using a clinical magnetic resonance showed that, the contrast produced by the complex  $[Mn(II)(L')_2] \cdot 2H_2O$  with  $L' = 1,4$ -dioxo-8-azaspiro[4.5]decane-8-carbodithioate (DASD) is equivalent to that produced by Gd-complexes currently used in medicine as paramagnetic contrast agents. Relaxivity values of the complex  $[Mn(II)(L')_2] \cdot 2H_2O$  were determined at  $25^\circ C$  at two magnetic field strengths: 0.5 T (20 MHz) and 1.5 T (60 MHz). Both longitudinal (T1) and transverse relaxation times (T2) were measured by appropriate spin-echo sequences. Stability and cytotoxicity with labelling studies are currently under examination.



**IAEA-CN-310/256**

### **Iron Oxide Nanoparticles Radiolabeled with $^{68}\text{Ga}$ and $^{177}\text{Lu}$ for Breast Cancer Theranostics**

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The present work aims to demonstrate the ability of radiolabeled magnetic nanoparticles to provide targeted imaging with Gallium-68 ( $^{68}\text{Ga}$ ) and therapy with its therapeutic analog Lutetium-177 ( $^{177}\text{Lu}$ ).

Condensed colloidal nanocrystal clusters comprising of iron oxide nanoparticles, coated with alginic acid and stabilized by polyethylene glycol, were functionalized with doxorubicin and bevacizumab. Direct radiolabeling was performed with both isotopes. Extensive in vitro studies were conducted to assess the cytotoxicity of the nanoparticles on five different breast cancer cell lines. In vivo biodistribution of the radiolabeled counterparts has been investigated with three different ways of administration. Finally, the therapeutic efficacy was assessed in tumor-bearing mice.

Pegylation improved the colloidal stability of the nanoparticles. Functionalization with the antibody reached 40% and drug loading 80%. Radiolabeling yields  $>90\%$  were achieved for both isotopes. Radiolabeled nanoconstructs were stable at RT even 7d post-radiolabeling whereas serum stability was moderate. In vitro evaluation showed an enhanced cytotoxic effect for the functionalized and the  $^{177}\text{Lu}$ -labeled nanoparticles. Intravenous and intraperitoneal administration did not give favorable biodistribution results. However, after intratumoral administration, a sufficient percentage of the  $^{177}\text{Lu}$ -labeled nanoparticles was retained at the tumor site. Enhanced therapeutic effect was also observed for the  $^{177}\text{Lu}$ -functionalized nanoparticles in 4T1 tumor-bearing mice.



## IAEA-CN-310/257

### **The Synthesis and Pre-Therapeutic Introduction of n.c.a. $^{177}\text{Lu}$ -PSMA I&T (“LuteScan”) as a SPECT compatible radioligand for Imaging of Metastatic Prostate Cancer Patients, Candidates for $^{177}\text{Lu}$ -PSMA Treatment**

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The synthesis of n.c.a.  $^{177}\text{Lu}$ -PSMA-I&T and its administration as a diagnostic whole-body scintigram (Fig-1), called by us “LuteScan” is aimed to be used as an alternative to the prerequisite  $^{68}\text{Ga}$ -PSMA staging PET/CT scan before the initialization of the radioligand therapy (RLT).

After institutional review board approval and informed consent in 17 patients with metastatic castration-resistant prostate cancer (mCRPC), candidates for radiopeptide therapy, 444 MBq of “LuteScan” was pre-therapeutically, i.v. infused. Twenty-four and forty-eight hr p.i., whole-body and tomo-acquisitions of the lower part of the head, counting the lacrimal and salivary glands and (b) the upper abdomen/lumbar region, including kidneys were performed.

In 15/17 (82,2%) mCRPC patients, pre-therapeutic “LuteScan” demonstrates them to be PSMA-avid. The absorbed dose for the lacrimal and parotid glands, kidneys and bone marrow was  $2.6 \pm 1.4$ ,  $2.1 \pm 1.2$ ,  $0.81 \pm 0.28$  and  $0.038 \pm 0.009$  Gy/GBq respectively.

The pre-therapeutic “LuteScan” in mCRPC patients (a) refers them as indisputable candidates for  $^{177}\text{Lu}$ -PSMA therapy and (b) it might represent a clinical alternative to  $^{68}\text{Ga}$ -PSMA, where the latter is restricted or not available. Dosimetry of kidneys, lacrimal and salivary glands, considered dose-limiting organs and exhibiting high physiological  $^{177}\text{Lu}$ -PSMA uptake, should be a necessary appendage.





**IAEA-CN-310/258**

## **Radiolabelling of Ciprofloxacin in the Detection of Abdominal and Gastrointestinal Infection**

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The aim of the study is detection and evaluation of the abdominal and gastrointestinal infective foci using Tc-99m-ciprofloxacin obtained from Laboratory for radioactive isotopes, Vinca.

Total of 26 patients with clinical suspicion on abdominal or gastrointestinal infection were investigated. In all the patients, planar liver/spleen scintigraphy was performed (99mTc-Sn-colloid, 500 000 imp, anterior, posterior and both lateral views, 30 min after application of radiopharmaceutical. Labeling of 3,5 mg ciprofloxacin chlorid was performed with 555 MBq 99mTc in 3 ml of physiological solution, mixed and incubated for 20 min. After slow i.v. injection in a cubital vein, static acquisition (500 000 imp) was performed (anterior and posterior view, abdomen and pelvis) after 1h and 4h in all patients. When needed, additional scintigrams were acquired after and 24h. In all the patients with negative or equivocal findings of planar scintigraphy, emission computed tomography (SPECT) was performed (60 positions, 6 degrees). Interpretation was made by three independent observers. Additional data were provided using clinical finding, ultrasonography, computer tomography and magnetic resonance imaging, laboratory analyses, and surgical or microbiological confirmation of infection.

There were 22 true positive (TP) findings (11 subhepatic abscesses after different types of surgery, two perianal fistula, 8 abdominal abscesses and 3 liver abscesses), 13 true negative (TN) (pneumonia virosa, liver cyst-2, paravertebral lipoma, Tu coeci-3, Tu pp Wateri, FUO-5), 5 were false negative (FN) (3 abscessus subphrenic and two with M.Crohn with enterocolic fistula) while 3 were false positive due to intestinal obstruction. The smallest lesion found was 19x20 mm. SPECT increased the number of TP findings from 14 to 22. Sensitivity was 81.5%, specificity 81.3%, positive predictive value 88%, negative predictive value 72% and accuracy 81.4%. In 10 patients infection was caused by Escherichia coli, 4 with Proteus mirabilis, 4 with Pseudomonas aeruginosa and 2 with Klebsiella, while in 2 only the surgical confirmation of infection existed. In 3 FN patients, infection was caused by anaerobes, while in two others E.coli was found.

According to our results, scintigraphy with infection is useful method for detection and assessment of exact localization of deep seated bacterial infections, which is very important for surgical intervention.





IAEA-CN-310/259

## Use of the Radiopharmaceutical Sodium Iodide I131 in Kazakhstan

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In 2021, the Institute of Nuclear Physics RSE on the REM began regular production of the radiopharmaceutical "Sodium iodide 131I, oral solution" under GMP conditions. In the same year, the drug was included in the Kazakh national formulary, and from this year, citizens of the Republic of Kazakhstan can receive radioactive iodine treatment under medical insurance and even use part of their pension savings for treatment. A weekly supply of radioactive iodine to Semey, where there are 15 "hot beds", allows the treatment of 780 patients per year, provided that the supply is uninterrupted, and the equipment operates without interruptions for maintenance and repair. Having only one center in a country capable of providing radioactive iodine treatment is not enough. The shortage of "active beds" in the Republic of Kazakhstan today is 52, and the potential annual need for radioiodine therapy in the Republic of Kazakhstan: thyrotoxicosis - 3570 people, thyroid cancer - 687 people. Until that time, this method was not available to all patients, many went abroad and received treatment on a paid basis. Radioiodine therapy offers the most efficient and safe treatment for differentiated thyroid carcinoma with distant metastases and thyrotoxicosis. The distinguishing characteristic of this technique lies in the fact that the beta particles emitted by sodium iodide I-131 affect the tissue within only 2 mm. This type of radiation is not dangerous to other organs. It is exactly the precision and targeting of the action of radioactive iodine lies behind the radioiodine therapy and determines its strength. Beta particles have an increased power to penetrate the biological tissues located around the iodine-131 accumulation zone due to its high escape velocity. Penetration depth of beta particles is 0.5-2 mm. Since their range is limited to these values only, radioactive iodine works exclusively within the thyroid gland. From this perspective, due to the selective accumulation of radiopharmaceutical "sodium iodide 131I" in abnormal focus of the body, destruction of cancer cells occurs while preserving the surrounding tissues. Advantages: it destroys remnants of thyroid cells after surgical treatment, detects tumor metastases and conducts therapy, refines subsequent detection of latent metastases or recurrence in radionuclide diagnostics. The East Kazakhstan region has one of the first line ranks in the incidence of malignant tumors in the country. In June 2021, a radionuclide therapy unit was opened at the "Center of Nuclear Medicine and Oncology in Semey". This is the first and only unit in the Republic of Kazakhstan, where the method of radioiodine therapy was implemented. To date, more than 500 patients have been treated in the Radionuclide Therapy Unit. Treatment efficacy is up to 95% of patients. The presentation will be dedicated to the manufacture and use of the radiopharmaceutical "Sodium iodide 131I" in Kazakhstan at the base of the "Center of Nuclear Medicine and Oncology in Semey".



**IAEA-CN-310/260**

**Dual Radiation and Immunotherapies through Green Nanotechnology of Mangiferin Functionalized <sup>198</sup>Gold Nanoparticles—Production, Preclinical and Clinical Investigations**

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Irradiation of normal cells by ionizing radiation results in systemic effects by triggering many molecular signaling pathways. Recent evidence suggests that radiation therapies act as double-edged sword as they induce pro-survival signaling pathways, which are directly involved in inducing cell cycle arrest and promoting DNA repair, while others are engaged in suppressing apoptosis induction. A major complication of these cellular pathways is their power to act synergistically to protect cancer cells from the cytotoxic effects of radiation, ultimately causing radio and chemo resistance of cancers. It is therefore important to develop therapeutic approaches that would offer dual radiation therapy as well as immunotherapy—all in a singular therapeutic regimen. We have discovered that carrier-added mangiferin functionalized gold nanoparticles (MGF-<sup>198</sup>AuNPs) to be an effective immunomodulatory agent being able to target tumor microenvironment, transform pro-tumor macrophages (M2) into antitumor M1 phenotype while enhancing anti-tumor IL-12 cytokines. This lecture will highlight preclinical and clinical evaluations of immunotherapeutic MGF-<sup>198</sup>AuNPs nanoparticles for stopping the infiltrating aggressive tumor proliferating M2 macrophages to achieve effective dual radiation and immuno therapy. The overall implications of Green Nanotechnology of MGF-<sup>198</sup>AuNPs as a dual radiotherapeutic ‘nanoradio—immuno—pharmaceutical’ in oncology will be discussed.



**IAEA-CN-310/261**

**Mo99 Production – Neutron Capture-Based Production via Power Reactor and Potential Market Penetration**

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Historically, the production of Molybdenum-99 (Mo99) via neutron capture has been limited, stemming from lower reaction efficiencies and extraction capacities based on low specific activity. A breakthrough in technetium generator technology, developed by BWX Technologies (BWXT) in the United States, has regained attention as a viable method for high-volume uranium-based Mo99 production. Through a partnership with Laurentis Energy Partners of Canada, a commercial CANDU (Canadian Atomic Natural Deuterium Uranium) nuclear reactor near Toronto, Canada, will generate Mo99 via neutron capture with subsequent processing at a local BWXT facility – both technologies being a first of a kind in the industry. Given the scale of power reactors, additional operating and safety considerations beyond those incorporated in research reactors will be required for the production and handling of Mo99. This paper discusses non-proprietary aspects of neutron capture-based Mo99 production through a commercial reactor in support of potential market expansion in other CANDU-type heavy water reactors or other future reactor designs.



IAEA-CN-310/263

## Development of a Novel Samarium-153 and Methotrexate loaded Particles for Chemical and Radiation Synovectomy of Rheumatoid Arthritis

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Rheumatoid arthritis (RA) is a chronic inflammatory disease that affects 1% of the population. Chemical and radiation synovectomy are promising treatment approach for RA by removing inflamed tissue in the joint. Although methotrexate (MTX) is an efficient drug for chemical synovectomy, it presents side effects such as gastrointestinal disorders. On the other hand, radiological synovectomy with  $\beta$ -emitting radioisotopes such as Samarium-153 ( $^{153}\text{Sm}$ ) stops the inflammation and synovial proliferation by the local radiation effect. This study was taken to develop a carrier formulation to deliver the both MTX and  $^{153}\text{Sm}$  for concurrent chemical and radiation synovectomy. The calcium carbonate ( $\text{CaCO}_3$ ) microspheres were synthesized via spontaneous precipitation and loaded with  $^{152}\text{Sm}$  and MTX. The  $^{152}\text{Sm}$ -MTX-loaded  $\text{CaCO}_3$  microspheres were neutron activated using a 1 MW nuclear research reactor (TRIGA MARK II, General Atomics), converting  $^{152}\text{Sm}$  to  $^{153}\text{Sm}$  ( $E_{\text{max}} = 807.6 \text{ keV}$ , half-life= 46.3 hours) through  $^{152}\text{Sm}(n,\gamma)^{153}\text{Sm}$  reaction. The microspheres before and after irradiation were characterized using scanning electron microscope (SEM), energy dispersive X-ray (EDX) spectroscopy, particle size analysis and gamma spectroscopy. The in-vitro retention efficiency of  $^{153}\text{Sm}$  on the prepared microspheres was performed in simulated synovial fluid. In addition, the MTX loading capacity, encapsulation efficiency and cumulative release of MTX from the microspheres were also determined. The Sm-MTX-loaded  $\text{CaCO}_3$  microspheres synthesized were spherical with a mean diameter of  $5.66 \pm 0.32 \mu\text{m}$ , as indicated by the SEM and particle size analysis results. Neutron activation of the microspheres produced a nominal activity of  $5.37 \pm 0.01 \text{ Gbq.g}^{-1}$  without affecting its morphology and size distribution. The EDX spectroscopy and gamma spectrometry suggesting no elemental impurities present in the irradiated microspheres. The  $^{153}\text{Sm}$ -MTX-loaded  $\text{CaCO}_3$  microspheres achieved retention efficiency of more than 95% in simulated synovial fluid over the duration of 400 hours. The Sm-MTX-loaded  $\text{CaCO}_3$  microspheres contained about 19 mg of MTX per gram of microspheres. The cumulative release of MTX from the microspheres achieved 80% over 50 hours in simulated synovial fluid.

A novel formulation of microspheres loaded with both Sm-153 and MTX was successfully developed in this study. The  $^{153}\text{Sm}$ -MTX-loaded  $\text{CaCO}_3$  microspheres are potentially useful for treatment of RA in view of its favorable physicochemical characteristics and excellent retention efficiency.



**IAEA-CN-310/265**

**High-purity  $^{52}\text{gMn}$  production:  $\text{natV}(\alpha,x)^{52}\text{gMn}$  and  $\text{natCr}(p,x)^{52}\text{gMn}$  at comparison**

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$^{52}\text{gMn}$  appears as a valid agent for positron emission tomography (PET) of biological complex with slow localization in the target tissues, thanks to its decay properties ( $\beta^+ = 29.4\%$ ,  $E(\beta^+) \text{ avg} = 242 \text{ keV}$ ) and its quite long half-life ( $t_{1/2} = 5.6 \text{ day}$ )<sup>1</sup>. Recently, the cyclotron production route  $\text{natV}(\alpha,x)^{52}\text{gMn}$  has been proposed as an alternative to the standard  $\text{natCr}(p,x)^{52}\text{gMn}$  one<sup>2</sup>. The cross sections comparison has been carried out by means of the nuclear reaction code Talys<sup>3</sup>. For the  $\alpha$ - $\text{natV}$  reaction, the  $^{52}\text{gMn}$  cross sections have been optimized by tuning the microscopic level densities parameters and, from there, yields and purities have been calculated. Dosimetric evaluations of  $[\text{xxMn}]\text{Cl}_2$  have been accomplished by means of the OLINDA software using adult female and male phantoms<sup>4,5</sup>. Finally, the dose increase (DI) has been calculated for both reactions by combining the estimated yield of  $\text{xxMn}$  radioisotopes with the dosimetric outcomes. Results indicate that  $^{52}\text{gMn}$  production from both  $\text{natV}(\alpha,x)$  and  $\text{natCr}(p,x)$  routes is acceptable for clinics. However, the  $\text{natV}(\alpha,x)^{52}\text{gMn}$  reaction provides a DI systematically lower than the one obtainable with  $\text{natCr}(p,x)^{52}\text{gMn}$  and a radionuclidic purity greater than 99% for a longer time window<sup>6</sup>.





**IAEA-CN-310/267**

### **Production by Mass-Separation of Non-Conventional Medical Radionuclides at the CERN-MEDICIS Facility**

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CERN-MEDICIS (Medical Isotopes Collected from ISOLDE) is a research facility at CERN which specializes in extraction and mass-separation of non-conventional medical radionuclides. The radionuclides of interest are produced in thick targets irradiated with 1.4 GeV or 1.7 GeV protons delivered to ISOLDE (Isotope Mass Separator Online Device facility at CERN) irradiation station by CERN Proton Synchrotron Booster (PSB). The CERN-MEDICIS mode of operation also uses externally irradiated targets produced at nuclear reactors and cyclotron facilities within the MEDICIS collaboration to proceed further to the radionuclide purification by mass-separation. Extraction, ionization and mass-separation of radioactive ion beams is efficiently applied to provide medical radionuclide ions implanted into metallic foils, followed when necessary by a radiochemical separation. Subsequently, the high molar activity sample is shipped to one of MEDICIS' partner research institutes. The radionuclides are typically extracted in the form of singly charged atomic or molecular ions, and thanks to its research and development programme, notably exploiting the MEDICIS laser ion source, MELISSA, higher mass-separation efficiencies and extraction of rare-earth refractory element have been achieved. The most recent upgrade provides the facility with the possibility to extract in parallel two radioisotopes at the same time, such as the  $^{165,167}\text{Tm}$  pair, doubling the output of MEDICIS operation when theranostic pairs can be produced from the same target. The CERN-MEDICIS facility was commissioned in December 2017 and since then has separated theranostic radiometals and radiolanthanides for biomedical research, such as  $^{44,47}\text{Sc}$ ,  $^{128}\text{Ba}$ ,  $^{149,152,155}\text{Tb}$ ,  $^{165,167}\text{Tm}$ ,  $^{169}\text{Er}$ ,  $^{191}\text{Pt}$  and  $^{225}\text{Ac}$ . Recent achievements of MEDICIS operations include promising first in-vitro and pre-clinical study results in targeted radionuclide therapy from isotopically pure, high molar activity  $^{175}\text{Yb}$  and  $^{153}\text{Sm}$  batches. Because of its unique capabilities, CERN-MEDICIS is quickly becoming a key player in translational research by providing novel medical radionuclides for cancer diagnostics, radionuclidic therapy and theranostics research to institutes within and outside European borders. This triggered PRISMAP, a consortium that comprises of 23 beneficiaries from 13 countries. PRISMAP (Production of high purity isotopes by mass separation) is the European medical isotope programme, supported by the European Commission that aims to provide a sustainable source of high purity grade novel radionuclides for medical research and create a single-entry point for all researchers and users active in this field.





**IAEA-CN-310/268**

### **Development of a In-House Method for the Synthesis of Sodium [18F]Fluoride Preparation**

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Sodium [18F]fluoride is PET radiopharmaceutical containing fluorine-18 in the form of sodium fluoride. To develop an in-house method for [18F]NaF production using only a dispensing module for both, radiopharmaceutical synthesis and dose dispensing. The semi-automatic dispenser for radiopharmaceuticals with a single-use sterile disposable kit (Clio, Comecer) was used. The kit includes four three-way valves, lines for different purposes, and a 0.22 µm sterilization filter. For the production of [18F]NaF, we made a modification of the kit. On the first valve we installed a Sep-Pak Accell Plus QMA cartridge, Y connector, and sterile vial with 0.9% sodium chloride. The preconditioned QMA cartridge was connected to the distal part of the Y connector and attached to the first valve of the kit. One proximal ending of the Y connector was connected to the [18F]F-cyclotron transfer line and the other proximal ending to the vial with 5 ml 0.9% NaCl for elution. After development of our in-house method for synthesis, the process optimization was carried out, 10 production batches were performed, with yield higher than 98%, decay-corrected. The quality control results confirm that the produced Sodium [18F]fluoride radiopharmaceutical meets the acceptance criteria defined in the specification, based on Ph. Eur. monograph. [18F]Sodium fluoride, production, in-house method



**IAEA-CN-310/269**

### **Challenges In Method Developing of $^{18}\text{F}$ -FMISO Synthesis with Cartridge Purification**

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$^{18}\text{F}$ fluoromisonidazole ( $^{18}\text{F}$ FMISO) as nitroimidazole derivative with  $^{18}\text{F}$  radioisotope is widely known and studied radiopharmaceutical for PET evaluation of imaging hypoxia. In recent years, there is increasing number of articles describing the modified syntheses with different synthesis modules and purification procedures of  $^{18}\text{F}$ FMISO.

The goal of this work was to take a view of solid phase extraction (SPE) method challenges in developing of  $^{18}\text{F}$ FMISO synthesis process with Synthera module. We synthesized  $^{18}\text{F}$ FMISO under various reaction conditions and different purification cartridges with Synthera synthesizer.

The synthesis was performed by nucleophilic substitution of 1-(2'-nitro-1'-imidazolyl)-2-O-tetrahydropyranyl-3-O-toluenesulfonylpropanediol precursor and subsequent acidic hydrolysis. A product mixture after was sent to waste over the Sep-Pak cartridges, whereby the final product was eluted from the cartridge with small amounts of ethanol in water. SCX, Alumina and six different RP extraction cartridge (HLB light, HLB plus LP, C18, tC18, C18 environmental, PS-RP) were used for SPE purification.

Product samples, cartridges elution samples and waste samples were observed for chemical by-products and radiochemical purity with HPLC and TLC analysis.

In this study, we successfully synthesized final product with reasonable radiochemical yield and high chemical and radiochemical purity of  $^{18}\text{F}$ FMISO. The product meets all the requirements of the Ph. Eur. Monograph.



**IAEA-CN-310/270**

### **How Does the Concentration of Technetium-99m Radiolabeled Gold Nanoparticles Affect Their In Vivo Biodistribution**

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Gold nanoparticles have been extensively investigated over the past few years for their theranostic applications due to their physicochemical properties, easy modification of their surface with different functional groups, low toxicity and biocompatibility. We have recently investigated gold nanoparticles functionalized with a ligand containing a thiol group for radiolabeling with  $[^{99m}\text{Tc}][\text{Tc}(\text{H}_2\text{O})_3(\text{CO})_3]^+$ . The radiolabeling yield and radiochemical purity were more than 95% and the complex was further evaluated by performing stability studies in cysteine, histidine and human serum solutions, lipophilicity and cytotoxicity studies as well as hemolysis assay. The results indicated that the resulting complex exhibited a very satisfactory in vitro profile and was further investigated for its behavior in vivo by performing biodistribution studies in healthy mice.

The aim of the present study is to investigate the effect of the concentration of the administered gold nanoparticles on their in vivo kinetics. For this purpose, we prepared samples with 3 different concentrations of gold nanoparticles (31.25, 3.125 and 0.3125  $\mu\text{g}/\text{ml}$ ). The biodistribution studies were performed in healthy female mice at different timepoints (1, 4 & 24h) via intravenous injection. The results indicated that at each concentration the accumulation in the organs of interest of the radiolabeled nanoparticles was different.



**IAEA-CN-310/271**

## **Radiopharmaceutical Drug Development While Using Adaptive Clinical Trial Design**

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The adaptive clinical design is an alternative of the randomized clinical trials. It differs from the randomized clinical trials with the preset prospective modifications in the protocol of one or more aspects which can be carried out in the work process based on the data received from trial participants. The main difference between an adaptive design and a randomized controlled design is that in the latter the users are distributed throughout controlled 'arms' of the trial. In the adaptive trials the process differs. Data from search participants is observed and analyzed during preliminary determination of intermediates points. This way can be implemented in advance definition modifications in the test that are based on these observations. The "seamless" adaptive clinical design would be very suitable for development of next Radiopharmaceutical drugs due to its ethical considerations and provide treatment to the participants from Phase I (first-time-in-human) until Phase III without interruption of drug treatment.



**IAEA-CN-310/272**

### **Innovative Medical Radioisotopes Production: A Focus on Pa Project**

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The PRISMA (Physics of Radiation Interaction with Matter and Applications), team of Subatech, conducts both fundamental and applied research on the interaction of radiation and particles with matter. One of its fields of expertise concerns the production of innovative radionuclides for diagnosis and therapy (RaMI for Innovative Medical Radioisotopes). For this purpose, it combines its skills in nuclear physics and radiochemistry in the acquisition of fundamental data in order to respond to the health challenges of the future.

Uranium-230 (U-230) is considered as a promising alpha emitter. The decay of a U-230 nucleus results in a chain of rapid decays accompanied by the emission of 5 alpha particles with a total energy of about 33.5 MeV. The half-life period of U-230 (20.8 d) is suitable for the production and transport of the radionuclide and subsequent radiopharmaceutical. In addition, the use of U-230 as the parent radionuclide for a short-lived period (31 min) Th-226 generator is of great interest. However, one of the major issues in the development of this technique is their availability.

The protactinium project takes its meaning. Indeed, U-230 can be produced by the decay of protactinium-230 (Pa-230), itself generated under irradiation of natural thorium by protons. In this context, the objectives of our Pa project are to optimize the production of Pa-230 with the C70XP cyclotron of GIP ARRONAX. Based on the acquired fundamental data, a production procedure for the recovery of Pa-230 and U-230 could be set up. These data will be used to meet the isotopic and chemical purity requirements for the production of U-230 for medical applications.



**IAEA-CN-310/273**

### **Latest Development of A Emitter Imaging and Quantification on a Large Field of View**

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Currently, the characterization of the nature and spatial distribution of radionuclides in a sample is time consuming and fastidious. Indeed, it necessarily requires the use of two distinct analytical techniques and detectors of a different nature. Moreover, the resolutions of the two methods are often different from each other because they also depend on the nature of the detector used, which makes it difficult to integrate and interpret these two types of measurements together.

To overcome these limitations and to simplify and accelerate the measurement process, it is now possible to use a digital autoradiograph capable of combining the measurement of the spatial distribution with the ability to separate and quantify each radionuclide.

For this purpose, a set of temporal and energy spectrometry techniques had to be specifically developed. On the one hand, the use of instruments capable of recording the location of each decay product allows measuring the evolution of the activity of the sample and thus, to deduce the contributions of several radionuclides. On the other hand, the development of an innovative method of autoradiography spectroscopy in particle energy also allows separating them by measuring their initial energy. Even if the efficiency of energy spectrum reconstruction is low (4.4%) compared to the efficiency of a simple autoradiograph (50%), this novel measurement approach offers the opportunity to select areas on an autoradiograph to perform an energy spectrum analysis within that area.

From an application point of view, this opens up possibilities for theragnostic applications that typically use two radionuclides. Further upstream, it can optimize the production and distribution challenge of  $\alpha$  radionuclides by allowing the identification and characterization of individual radionuclides in radionuclide chains such as  $^{225}\text{Ac}$ .





**IAEA-CN-310/274**

### **Automated Synthesis and Quality Control of [<sup>11</sup>C]Metoclopramide Using Iphase C-11 Pro2 for Clinical PET Imaging**

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<sup>11</sup>C radiopharmaceuticals allow studying neuropharmacokinetics of brain-targeting drugs. Metoclopramide is a medicine, substrate of the P-glycoprotein, a blood-brain-barrier efflux-transporter that plays a crucial role in eliminating xenobiotics from the brain. We aim to develop [<sup>11</sup>C]metoclopramide automated synthesis on iPhase C-11 Pro2 compliant with human use requirements. Cyclotron-produced [<sup>11</sup>C]CO<sub>2</sub> is reduced to methanol by LiAlH<sub>4</sub> 0.1M in THF and then to [<sup>11</sup>C]CH<sub>3</sub>I by HI. [<sup>11</sup>C]CH<sub>3</sub>I was heated and converted to [<sup>11</sup>C]methyltriflate. [<sup>11</sup>C]methyltriflate is bubbled into a reactor containing 1.1mg of desmethyl-metoclopramide in 400μL acetone and 7μL NaOH 3M (110°C; 2 min). HPLC purification (Waters SymetryPrep, H<sub>2</sub>PO<sub>4</sub> 20 mM/ACN/H<sub>3</sub>PO<sub>4</sub> 70%,85:15:0.1%) afforded a satisfactory separation between [<sup>11</sup>C]metoclopramide (R<sub>t</sub>=10 min) and its precursor (R<sub>t</sub>=7 min). Formulation was carried out by eluting [<sup>11</sup>C]metoclopramide with 1mL ethanol+9 mL NaCl 0.9% from a C18-cartridge. The final product was transferred in an ISO 5 hotcell through a sterile tubing ending with a PVDF-0.22μm filter. 3.38±0.47GBq of [<sup>11</sup>C]metoclopramide was produced after 30 min with chemical and radiochemical purities > 99.9%. Molar activity was 122.9±9.2GBq/μmol (at end of bombardment). All quality controls conformed to specifications. [<sup>11</sup>C]metoclopramide production was successfully implemented on iPhase C-11 Pro2 and was followed by [<sup>11</sup>C]PIB and [<sup>11</sup>C]flumazenil. [<sup>11</sup>C]UCB-J is under development.



**IAEA-CN-310/275**

### **Recent Developments and Contribution to TAT of Systems Dedicated to Alpha Autoradiography**

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One of the main difficulties in the development of TAT remains the difficulty of identifying and localizing the distribution of radiopharmaceuticals in the human body. Since the decay chain of the associated alpha emitter is generally composed of beta and alpha emitters, it makes them difficult to locate accurately by techniques using gamma detection of the decays.

To address the need to qualify and quantify the spatial distribution of alpha-emitting radiopharmaceuticals in tissues at high spatial resolution, important developments or improvements have been made in autoradiography systems.

Indeed, as the first molecular imaging technique used for the localization of radiolabeled compounds in biological specimens, autoradiography remains the only technique that allows the imaging of charged particles with an unequaled spatial accuracy. In addition, the new generation of real-time counting imagers allow researchers to optimize acquisition time, have a very high sensitivity allowing the detection of short half-life radionuclides, offer the possibility to image in real time and quantify radioactive concentrations over a wide dynamic range. Moreover, their specific detection process allows the discrimination of several radionuclides in the same experiment and sometimes determine the equilibrium state of the radioactive chains.

Nevertheless, as there are many types and configurations of detectors with various compromises in terms of activity quantification, spatial resolution, energy resolution and detection area, it remains complicated to be able to understand the different systems and their respective possibilities of evolution. This work therefore proposes to present the current and future applications of autoradiography and their associated detection systems.



**IAEA-CN-310/276**

### **Computational Approach to the Evaluation of Stability In Radiotracers**

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One of the first and foremost stages in the development of a potential radiotracer is the design of a plausible molecule to be radiolabeled. An effective design allows the time and resource optimization when it comes to perform tests in the laboratory.

Once a design is proposed, it is essential to evaluate the stability of the formed complexes. In silico, is a convenient way to do this. These studies successfully predict some of the physicochemical properties as well as information about kinetic and thermodynamic stability.

The aim of this project is to present the computational development of a potential  $^{68}\text{Ga}$  PET radiotracer for early infection foci diagnosis, using NOTA as bifunctional chelator agent. An antimicrobial peptide, derivatized from the EcgDf1, will be performing the biological activity of the tracer.

The structure of  $^{68}\text{Ga}$ -Ga-NOTA complex in aqueous solvent (IEFPCM) was optimized using DFT methods. Initially using B3LYP with the combination of 6-31G\* basis set on nonmetal atoms and LANL2DZ effective core potential on the gallium center. In sequence, the geometry was confirmed using M06-2X/GD3 and wB97XD functionals with cc-pVTZ basis set. This complex will be later incorporated into each optimized peptide model in the series.



**IAEA-CN-310/277**

### **Initial Experience on the Cyclotron Production of Gallium-68 Using Solid Targets with 11 Mev Protons**

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The most common method to obtain Gallium-68 (Ga-68) for PET imaging is using Ge-68/Ga-68 generators, however, one of the main drawbacks related to the use of generators is the limited loaded activity in addition to supply challenges due to increased demand. Given these facts, the direct cyclotron production of Ga-68 has garnered interest as an alternative source of this important radionuclide. The most common method for the high yield production of Ga-68 comprises the irradiation of a solid target that consists of a layer of isotopically enriched Zn-68 on a suitable target substrate. We present our initial experience on the production of Ga-68 via the  $^{68}\text{Zn}(n,p)^{68}\text{Ga}$  route using an 11 MeV cyclotron (Eclipse HP, Siemens). Enriched Zn-68 (98.2%) in the chemical form of  $\text{ZnCl}_2$  was electrodeposited onto a gold substrate using an acidic electrolytic solution (0.05M HCl). A thin target ( $E_{\text{in}}=11\text{ MeV}$ ,  $E_{\text{out}}=9.5\text{ MeV}$ ) was irradiated for 68 min at 20  $\mu\text{A}$ , obtaining 21.0 GBq of Ga-68 at EOB with a saturation yield of 2.1 GBq/ $\mu\text{A}$ . Following irradiation target material was dissolved with a mixture of 6M HCl/30%  $\text{H}_2\text{O}_2$  and chemical separation was performed in a commercial synthesizer (mini-AllinOne, Trasis) using a combination of ZR and TK200 resins (Triskem). Purification process was performed in approximately 30 min obtaining gallium in the chemical form of  $^{68}\text{GaGaCl}_3$  (~4 ml of Milli-Q water) with an overall yield >50% (non-decay-corrected). This research was supported by International Atomic Energy Agency (IAEA) CRP F22073-RC24380.



**IAEA-CN-310/279**

**In Vitro and In Vivo Evaluation of the Theranostic Radiopharmaceutical [<sup>197m</sup>Gh/gHg]Hg-Tcmc-Psma-617**

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Theranostic radiopharmaceuticals offer a unique opportunity to assess and monitor disease progression for personalized medicine. The success of radiotheranostics is highly dependent on the availability of drug complexes with very similar or identical chemical and biological properties. Ideally, radiopharmaceuticals would contain same-element isotope pairs (i.e., <sup>123</sup>I/<sup>131</sup>I) for pre- and post-treatment imaging and subsequent therapy. In this context, [<sup>197m</sup>gHg]Hg<sup>2+</sup> is among the few unique radiometals which form a same-element theranostic pair: the SPECT imaging isomer <sup>197m</sup>Hg ( $t_{1/2} = 23.8$  h, IT (91%),  $E(\gamma) = 134$  keV (I = 34%)) and the Meitner-Auger electron (MAE) emitting isomer <sup>197g</sup>Hg ( $t_{1/2} = 2.67$  d, EC (100%), 16.1 keV/decay) for therapy. In this study, we present the in vitro and in vivo evaluation of [<sup>197m</sup>gHg]Hg-TCMC-PSMA-617, the first [<sup>197m</sup>gHg]Hg<sup>2+</sup> peptide-bioconjugate evaluated in vitro and in vivo. A preliminary in vitro competition-binding assay demonstrated that the <sup>197m</sup>gHg-tracer inhibited the binding of [<sup>18</sup>F]-DCFPyL to PSMA on LNCaP cells in a dose-dependent manner ( $K_i = 19$  nM,  $n = 3$ ). A pilot biodistribution study (3.5 MBq) was performed in mice bearing LNCaP xenografts at 1 h after injection; with data analysis currently underway. Further in vitro tracer characterization (i.e., cell fractionation studies) is planned for the near future.



**IAEA-CN-310/280**

### **Challenges of Adapting $^{18}\text{F}$ -Fluoroestradiol PET Imaging for Routine Clinical Applications in Brazil**

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Fluoroestradiol F-18 ( $[^{18}\text{F}]\text{FES}$ ) is a PET imaging agent used to detect estrogen receptor (ER)-positive lesions in patients with recurrent or metastatic breast cancer. The Nuclear Technology Development Center (CDTN) is the first institute in Brazil to obtain market authorization from the Brazilian Health Regulatory Agency (Anvisa) for this radiopharmaceutical. This Abstract highlight challenges for production of  $[^{18}\text{F}]\text{FES}$  for clinical applications and the experience in initial patient scans. Manufacturing process and analytical method validations were concluded before clinical use, and GMP were fully implemented. The radiopharmaceutical was regularized by notification after meeting specific requirements, containing evidence of risk assessment referring to its safety, efficacy, and quality. Since Anvisa approval,  $[^{18}\text{F}]\text{FES}$  has been produced once a week by CDTN. Maximum synthesis yield was 21.2%, and radiochemical purity ranged from 95.1 to 99.8% (n= 21). One year after its first use,  $[^{18}\text{F}]\text{FES}/\text{PET}$  have demonstrated promising potential uses in visualizing ER-positive cancer lesions. Although there are strong barriers to widespread new radiopharmaceuticals in the country, additional studies will shed light on the uses of  $[^{18}\text{F}]\text{FES}$ . Further clinical studies and prospective multicentre trials will contribute to demonstrate the value of  $[^{18}\text{F}]\text{FES}/\text{PET}$  and to increase public access to this new technology.





## IAEA-CN-310/281

### **Translational Study to Determine the Diagnostic Efficacy of $^{68}\text{Ga}$ -Duramycin for Anthracycline Induced Cardiotoxicity**

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Early detection of anthracycline-induced cardiotoxicity (AIC) is possible through molecular imaging of cardiac cell death. In this study, duramycin, a well-known cell death marker was conjugated with bifunctional chelators to facilitate radiolabeling with Ga-68. MALDI-TOF showed mass peaks at 2470 Da and 2641 Da for NOTA-duramycin and DOTAGA-duramycin respectively. The  $^{68}\text{Ga}$ -duramycin with radiochemical purity of >99.9% showed favorable biodistribution in healthy rats with both renal and hepatobiliary clearance. To investigate the diagnostic potential of radiotracer for AIC, rat models were developed using 2.5 mg/kg/week doxorubicin for six weeks. The %ID/g of  $^{68}\text{Ga}$ -duramycin in the myocardium of treated rats was 5 times higher than control rats. The maximum myocardial uptake was noted in rats injected with three doses of doxorubicin (7.5 mg/kg). The radiotracer uptake pattern was in-concordant with the change in Troponin T and histopathological outcomes. Further, the positive caspase 3 expressions on IHC confirmed the myocardial apoptosis in response to anthracyclines administration. However, in clinical study, high blood pool activity was observed up to the imaging period of 3 h that masked the myocardial uptake. The increased blood pool was due to high plasma protein binding (>90%). Consequently, further investigations are warranted to improve image quality in the clinical setup.



**IAEA-CN-310/282**

### **Application of Data Science and Artificial Intelligence in the Productive Efficiency of Radiopharmaceuticals**

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The present research addresses the application of Data Science and Artificial Intelligence in the production processes of injectable radiopharmaceuticals in the Radiopharmacy Center, at IPEN-CNEN. Center of greatest relevance and production scale in Latin America and one of the main international ones, which is currently undergoing technological adaptation of its production processes.

Given the economic and therapeutic importance of the Nuclear Medicine market in global health systems, valued at USD 5,351.90 million in 2017, it is estimated that it will reach USD 9,981.30 million by 2026, growing at an annual rate. Average of 7.2% over the forecast period.

As a main objective, the study proposes to develop and obtain an innovative operating model applying automation, Artificial Intelligence resources and Data Science techniques (analytics), to make the routine of processes and operational indicators safer, predictable, effective and efficient.

This Doctoral study will provide the scientific community of medicine and nuclear technology with the benefits and returns of the application of artificial intelligence and data science in critical regulatory, diagnostic and therapeutic activities. And the results will lead to the Radiopharmacy Center, modernization, innovation and a differential in the practices of its core activities.

Therefore, it is expected to implement through these technologies the improvement in the critical stages of its production processes, combined with the digital trends of efficiency and good manufacturing practices.



IAEA-CN-310/283

### The Effect of Particle Size $[^{32}\text{P}]$ -Chromic Phosphate on the Stability of $^{32}\text{P}$ Radioisotopes in Silicone Patch

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Phosphorous-32 ( $^{32}\text{P}$ ) solution and silicone have been used for some time in keloid therapy and postoperative keloid therapy as prophylaxis respectively. The use of these modalities when combined together in form of a  $^{32}\text{P}$ -labeled silicone patch could be more effective for keloid therapy. In this project chromic phosphate ( $[^{32}\text{P}]\text{-CrPO}_4$ ) powder is used as an active ingredient in the manufacture of a  $^{32}\text{P}$ -labeled silicone patch. The purpose of this current study was to optimize the reaction condition for the preparation of stable (low release of  $^{32}\text{P}$ ) chromic  $^{32}\text{P}$ -phosphate ( $\text{Cr-}^{32}\text{PO}_4$ ) powder on a silicone patch. Stability of  $[^{32}\text{P}]\text{-CrPO}_4$  chromic trapped in a  $^{32}\text{P}$ -labeled silicone patch is depended on its particle size and uniformity. Chromic  $^{32}\text{P}$ -phosphate was prepared using a condensation method with an oxidation-reduction reaction. Chromic acid is reacted with  $[^{32}\text{P}]\text{-phosphoric acid}$  to obtain  $[^{32}\text{P}]\text{-CrPO}_4$  which was followed by reducing  $\text{Cr(VI)}$  to  $\text{Cr(III)}$  using  $\text{Na}_2\text{SO}_3$  as a reducing agent. The stirring speed and duration of sonification of the above-mentioned reactions were varied in order to obtain the optimum particle size of  $[^{32}\text{P}]\text{-CrPO}_4$ . The resulting  $[^{32}\text{P}]\text{-CrPO}_4$  powder was then characterized. Preparation of a  $^{32}\text{P}$ -labeled silicone patch was performed by mixing  $[^{32}\text{P}]\text{-CrPO}_4$  powder with liquid silicone which was then molded to form a  $^{32}\text{P}$ -labeled silicone patch. The stability of this patch was examined by measuring the percentage of  $^{32}\text{P}$  released from the patch under hydrolyzed conditions. This test was carried out by immersing the  $[^{32}\text{P}]\text{-labeled silicone patch}$  in three different solutions, water, saline, and hyamine for 3 consecutive days. Each day the activity of each solution was measured using a dose calibrator. The percentage of  $^{32}\text{P}$ -released from the  $[^{32}\text{P}]\text{-labeled silicone patch}$  was then determined. The release of  $^{32}\text{P}$  radioisotope under extreme conditions is expected to be extremely low ( $< 1,0\%$ ) in order to avoid damage to red blood cells. The results of this study show that the optimized reaction condition for preparation of  $[^{32}\text{P}]\text{-CrPO}_4$  was 300 RPM stirring speed and 10 minutes of sonication. These conditions gave  $[^{32}\text{P}]\text{-CrPO}_4$  powder with a size of  $919.4 \pm 168.8$  nm with a composition of  $\text{Cr (III)}$  of 47.43%,  $\text{P}$  10.28%, and 3.51%  $\text{Na}$ . Chromic  $[^{32}\text{P}]\text{-phosphate particles}$  were found to be polydisperse as its  $\sigma_g$  value  $> 1.25$  nm. The results of the stability test of the  $[^{32}\text{P}]\text{-labeled silicone patch}$  prepared from the above-mentioned  $\text{Cr-}^{32}\text{PO}_4$  powder showed that  $^{32}\text{P}$  was strongly trapped in silicone, not easily decomposed, and hydrolyzed as less than 0.2% of  $^{32}\text{P}$  was released under hydrolyzed conditions.



**IAEA-CN-310/284**

**Design of Feasibility Study for the Establishment of  $^{89}\text{Zr}$  Production – Tailored Approach to Introduce New Radiopharmaceuticals in a Developing Country**

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Establishing radiopharmaceutical production in a developing country is challenging, mainly in the economic aspect. A feasibility study provides an objective insight into many aspects of the feasibility of the idea of introducing new radiopharmaceutical. The feasibility study for establishing production of  $^{89}\text{Zr}$  is designed to include preliminary analysis, market research, technical feasibility analysis, economic analysis, review and analysis of all data, and feasibility conclusion. The preliminary analysis comprises a review of the application of  $^{89}\text{Zr}$ -radiopharmaceuticals in clinical trials and a review of the cancer statistics on a national level. The technical feasibility determination is based on the analysis of the technical capacities of the production site – University Institute of Positron Emission Tomography. The economic feasibility estimation comprehends financial and pharmacoeconomic analysis, which aims to assess the justification for implementing a new radiopharmaceutical in clinical practice. For this purpose, a cost-effectiveness analysis is performed.  $^{89}\text{Zr}$ -trastuzumab is selected as a subject of the pharmacoeconomic estimation, based on the results of the preliminary analysis:  $^{89}\text{Zr}$ -trastuzumab is one of the most common  $^{89}\text{Zr}$ -radiopharmaceuticals in clinical trials, and on the national level the breast cancer is the most common malignancy and the most common cause of death from cancers in the female population.



**IAEA-CN-310/285**

### **Routine Production of [<sup>18</sup>F]Alf-NOTA-Octreotide for PET Neuroendocrine Tumor Imaging at UNAM**

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Radiolabeled somatostatin analogues (SSTA) are the current gold standard for functional imaging of neuroendocrine tumors (NET), and Gallium-68 is by far the most widely used radionuclide to label SSTA for PET imaging of NET. In 2013 we implemented in Mexico the production of <sup>68</sup>Ga-labeled radiopharmaceuticals, mainly <sup>68</sup>Ga-PSMA-11 and <sup>68</sup>Ga-DOTA-NOC. The clinical demand of these tracers was so high that the limited loaded activity in addition to supply challenges of generators struggled our capacity to meet the demand. Given these facts, we looked for alternatives and in 2015 implemented the production <sup>18</sup>F-labeled-PSMA (PSMA-1007) and most recently, in 2021, the production of <sup>18</sup>F-labeled-Octreotide. Labeling of octreotide with F-18 is performed via chelation of the chemical precursor NOTA-Octreotide trifluoroacetate (ABX GmbH, Germany) with aluminum-<sup>18</sup>F]fluoride (<sup>18</sup>F]AlF) in a Trasis AllinOne synthesizer using a commercial PSMA-1007 cassette with minor changes. Synthesis of [<sup>18</sup>F]AlF-NOTA-Octreotide (<sup>18</sup>F]FOC) is now weakly produced in our facility with a radiochemical yield of 17-20% (ndc) and a radiochemical purity >98% as determined by analytical HPLC. Over 37 GBq of [<sup>18</sup>F]FOC have been obtained from a production run which have been used for up to 30 patients.

This research was supported by UNAM-DGAPA grant PAPIIT-IT200221.



**IAEA-CN-310/286**

### **Assessment of Mo-99 Radioisotope Supply Chain Using LEU in Iran**

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Tc-99m is the most important nuclear medicine radioisotope produced from the decay of Mo-99. Currently, Iran's demand for Mo-99 is 120 Ci per week. More than 90% of the Mo-99 in the world is produced via U-235 fission. The supply chain of this radioisotope includes the Uranium target supplier, the nuclear reactor, the Mo-99 processing facility, and the Mo-99/Tc-99m generator manufacturer. Investigation of the domestic existing facilities of Iran shows that its production is feasible inside the country. The present study focuses on the Mo-99 production chain in Iran and presents the appropriate radiochemical method. Uranium targets by irradiation capability in TRR were accepted as feed for processing facility. The Modified-AMOR process, which is a combination of AMOR and ROMOL processes, is identified as the appropriate method for the available U<sub>3</sub>O<sub>8</sub>-Al targets. The researches and the experimental activities are proposed based on this method.





**IAEA-CN-310/287**

**Evaluation of the produced  $^{177}\text{Lu}$ -specific activity via direct and indirect method using Tehran Research Reactor**

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The present research investigates the feasibility of producing the radionuclide Lutetium-177 ( $^{177}\text{Lu}$ ) at the Tehran research reactor, TRR.  $^{177}\text{Lu}$  with suitable nuclear decay characteristics, as well as favorable chemical behavior, is an ideal therapeutic radionuclide. Some  $^{177}\text{Lu}$ -containing radiopharmaceuticals are currently applied in the treatment of various cancers and many are under development being tested as clinical trials in Iran. The radionuclide  $^{177}\text{Lu}$  can be produced either directly by the  $^{176}\text{Lu}(n,\gamma)^{177}\text{Lu}$  reaction or indirectly by the  $^{176}\text{Yb}(n,\gamma)^{177}\text{Yb} \rightarrow \beta^- ^{177}\text{Lu}$  reaction. The irradiation yield of  $^{177}\text{Lu}$  in both production routes was experimentally determined for 14 days of irradiation at a thermal neutron flux of  $5 \times 10^{13} \text{ cm}^{-2} \cdot \text{s}^{-1}$  and was compared with the theoretical calculations. The effects of higher neutron fluxes, as well as a reduction in  $^{176}\text{Yb}$ -enrichment-percentage, on the produced activity/specific activity variations, were assessed theoretically using the MATLAB software. It was found that higher neutron fluxes led to higher activity. However, it has no impact on specific activity-fall-rates that happen two weeks after the end of the bombardment. In addition, a lower enrichment percentage of the target material that is utilized in the indirect method leads to a faster specific activity-fall two weeks after the end of the bombardment.



**IAEA-CN-310/288**

**Optimization of Cerium/Praseodymium Separation parameters with the aim of Production of Pure Beta-Emitter Radioisotope  $^{143}\text{Pr}$  for Therapeutic Application in Nuclear Medicine**

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In this study, an effective and efficient separation method for separating praseodymium from cerium was designed, optimized and successfully implemented. In this method, a special adsorbent for lanthanides (Ln-resin with dimensions of 100 to 150 microns) was used. Peristaltic pump and column with different dimensions (15 to 45 cm) were used to design the desired method. Systematic studies were performed to determine the eluent concentration of nitric acid (from 0.1 to 1 M). The oxidizing properties of cerium were exploited to differentiate the chemical behavior of these two lanthanides.  $\text{NaBrO}_3$  was used as an oxidizer. Because in the continuation of this research, the target material of enriched cerium will be used, it is necessary to recover cerium as well. Ascorbic acid was used for reduction of cerium. After changing the oxidation number of cerium, by changing the concentration of nitric acid, it is easily possible to wash the praseodymium and cerium separately and high resolution using the commonly available acids and low column pressures with an efficiency of over 99%. This method was successfully used to separate praseodymium-143 from irradiated cerium in the reactor, and also to separate  $^{143}\text{Pr}$  from the fission-produced lanthanides, the results of which will be presented in another report.



**IAEA-CN-310/289**

**Synthesis of Iodine-Sorbent with Applicability in Decontamination of the Gaseous Phase of Dissolution Stage of Fission-Molly Production**

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To produce Technetium-99 isotope from Molybdenum-99 radioactive decay and purifying the product of small-scale acidic target dissolution, the gaseous Iodine impurity has to be reduced to AN acceptable level. Solid adsorbents are used for this reason. One of the best adsorbents is based on Silver-Exchanged Mordenite. In this research, the synthesis procedure and characteristics of synthesized adsorbent have been discussed. To prepare solid adsorbent, spheric mordenite hollow crystals of about 10 micrometers and the Si/Al ratio of 5.2 were synthesized and granulated using a binding agent, stabilizer, and foaming agent. Prepared granules were silver exchanged. The silver content of the end product was evaluated 8.1 weight percent. Results from gaseous Iodine adsorption indicated that 99.2 percent of passing Iodine was adsorbed.



**IAEA-CN-310/290**

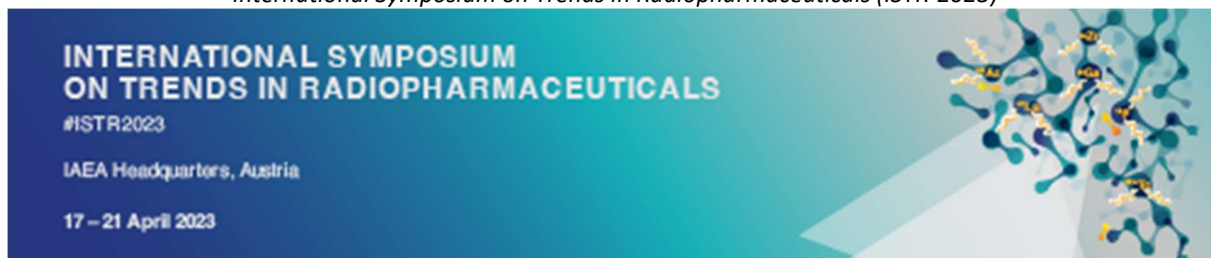
## **Production of Zr-89 Via Pressed Y-89 Powder Solid Target and Its Application to Biomolecule Labelling**

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Zr-89 is a new radioisotope introduced in the PET technology. Zr-89 has been produced by the bombardment of Y-89 with protons via Y-89 (p,n)Zr-89 reaction, with the help of Sumitomo cyclotron-18MeV. After the bombardment, Y-89 was dissolved in 6M HCl & separation of Zr-89 was done with final elution at 0.05M oxalic acid through hydroxamate resin. Radionuclide purity has been performed using multichannel Analyzer. The purified Zr-89 was chelated with DFO and found ~99% chelation efficiency. Based on the  $^{89}\text{Y}(p,n)^{89}\text{Zr}$  route, the production process for  $^{89}\text{Zr}$  on HM-18 cyclotron using 12 MeV proton had been developed. The solid target system of HM-18 cyclotron, Y- target was made by pressed target of the Y-89 powder and stacked over the engraved Platinum/Tantalum/Niobium coins.  $^{89}\text{Y}$  target was dissolved in 6M HCl solution. and radiochemical separation of  $^{89}\text{Zr}$  from target was achieved using ZR-resin (Ttriskem, Inc) was successful with approx 80% and the final  $^{89}\text{Zr}$  oxalate solution was pure with higher than 99% of radionuclidic purity. Both manual and automated process of purification were developed and optimized with almost equivalent recovery yield of 80%. The  $^{89}\text{Zr}$  oxalate was explored with DFO conjugation and labelling efficiency is more than 99%. The Synthesis of DFO-Sq-Rituxmab, and this modified mAb was used for radiolabeling with  $^{89}\text{Zr}$  Oxalate. The labelling efficiency was achieved more than 99% and radiolabelled conjugate was stable upto 80 hr post labelling. Produced  $^{89}\text{Zr}$  via  $^{89}\text{Y}(p, n)^{89}\text{Zr}$  was purified using Hydroxamate based solid phase media and isolated in the form of  $^{89}\text{Zr}$ -oxalate. The  $^{89}\text{Zr}$ -oxalate was chelated with modified mAb (Rituxmab) via DFO-Squaric acid linker and purified using size exclusion column (PD10 column). The radiolabelled mAb's quality assurance was performed and its in-vitro stability was analysed its chelation stability. The in-vivo studies were performed to study the pharmacokinetic as well pharmacodynamic profile in healthy Wistar rat at different intervals. The cyclotron produced  $^{89}\text{Zr}$  via  $^{89}\text{Y}(p, n)^{89}\text{Zr}$  was isolated in good radionuclidic purity and chelate with modified DFO tagged mAb (DFO-Sq-Rituxmab) in good yield with high specific activity. All the QC analyses (HPLC, iTLC,  $\gamma$ -well counter) were performed and qualify. The in-vivo studies were performed and bio-distribution among different organs at different point of time were analysed.

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IAEA-CN-310/291

### **Physicochemical Characterisation and In-Vitro Cytotoxicity Test on a Novel Biodegradable Microsphere Loaded with Samarium-153 and Doxorubicin for Chemo-Radioembolization of Liver Cancer**

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Liver cancer is the 6th most common cancer and the 4th leading cause of cancer death worldwide. Chemoembolization and radioembolization are both useful treatments for unresectable liver cancer. Recently, combination of chemotherapy and radiation therapy has shown a promising synergistic anti-cancer effect. Hence, this study aimed to develop a biodegradable microspheres formulation loaded with radioactive samarium-153 (Sm-153) and chemotherapy drug, Doxorubicin (Dox) for chemo-radioembolization of advanced liver cancer

10 mg of Dox and 215 mg of non-radioactive samarium-152-acetylacetonate were loaded into 150 mg of polyhydroxybutyrate-co-3-hydroxyvalerate (PHBV) using water-in-oil-in-water solvent evaporation method. The formulation (Dox-Sm-PHBV microspheres) was then sent for neutron activation using a 1 MW research reactor (TRIGA MARK II, General Atomics). The physicochemical properties, radioactivity, radionuclide retention efficiency and Dox release profile were analysed after neutron activation. In addition, in-vitro cytotoxicity effect of the Dox-Sm-PHBV microspheres was evaluated using HepG2 liver cancer cell line.

The Dox-Sm-PHBV microspheres had a mean diameter of  $33 \pm 1.05$   $\mu\text{m}$  (ranged 20-60  $\mu\text{m}$ ). The specific radioactivity was  $8.68 \pm 0.17$  GBq.g<sup>-1</sup>, or 177.69 Bq per microsphere. The Sm-153 retention efficiency was > 99% tested in both phosphates buffered saline (PBS) and human blood plasma over a duration of 624 hours. The cumulative release of Dox from the microspheres achieved  $50.62 \pm 2.01\%$  and  $65.21 \pm 1.96\%$  in PBS pH 7.4 over 672 and 984 hours, respectively. From the in-vitro cytotoxicity test, the Dox-Sm-PHBV microspheres achieved greater cytotoxicity effect on HepG2 cells ( $85.73 \pm 3.63\%$ ) than <sup>153</sup>Sm-PHBV ( $70.03 \pm 5.61\%$ ) and Dox-PHBV ( $74.06 \pm 0.78\%$ ) microspheres at 300  $\mu\text{g/ml}$  at 72 hours.

A novel formulation of a biodegradable PHBV microsphere loaded with both radioactive Sm-153 and Dox was successfully developed in this study. The Sm-Dox-PHBV microspheres fulfilled all the desired physicochemical properties of a chemo-radioembolic agent and achieved better cytotoxicity tested on in-vitro HepG2 cells. Further investigations are required to test the safety and synergetic anti-cancer properties using in-vivo animal models.





IAEA-CN-310/292

### **The Introduction of Novel Multipurpose Automated Module for Hospital Preparation of Theranostic Radiopharmaceuticals**

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The preparation of the small-scale radiopharmaceuticals for non-commercial purposes is a very important part of daily work in the hospital radiopharmacies. With the emergence of novel theranostic molecules for the management of neuroendocrine and prostate cancer patients in the last years also the demand for reliable automated synthesis modules for in-house preparation of PET and therapeutic radiopharmaceuticals (RPs) arose. Such synthesis modules enable lower radiation exposure to the operator, high reproducibility of the preparation in accordance to good practices, higher number of production runs if needed, and the ease of handling. Here we describe the introduction of  $^{68}\text{Ga}$ ,  $^{177}\text{Lu}$  and  $^{90}\text{Y}$  RPs into everyday clinical practice with multipurpose automated synthesis module iQS-TS. iQS-TS module was housed in ISO class 5 environment (lead-shielded isolator). Single use cassettes (ITM Garching, Munchen, Germany) were used for the preparation of variety of RPs.  $^{68}\text{Ge}/^{68}\text{Ga}$  generator (ITM) was eluted with 4.15 mL 0.05M HCl.  $^{177}\text{LuCl}_3$  n.c.a. (EndolucinBeta®) was purchased from ITM and  $^{90}\text{YCl}_3$  from Polatom (Poland). DOTATATE (50  $\mu\text{g}$ ) and PSMA-11 (20  $\mu\text{g}$ ) were radiolabelled with  $^{68}\text{Ga}$  using reagent set (ITM).  $^{177}\text{Lu}$  reagent set (ITG) was used for DOTATATE (200–600  $\mu\text{g}$ ) radiolabelling and was also tested for  $^{90}\text{Y}$  radiolabelling DOTATOC (200-600  $\mu\text{g}$ ). Process validation was performed with a series of three consecutive validation syntheses, followed by daily routine preparation. Quality testing of the final products was done in concordance with pharmacopoeial requirements and/or in-house validated analytical methods. DOTATATE and PSMA-11 were radiolabelled quantitatively with  $^{68}\text{Ga}$  (up to 1800 MBq) with radiochemical purities >92% (HPLC+TLC; n=526). On average, the d.c. radiochemical yields were 85 % with inevitable minor residual activity; predominantly found in sterile filter and waste. In case of  $^{68}\text{Ga}$  radiolabelling  $^{68}\text{Ge}$  breakthrough, radionuclidic purity, half time, ethanol content, bacterial endotoxins and sterility conform to PhEur requirements.  $^{177}\text{Lu}$ -DOTATATE (up to 28 GBq; n=61) and  $^{90}\text{Y}$ -DOTATOC (up to 20 GBq; n=3) were synthesised reproducibly with quantitative yield and radiochemical purity of > 97% (HPLC). iQS-TS automated synthesis module is a robust system for fast and convenient GMP-compliant preparation of theranostic RPs. When placed in an ISO 5 lead shielded isolator the environment is suitable for preparation of parenteral solutions and also offers an adequate radiation protection for the operator. Remotely controlled module with a syringe-driven processes enables fast and efficient radiolabelling ( $^{68}\text{Ga}$  in 16 minutes,  $^{177}\text{Lu}$  and  $^{90}\text{Y}$  labelling in 45 minutes). The system proved to be very reliable in more than 500  $^{68}\text{Ga}$ ,  $^{177}\text{Lu}$  and  $^{90}\text{Y}$  preparations for daily clinical use.





**IAEA-CN-310/293**

**Optimisation of selected Radiopharmacy services in a multidisciplinary Nuclear Medicine setting in South Africa**

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In Africa there is a shortage of radiopharmacists to support Nuclear Medicine service expansion.

This study investigated three radiopharmacy services at a tertiary hospital in South Africa: drug/radiopharmaceutical interactions/adverse drug reactions, inventory management and reasons for [<sup>18</sup>F]F-FDG wastage in PET.

In the ADR study, patients' medication details were recorded over a period of 10 weeks in 2020. DatinRad was used to identify potential drug/RP interactions and ADRs. In the inventory study a situational analysis in the Nuclear Medicine Department was conducted in 2020 using GPP guidelines; problem areas were identified and appropriate interventions were made. The daily operations in the PET facility were studied retrospectively from 2017 to 2019.

Patient medication histories for drug/RP interactions and ADRs were inadequate, but improved after researcher intervention. The current inventory management system in the Nuclear Medicine Department was poor. An independent demand inventory system was recommended. SA Rands 522,000 of [<sup>18</sup>F]F-FDG was wasted over the study period due to operational, patient preparation and appointment challenges, which can now be avoided.

All RP services were improved with relevant radiopharmacist interventions. Radiopharmacist roles are often underestimated and Nuclear Medicine patient services will be compromised by low radiopharmacist availability.



**IAEA-CN-310/294**

**Breast Tumor Specific  $^{99m}\text{Tc}$  Carbonyl Conjugates of Trimeric (D and L) Alanine-Katti Peptides—Radiolabeling and Preclinical Investigations**

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It is well-known that a variety of amino acids serve as important nutrients for the growth and proliferation of cancer cells. This results in increased demand from cancer cells for amino acids through upregulation of amino acid transporters which are over expressed on the surface of tumor cells. We herein present the utility of both the trimeric D- and L Alanine called as 'Katti Peptides' (See Figure 1), discovered in our laboratories [1,2] for radiolabeling with a SPECT imaging  $^{99m}\text{Tc}$ -Tricarbonyl probe.

Both D- and L-Trimeric Alanine (Katti Peptides) were prepared according to published procedures [1,2] and radiolabeled with Technetium-99m ( $^{99m}\text{Tc}$ ). Biodistribution studies were then performed in SCID mice bearing 4T1 breast cancer xenografts, to compare the in vivo kinetics of the radiolabeled Katti Peptides. Radiolabeling yield was >92% for both D- and L-Trimeric Alanine (Katti Peptides). Animal studies showed that both peptides exhibited fast in vivo kinetics and rapid renal excretion. Higher tumor:blood and tumor:muscle ratios at 60 min p.i. were observed for [ $^{99m}\text{Tc}$ ]Tc-D-trimeric Alanine peptide, in comparison to [ $^{99m}\text{Tc}$ ]Tc-L-trimeric Alanine peptide. The above results indicate that the Katti Peptides can be used as a new generation of tumor cell metabolisable peptides toward the development of SPECT imaging agents.



**IAEA-CN-310/295**

## **Dual Radiation and Immunotherapies through Green Nanotechnology of Mangiferin Functionalized $^{198}\text{Au}$ Nanoparticles—Production, Preclinical and Clinical Investigations**

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Irradiation of normal cells by ionizing radiation results in systemic effects by triggering many molecular signaling pathways. Recent evidence suggests that radiation therapies act as double-edged sword as they induce pro-survival signaling pathways, which are directly involved in inducing cell cycle arrest and promoting DNA repair, while others are engaged in suppressing apoptosis induction. A major complication of these cellular pathways is their power to act synergistically to protect cancer cells from the cytotoxic effects of radiation, ultimately causing radio and chemo resistance of cancers. It is therefore important to develop therapeutic approaches that would offer dual radiation therapy as well as immunotherapy—all in a singular therapeutic regimen. We have discovered that carrier-added mangiferin functionalized gold nanoparticles (MGF- $^{198}\text{Au}$ NPs) to be an effective immunomodulatory agent being able to target tumor microenvironment, transform pro-tumor macrophages (M2) into antitumor M1 phenotype while enhancing anti-tumor IL-12 cytokines. This lecture will highlight preclinical and clinical evaluations of immunotherapeutic MGF- $^{198}\text{Au}$ NPs nanoparticles for stopping the infiltrating aggressive tumor proliferating M2 macrophages to achieve effective dual radiation and immuno therapy. The overall implications of Green Nanotechnology of MGF- $^{198}\text{Au}$ NPs as a dual radiotherapeutic ‘nanoradio—immuno—pharmaceutical’ in oncology will be discussed.



**IAEA-CN-310/296**

### **Capturing the Theranostic Meitner-Auger Emitter Mercury-197m/g with Sulfur-Rich Macrocyclic Platforms**

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The recent interest in mercury radioisotopes, namely mercury-197m ( $t_{1/2} = 23.8$  h) and mercury-197g ( $t_{1/2} = 64.14$  h), has been recently awakened by their dual diagnostic and therapeutic nature which combines the emission of  $\gamma$ -rays suitable for SPECT imaging with a cascade of Meitner-Auger electrons exploitable for the treatment of metastatic tumours. However, the prospect to exploit the theranostic potential of mercury-197m/g is presently hindered by the shortage of chelating agents capable of firmly ligating them to a tumour-seeking vector. In the present contribution, we describe our effort to address this challenge by exploring a series of chemically tailored macrocyclic platforms functionalized with sulfur-containing side arms.

Through a combination of fundamental coordination chemistry studies, radiolabelling and *in vitro* stability assays, we demonstrated the utmost role of the S in Hg coordination and that subtle modifications of either the pendant arms or the polyazamacrocyclic backbone have a drastic impact on Hg binding ability. Among the series of investigated ligands, S-containing chelators based on cyclen ring revealed to be viable candidates for nuclear medicine applications due to their ability to form stable complexes in human serum. Our results pave the way to the *in vivo* application of mercury as a theranostic radiometal when bound to a tumour-seeking vector.



**IAEA-CN-310/297**

### **Deep Learning-Based Model for Internal Dosimetry at Patient-Specific Level**

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Cancer is now the second most common cause of death globally, second only to cardiovascular diseases. Ionizing radiation is one of the main tools for cancer treatment. In particular, nuclear medicine has significantly impacted diagnosing and treating this type of disease. The advance of the new integrated methodology called theranostics, which allows imaging at the same time as the treatment is being carried out, has opened up a wide range of possibilities and potentialities, particularly in improving the capacity for planning and subsequent evaluation of treatments.

In this context, different methods have been developed for estimating the patient's dose, including Monte Carlo simulations, point kernel convolution (DPK), S-factors, etc. However, these models have specific limitations, such as the calculation time or the considerations to be made on the activity distribution, etc. The development of models for internal dosimetric based on Deep Learning has shown to have the ability to solve the problem of calculating the absorbed dose at a patient-specific level using metabolic images (SPECT, PET) and anatomical images (CT).

This work will show advances in developing patient-specific calculation models using artificial intelligence techniques applied to image segmentation and patient-specific dosimetric calculation in nuclear medicine procedures with beta- and alpha-emitting radioisotopes.



**IAEA-CN-310/298**

**Establishment of the African Association of Radiopharmacy: Significant Steps Towards Improving Radiopharmacy Services in Africa**

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Establishment of African Association of Radiopharmacy (AfrAR) is anticipated to play significant role in pushing forward the meaningful development of Radiopharmacy services, in Africa. Radiopharmacy is one of the vital milestones to ensure the momentous developments of nuclear medicine services. Despite the fact the African radiopharmacy is unacceptably underdeveloped. The AfrAR has been established to address this imperative challenge. The objective of this study is to show the significance of establishing AfrAR & its positive impacts on improving radiopharmacy. This descriptive observational study was made based on the meticulous in depth analysis of the objectives of establishing the AfrAR from its formation documents & examine its impacts on improving the radiopharmacy services in Africa. On the basis of the results obtained from this study thorough discussions will be conducted focusing on the establishment of AfrAR & its impacts on improving African radiopharmacy services along with the complementary roles of the IAEA synergizing it.





## IAEA-CN-310/299

### **Enhancing the Life Expectancy of Cancer Patients by Setting up the First Radiopharmaceutical Production Facility in Sri Lanka**

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Cancer is a major health burden in Sri Lanka. 29,604 new cases and 16,691 cancer deaths were recorded in 2021. Further, 81 new cases and 45 deaths were recorded daily. Trend will increase 23% every year till 2030. Sri Lanka imports  $^{18}\text{F}$ -fluorodeoxyglucose (FDG) for PET/CT scanning of cancer patients from India. A dose of 3400 mCi (cost 3000 USD) purchases and it decays to 100 mCi at the destination, which is sufficient for 10 cancer patients. FDG cost per patient is 300 USD. 97% of FDG worth 2600 USD is lost during transportation. Sri Lanka spends about 0.54 M USD annually to import FDG to treat 1,500 patients. It is estimated that 35,000 cancer patients needed PET/CT scans per year. Establishing a cyclotron based radiopharmaceutical production facility is one of the country's priorities. Sri Lanka Atomic Energy Board is arranging the funding (about 7.5 M USD) and land. IAEA has approved 0.15 M Euros for this project through TCSRL6037/38. Initially, it will produce 1 Ci of FDG a day to treat 10 patients and increase to about 30 patients per day. Through the project, the life expectancy of cancer patients would be increased while reducing the FDG cost to 85 USD.



**IAEA-CN-310/300**

### **Status of the Cyclotron Driven LARAMED Project at INFN Legnaro National Laboratories**

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LARAMED (acronym for LAboratory of RADionuclides for MEDicine) is a research facility, currently under completion at Legnaro National Laboratories (INFN-LNL), equipped with one of the few high-energy (70 MeV), high-current (750  $\mu$ A max, dual exit) proton cyclotron currently installed worldwide [1]. LARAMED project has been conceived, since the beginning, to meet a double scientific and technological goal. To explore, first, alternative routes for a more efficient production of radionuclides (RNs) playing already a key role in nuclear medicine (NM), as well as to uncover new routes for producing novel RNs having potential interest for medical applications. Ultimately, the main scope of this project is to establish a facility at LNL for producing medical RNs with the characteristics necessary to ensure their use in clinical practice.

LARAMED has been planned with a dedicated high intensity beamline, as well as with a dedicated, low-current, beamline for nuclear cross section determination useful for evaluating new routes for RNs production, e.g., the theranostic ones. A key activity in LARAMED will be also devoted to the development of advanced technologies for assembling high-power targets capable of sustaining and dissipating intense heat loads. A significant number of RNs is expected to be produced at LARAMED, such as, e.g.,  $^{64}/^{67}\text{Cu}$ ,  $^{44}/^{47}\text{Sc}$ ,  $^{155}\text{Tb}$ .

An overview about the facility status and the parallel research programs carried out by the LARAMED research group in the last years is the purpose of this presentation.



## **IAEA-CN-310/301**

### **A European Network Dedicated to Targeted Alpha Therapy (TAT) with Astatine-211 – NOAR COST Action**

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COST project Network for Optimized Astatine-labeled Radiopharmaceuticals (NOAR) brings together European and international laboratories of excellence, Astatine-211 production centers, hospitals, industry and patient associations thus covering the entire innovation value chain.

The main goal is to demonstrate that Astatine-211, promising radionuclide used for targeted alpha therapy (TAT), can be established as the standard for the treatment of cancerous tumors.

The project implementation includes: European network of Astatine-211 treatment nodes, identification of vectors, defining better therapeutic strategies through internationally harmonized protocols, exchange of good practices for production and quality control.

The results so far show that the projected goals through the 5-working groups have already generated interest in the development of the production of radiopharmaceuticals, dosimetry, preclinical and clinical research and through strong partnerships ensures a critical mass that will raise the capacity for further collaboration and expertise to establish a worldwide network dedicated to Astatine-211.

The important contribution is to train a new generation of early career researchers and PhD students, promoting interdisciplinary competences through international mobility.

The COST-NOAR action will ensure efficient interdisciplinary, cross-sectoral and international exchange of knowledge, effective networking within all stakeholders, promoting the medical application of Astatine-211, significantly increase fundamental and applied knowledge of TAT technology.



### **IAEA-CN-310/303**

#### **We Are Explorers in Radiochemistry Space: Adventures in $^{11}\text{C}$ -Radiochemistry, Automation and Artificial Intelligence**

Peter Scott

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With the emergence of theranostics and the expected impact of artificial intelligence on our work, it is an exciting time to be in the field of nuclear medicine. For 70 years, the Division of Nuclear Medicine at the University of Michigan has been developing radiopharmaceuticals for diagnostic imaging (e.g. positron emission tomography, PET) as well as radiotherapy, and translating them for clinical care. This keynote presentation will give an overview of both the clinical and basic research being conducted by our division today, including development of new methods for labeling PET imaging agents with carbon-11 (including novel strategies for  $^{11}\text{C}$ -methylation, copper-mediated radiocyanation, and  $^{11}\text{C}$ -carbonylation), and introduce the latest  $^{11}\text{C}$ -labeled radiopharmaceuticals being developed and translated at our academic medical center (including  $[^{11}\text{C}]$ butyrate for keto body imaging and  $[^{11}\text{C}]\text{COU}$ , a new radiotracer for quantifying monoamine oxidase activity via a trapped metabolite approach). The presentation will conclude imagining the future impact of artificial intelligence on the radiopharmaceutical sciences at every step from bench to clinic.



**IAEA-CN-310/304**

### **Novel $^{177}\text{Lu}$ Exosome-Based Nanoprobes for Theranostic in Cancer**

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Exosomes are lipid-based nanoparticles naturally secreted by cells in terms of intercellular communication. Their physicochemical features, highlighting nanometer size, negative surface charge and lipid bilayer structure, along with their inherent ability to target the tumor microenvironment and the efficient exo-labeling strategies already published support their use as novel nanoplatforms for cancer theranosis.

Exosomes were isolated from milk and characterized by TEM, DLS, NTA and Zeta-potential. Then, radiolabeling of the nanoparticles with  $^{177}\text{Lu}$  was performed by passive entrapment in the lipid bilayer, at  $95^{\circ}\text{C}$  for 30 min and  $\text{pH}=5$ . Integrity of exosomes after the labeling was evaluated by DLS, NTA and protein quantification. Radiolabeling efficiency, purity and stability of the nanotracer were established by radio-TLC (citrate buffer, silica paper).

Physicochemical characterization confirmed the integrity of the nanovesicles after labeling, which leads on a  $33.99 \pm 2.72\%$  radiochemical yield and  $>95\%$  purity, and a low stability of the radiotracer.

We have evaluated for first time the  $^{177}\text{Lu}$  labeling of exosomes to develop a novel and natural theranostic tool. The low stability of the labeling highlights the need for the use of chelators for radiometal fixation.



IAEA-CN-310/306

**Synthesis, Characterization, and in Vitro Tumor Assay of the Fac-[M(CO)<sub>3</sub>-N', N'''-Dibenzo-Diethylenetriamine] (M= Re and <sup>99m</sup>Tc)**

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[<sup>99m</sup>Tc]Technetium is still an important radioisotope for nuclear medicine because of its physical characteristics, such as a half-life of 6.01 h and gamma emission of 140 keV, and the chemicals, as multiples coordination and oxidation numbers, allowing the use of several chelator structures. Since technetium doesn't have stable isotopes, all chemical characterization needs to be done using a rhenium analog for further comparison by a chromatographic method. This work aims to prepare Re and <sup>99m</sup>Tc complexes based on triamine and tricarbonyl ligands under thermal and microwave heating and evaluate the uptake of the radioactive compound in tumor cell culture as a candidate for tumor diagnostic imaging agent. The [ReBr(CO)<sub>5</sub>] was reacted with the ligand ((N', N'''-dibenzo)diethylenetriamine (L) to give the standard [Re(CO)<sub>3</sub>(L)]Br, which was characterized by spectrometric and spectrophotometric analysis. The precursor [<sup>99m</sup>Tc(H<sub>2</sub>O)<sub>3</sub>(CO)<sub>3</sub>]<sup>+</sup>, was prepared by reaction of <sup>99m</sup>TcO<sub>4</sub><sup>-</sup> in a vial containing Na<sub>2</sub>CO<sub>3</sub>, NaK-tartrate and NaBH<sub>4</sub>, at 75 °C. The fac-[<sup>99m</sup>Tc(CO)<sub>3</sub>(L)]<sup>+</sup> was prepared by the addition of the precursor in a vial containing the ligand ((N', N'''-dibenzo)diethylenetriamine in a phosphate buffer 0.01 M (PB) solution; the vial was heated at 75 °C by 30 min or by irradiation in a microwave. Radiochemical yield (RY) and radiochemical purity (RP) was accessed by planar chromatography and by HPLC (Reverse Phase-C18 column, and aqueous TFA 0,05 % and acetonitrile TFA 0,05 % solution, in a mobile gradient phase). <sup>99m</sup>Tc(H<sub>2</sub>O)<sub>3</sub>(L)<sup>+</sup> and radiochemical impurities (RI) were separated by preparative chromatography for further analysis. Electrophoresis was performed in Whatman n°1 paper and PB as electrolyte (50 mM, pH 7.4), at 275 V. LogP was accessed in n-octanol / PB system. Radiocomplex stability was accessed in 0.01 M L-cysteine and 0.01 M L-histidine PB solution at 37 °C during 6 h. Cell uptake study was performed by addition of fac-[<sup>99m</sup>Tc(CO)<sub>3</sub>(L)] in culture medium containing 5x10<sup>5</sup> murine melanoma cell B16F10, and incubation for 15, 30, and 60 min at 37 °C. The fac-[Re(CO)<sub>3</sub>(L)]Br was obtained in 38 % yield, IR showed ν(CO) = 2017, 1909 and 1890, mass spectrometry gave 554.14441 (m/z) against calculated 554.14538 (m/z); UV, <sup>1</sup>H-NMR and <sup>13</sup>C-NMR are in agreement with the expected for the compound. RY for [<sup>99m</sup>Tc(H<sub>2</sub>O)<sub>3</sub>(CO)<sub>3</sub>]<sup>+</sup> was 95 %, and for the fac- [<sup>99m</sup>Tc(H<sub>2</sub>O)<sub>3</sub>(L)]<sup>+</sup>, by thermal heating, the RY was 90 %; however, RP was 59.1 %, based on the HPLC retention time for Re standard, and three radiochemical impurities (RI) were observed at 3.5 min = 3.9 % (<sup>99m</sup>TcO<sub>4</sub><sup>-</sup>), 11.5 min = 13.3 % (RI1) and 12 min = 24.6 % (RI2). Using microwave, fac-[<sup>99m</sup>Tc(CO)<sub>3</sub>(L)]<sup>+</sup> was obtained in RY = 97.3 % and RP = 81.0 %, with RI1 = 4.9 % and RI2 = 10.9 %. The three isolated radiochemical species of <sup>99m</sup>Tc(CO)<sub>3</sub>-complex (L, RI1, and RI2) moved to the cathode, confirming the positive charge, while LogP (n=3) was 1.5±0.03 for fac-[<sup>99m</sup>Tc(CO)<sub>3</sub>(L)]<sup>+</sup>; 0.4±0.4 for fac-[<sup>99m</sup>Tc(CO)<sub>3</sub>(RI1)]<sup>+</sup> and 0.9±0.03 for fac-[<sup>99m</sup>Tc(CO)<sub>3</sub>(RI2)]<sup>+</sup>. The fac-[<sup>99m</sup>Tc(H<sub>2</sub>O)<sub>3</sub>(L)]<sup>+</sup> was stable for 3 h in L-histidine, L-cysteine, and PBS; the impurities RI1 and RI2 are stable less than 1 h. Uptake of fac-[<sup>99m</sup>Tc(H<sub>2</sub>O)<sub>3</sub>(L)]<sup>+</sup> in tumor cells was 4.2±0.1 % at 15 min, decreasing to 3.8±0.1 at 60 min; IR 1 uptake was 0.6±0.1 during all time, and IR 2 was not evaluated by its instability. fac-[Re(CO)<sub>3</sub>(L)]Br was satisfactorily obtained and structurally characterized. The Re complex was helpful to determine, within three technetium complexes formed, that the main of them match in HPLC retention time, assuming that both have the same structure. Furthermore, the isolated radioactive species showed different physicochemical characteristics, and the fac-[<sup>99m</sup>Tc(CO)<sub>3</sub>(L)]<sup>+</sup>, showed in vitro the potential for the development of a radiopharmaceutical for tumor imaging.





**IAEA-CN-310/308**

### **18F-PSMA 1007 Production in a Cyclotron Facility: A Brazilian Experience**

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Radiopharmaceuticals are indispensable to assisting in the diagnosis and therapeutic management of patients affected by prostate cancer. In Brazil, prostate cancer is the second most common among men; therefore, the search for this radiomarker is growing. Nuclear medicine (NM) uses these drugs in imaging tests such as positron emission tomography (PET/CT) and single photon emission computed tomography (SPECT) to get morphofunctional images that are possible to evaluate and quantify pathological processes in a non-invasive manner. In this case, a radiopharmaceutical of great importance is the prostatic specific membrane antigen (18F-PSMA-1007), which can identify tiny lesions and metastatic tumours. The radioisotope - 18F - was produced by a cyclotron via the  $^{18}\text{O}(p,n)^{18}\text{F}$  reaction and the synthesis of the referred radiopharmaceutical was through nucleophilic substitution, using the PSMA-1007 precursor in the Trasis All in One synthesis module. Briefly, the synthesis consisted of 18F purification using a QMA column and 18F elution with TBA, followed by a drying step. The precursor was added to the reactor vial and labelled with 18F. The reaction mix was purified using a sequence of two different cartridges (C18 and a cation exchange column) and eluted with ethanol 30%. Finally, it was diluted in PBS with sodium ascorbate and submitted to sterilized filtration in a final volume of 20 mL with activities of about 3700 MBq/mL.



**IAEA-CN-310/309**

### **A Multimodality Training Program Focusing on the Qualification of Professionals for Radiopharmacy: The Medicine School of the University of São Paulo Case**

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The growth in radiotracer or radiopharmaceuticals uses for biomedical research, medical diagnosis or therapy has demanded the qualification of professionals to work in research laboratories, as well as in industrial, centralized, and hospital radiopharmacy. For each activity, in addition to basic acknowledgments about radiation science, some specific issues must be considered. For example, for training focusing on research activities, organic and inorganic applied to radiopharmaceuticals preparations, cells and animal handling, imaging acquisition, processing, and interpretation, must be included; considering the training the work in centralized or hospital radiopharmacy, issues like fundamental of good laboratory and good manufactory practices (GLP and GMP), aseptic preparation processes, physicochemical and biological controls, data manage, etc., must be considered. To cover the demands for the qualification of professionals in radiopharmaceutical and molecular imaging science, we developed at the Medicine School of the University of São Paulo different training strategies or programs. Practical training has three admission ways: undergraduate students from different areas start training by scientific initiation, a program allowing two years of practice activity involving a basic research project; graduates in chemistry or pharmacy can access the one-year program (1,700 h) of practical training involving routines of the hospital ou centralized radiopharmacy, furthermore the development of project involving new kit formulation or optimization of quality control procedure; finally, the third admission process is related to the master or PhD post-graduation programs, in the areas of neurology, oncology or radiology, focusing radiopharmaceuticals development or application. To support these practical training programs, students have access to lecture presential or webpages covering at least 15 topics, in different deep, depending on class categories. Regular programs are the post-graduation course: 1) Fundamentals of radiopharmacy: from research to applications with 15 issues and 90 h of studies, covering bases in nuclear physics and general aspects of radiopharmaceuticals science; 2) Radiopharmacy and Molecular Imaging Practices, a 60 h of practical activities on radiolabeling molecules, in vitro and in vivo studies, and imaging processing. In addition, for undergraduates, we offer the Winter School of Radiopharmacy and Radiochemistry, which during six years was a presential activity allowing no more than 70 attendees per year; exchange the activity, in 2022, to a virtual edition, it allowed the participation of 472 people including students speaking Portuguese from countries others than Brazil. This structure stimulates undergraduate students to be involved with radiation science and allows specialization students to move to the post-graduation program or to work in commercial radiopharmacy.



## **IAEA-CN-310/311**

### **Strengthening Capabilities for Non-clinical and Clinical Trials of New Radiopharmaceuticals for Medical Use in Brazil**

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During the last decades, Brazil has seen a consistent growth in the use of radiopharmaceuticals. Non-clinical and clinical trials are essential to support the development of new radiopharmaceuticals. However, the lack of harmonized non-clinical protocols to support clinical tests and few trained human resources remain an obstacle to overcome. The aim of this project is to contribute to the development of new radiopharmaceuticals for medical use in our country by establishing harmonized non-clinical and clinical trials based on IAEA and international standards. The project encompasses outlining harmonized procedures/protocols to introduce new radiopharmaceuticals and bringing together different institutions in the country to address the non-clinical requirements from the regulatory perspective. In this regard, three locally coordinated workshops were successfully completed. The workshops were joined both in-person and virtually by participants from all over the country, and even from other countries in Latin America. In addition, an e-learning module is ready to be issued for training. Both opportunities will contribute to compile harmonized protocols that can be helpful to guide non-clinical tests and address regulatory questions. Finally, we would like to highlight that our institutions already contributed to the introduction of at least two new radiopharmaceuticals in Brazil: [ $^{18}\text{F}$ ]PSMA and [ $^{18}\text{F}$ ]FES.



IAEA-CN-310/312

### **Toward Understanding $^{225}\text{Ac}^{3+}$ Radionuclide Bonding Properties within Radiopharmaceuticals: The Study of $\text{La}^{3+}$ Homologues**

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Much attention has recently been paid to the development of  $^{225}\text{Ac}^{3+}$ -labeled radiopharmaceuticals for the targeted alpha therapy of cancer. Radiopharmaceuticals often consist of inorganic or organometallic compounds which are predominantly administered via intravenous injection. Therefore, there is great deal of understanding the stability of such radiopharmaceuticals in real close to physiological conditions. The study of  $\text{La}^{3+}$ -coordinating compounds is considered as an important homolog for extrapolating the knowledge of the lanthanide's chemistry to the  $^{225}\text{Ac}^{3+}$ -labeled radiopharmaceuticals. In particular, we aim to understand relations between bonding properties and bond stability of such compounds. In this work, three  $\text{La}^{3+}$ -coordinating compounds, LaDOTA, LaMACROPA and LaPSMA, have been prepared and characterized. We measured La L2-edge high-energy resolution X-ray absorption spectra (HR-XANES) at the Synchrotron Laboratory for Environmental Studies (SUL-X) beamline and La L3-edge extended X-ray absorption fine structure spectra (EXAFS) at the INE beamline at the KIT light source. Moreover, we also performed electronic structure calculations based on Density-Functional Theory (DFT) to simulate X-ray spectra and to derive the bonding interactions between  $\text{La}^{3+}$  and the ligands via metrics such as the Energy Decomposition Analysis (EDA) and Quantum Theory of Atoms in Molecules (QTAIM). This study provides us with more insights into the bonding properties of the  $\text{La}^{3+}$  ion, which will be particularly important in the pursuit of stabilizing the  $^{225}\text{Ac}^{3+}$  homologue.

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**IAEA-CN-310/313**

**Prevention and Treatment of Unintended Dose: From Safer Therapies to Accident Preparedness**

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Any unintentional radiation dose to the body presents potential safety concerns, particularly in the case of internal contamination with radioactive material. For researchers, technicians, radiopharmacists, and other personnel involved in the production, distribution, and preparation of medical isotopes, there is always the possibility of accidental exposure even with the most rigorous safety measures in place. Particularly in the case of therapeutic alpha-emitters, such an exposure can lead to a substantial internal dose in highly radiosensitive organ systems in the body.

We are developing a new oral chelating agent that has shown exceptional safety and potent efficacy for removal of actinides throughout preclinical studies. The US FDA has approved the IND application and the Phase 1 clinical trial begins Q4 2022. If approved, this chelating agent would offer a new frontline treatment for accidental exposure to radioactive material, available to carry and self-administer in a convenient pill form. Additional applications include methods to improve the safety of therapeutic radiopharmaceuticals for patients undergoing such treatment.



IAEA-CN-310/315

**Coordination, Radiolabeling and Kinetic Inertness of the Theranostic Radiometals Mercury-197m/g with p-SCN-Bn-TCMC-PSMA-617**

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Theranostic radiometals such as mercury-197m/g ( $^{197m}\text{gHg}$ ,  $t_{1/2} = 23.8 \text{ h}/64.1 \text{ h}$ ) continue to attract interest in the nuclear medicine community as their incorporation into radiopharmaceuticals have the potential to simultaneously image (diagnostic, gamma-rays) and treat (therapeutic, Meitner-Auger electrons [MAE]) cancer, using the same drug construct.<sup>1</sup> The literature surrounding MAE therapy is limited, particularly  $^{197m}\text{gHg}$ -based radiopharmaceuticals. This is because the commonly utilized chelators in metal-based radiopharmaceuticals (e.g. DOTA) contain hard donor groups which do not suit the coordination requirements of the soft  $\text{Hg}^{2+}$ . To better match the coordination chemistry of  $\text{Hg}^{2+}$ , p-SCN-Bn-TCMC was chosen for initial testing with this radiometal, as the amide arms provide a soft donor set. Non-radioactive complex formation, stability and geometry were investigated using nuclear magnetic resonance spectroscopy and mass spectrometry. Quantitative  $^{197m}\text{gHg}$  radiolabeling ( $> 90\%$  RCY) of p-SCN-Bn-TCMC was achieved at  $80 \text{ }^\circ\text{C}$  after 1 hour up to a ligand concentration of  $10^{-7} \text{ M}$ . The formed  $^{197m}\text{gHg}$  complex displayed a high kinetic inertness when tested against glutathione and human serum. Considering these promising properties, p-SCN-Bn-TCMC was conjugated to prostate-specific membrane antigen (PSMA-617)<sup>2</sup> to evaluate the first in vitro targeted  $^{197m}\text{gHg}$  radiopharmaceutical against prostate cancer. The bioconjugate labeling and competition assays demonstrated promising results for future studies.





**IAEA-CN-310/316**

### **Medical Radioisotope Production Technology Development in Armenia**

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Research on the production of medical radioisotopes in Armenia began in the second half of the 2000s at the A. I. Alikhanyan National Science Laboratory (Yerevan Physics Institute). Initially, a linear electron accelerator with an electron energy of up to 40 MeV was used for this purpose. The technology of photoproduction of Tc-99m and I-123 has been developed.

Research on the development of technology for the production of radioisotopes on cyclotrons began in 2013. At the end of 2019, the IBA C18 cyclotron was launched at the Radioisotope Production Center near the A. I. Alikhanyan National Science Laboratory (Yerevan Physics Institute).

At present, the activity is mainly focused on the cyclotron technique. Technologies for the production of Tc-99m, Ga-68, Ga-67, and Cu-64 with solid targets are being developed. Automatic and remotely controlled systems for the production of radioisotopes are being developed, as well as new target holders with highly efficient cooling for the production of higher activities.



IAEA-CN-310/317

## CANDU Role in Strengthening the Radioisotope Supply Chain

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Ontario Power Generation's (OPG's) 10 Commercial CANDU reactor units are responsible for generating about 60% of Ontario's electricity needs. In addition to providing low-cost, safe, reliable, and clean energy to 14.8 million Ontarians every day, OPG has also been reliably irradiating targets for the production of radioisotopes for over 50 years. Reactor reliability, high neutron flux, online fueling and capacity to produce in high quantities make power reactors an ideal source of neutrons for large scale radioisotope production. The predictable and reliable nature of commercial reactors enable dependable supply chains for some well established isotope markets (such as Cobalt-60), however there is opportunity to expand offerings to other isotopes markets providing greater stability to supply chains for decades to come. In terms of existing and well-established isotope markets, OPG produces and sells 50% of the world's supply of Cobalt-60, a critical medical isotope used in medical radiotherapy to treat cancer, in medical device sterilization, and in food production. About 40% of the world's single-use medical devices, such as syringes, gloves, implants and surgical instruments, are irradiated and sterilized with Co-60. Recent advancements in target delivery technology have made online irradiation and harvesting more effective and efficient, expanding the scope of radioisotopes that can be made available to the market through CANDU reactors. Laurentis Energy Partners (Laurentis), pending regulatory approval, will produce a stable supply of Molybdenum-99, a critical life-saving isotope, from Darlington Nuclear Generating Station, for Canada and internationally. Laurentis leads this effort, in collaboration with OPG (as the irradiator) and BWXT. BWXT will utilize its newly designed proprietary generators, called NeuCap1, to process the Molybdenum-99 into Technetium-99m, the final product that will be used in diagnostic imaging. Darlington Nuclear will be the only source of Molybdenum-99 in North America, ensuring a stable domestic supply of this critical product. In addition to having the ability to irradiate targets online and in the core, CANDU safety and recycling processes provide important isotopes, such as tritium, a nuclear by-product harvested through heavy water detritiation. Tritium is a radioactive form of hydrogen that occurs both naturally and as a by-product of the operation of nuclear reactors. Once thought of as waste, it is now seen as a strategic asset, valuable to other sectors including health care and high tech. Advancements in nuclear by-product processing technologies are creating additional opportunities to reduce, reuse and recycle products that are needed for, or result from, the nuclear fission process. The reliability of OPG's CANDU reactors and expanding the breadth of ways that isotopes can be generated will be a key component to strengthening the radioisotope supply chain for the coming decades.



**IAEA-CN-310/318**

### **Cyclotron Produced Gallium-68 chloride $[^{68}\text{Ga}]\text{GaCl}_3$ as an Alternative to $^{68}\text{Ge}/^{68}\text{Ga}$ Generators**

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The  $^{68}\text{Ga}$  isotope is usually eluted from the  $^{68}\text{Ge}/^{68}\text{Ga}$  generator and is therefore readily available in PET (Nuclear Medicine) laboratories which do not have a cyclotron in place. The characteristics of the  $^{68}\text{Ga}$  isotope that it possesses make it a desirable radionuclide for PET diagnostics and the first widely available PET radioactive metal ion for routine use worldwide. Due to serious disadvantages of  $^{68}\text{Ge}/^{68}\text{Ga}$  generators, such as a very high purchase cost, short expiry date of the generator, low activity of the obtained isotope, low availability on the market and the need to keep a break between successive elutions, the number of PET studies with the use of  $^{68}\text{Ga}$ -based radiopharmaceuticals do not meet the market demand. The developed method of obtaining  $[^{68}\text{Ga}]\text{GaCl}_3$  via a solid target technology in a medical cyclotron at the VOXEL S.A. Radiopharmaceuticals Production Center in Kraków, in quality compliant with the requirements of the European Pharmacopoeia leads to obtain much greater activities with not worse quality. This may be an attractive alternative to  $^{68}\text{Ge}/^{68}\text{Ga}$  generators and in the future, by increasing the availability of the  $^{68}\text{Ga}$  isotope, may contribute to changing the cancer diagnosis strategy.



**IAEA-CN-310/319**

### **Advancing Nuclear Imaging of Infection: A South African Initiative Using Gallium-68-Functionalized Peptides – An Experience Report**

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About 50 years ago Nuclear Medicine has made its first mark in history using a radiopharmaceutical to vitalize infection. Nowadays, the diagnostic toolbox of clinical routine may include metabolic imaging using [18F]FDG or [67/68Ga]citrate, imaging host response to infection using radiolabeled blood elements, or radiolabeled antibodies. However, the initial diagnosis or monitoring response to antimicrobial therapy can be intricate due to the limited properties of the latter radiopharmaceuticals to decipher any sterile inflammatory processes from active infection. On the other hand, peptide-based radiopharmaceuticals have emerged as innovative, valuable, and often more-selective tools allowing for more precise targeted imaging strategies, which now also includes better strategies to localize infection.

To this end, in the past decade, Nuclear Medicine in South Africa has created a noticeable footprint in literature by applying [18F]FDG-PET or [67/68Ga]citrate-SPECT/PET imaging (and other such techniques) to diagnose and better understand complex infectious diseases, such as tuberculosis, HIV/AIDS, or Malaria. Also, the authors were instrumental in driving the PET-based radiopharmaceutical development of an antimicrobial peptide fragment of ubiquicidin (UBI29-41), which has now entered early clinical investigations. For us, Ga-68-labelled UBI was an essential key component to further investigate this research field, thereby seeking new approaches for the discovery of various novel peptides with predetermined functionalities, e.g., using a bacteria-specific mechanism of action or target, which may facilitate diagnosis of infection or fast-track current antimicrobial drug development (by way of becoming sensitive imaging biomarkers). This report will present an experience on our South African initiative to advance various infection-specific peptide-derived radiopharmaceuticals. It includes our view on compound discovery along with design considerations and peptide modifications, radiochemical aspects and challenges, further compound characterization *in vitro* and *in vivo* and mentions on unique requirement for bench-to-bedside translation for imaging of infection. A particular attention was given to Gallium-68 as the matching radioisotope for radiolabeling of peptides.



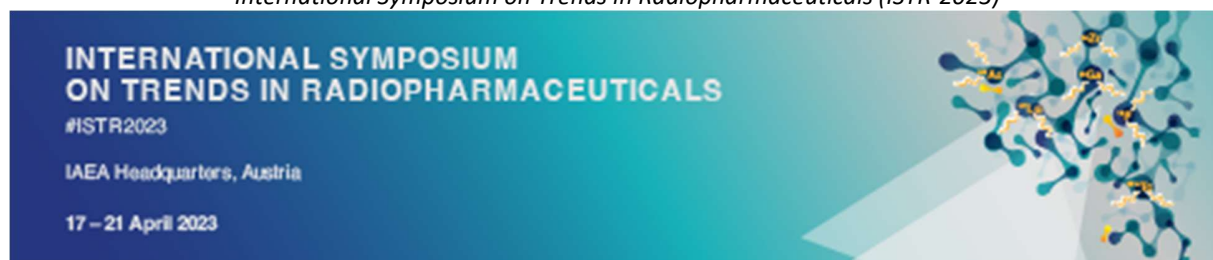
**IAEA-CN-310/321**

**The Use of Radioactive Tracers on Conventional Drug Development: A Critical View**

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Radiotracers have been used for decades, when coupled to molecules, in diagnostic and therapeutic procedures in Nuclear Medicine due to their powerful imaging properties and cell or cell environment harmful properties, respectively. Besides the use in Nuclear Medicine, radiotracers have also been used for conventional drugs discovery and development for decades, due to their easy and speed of detection when compared to other analytical techniques. Some important aspects will be discussed here, such as the safety aspects of use of radiotracers, the assurance that the labelled drug does not change its chemical or biological behaviour, the stability of the labelled drug and the possibility of radiolytic products being formed and their behaviour. Comparison between conventional analytical techniques and the use of radiotracers will be presented together with examples of studies performed by the group. A short review of literature, focusing specifically on Neglected tropical diseases (NTDs), such as leishmaniosis, and other infectious diseases, will also be shown.



## IAEA-CN-310/322

### Production of n.c.a. Lu-177 at McMaster University

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McMaster University is a student-centred research-intensive university in Hamilton, ON, Canada, that consistently ranks among the world's top 100 universities. McMaster is home to a world-class suite of nuclear research infrastructure that is anchored by the McMaster Nuclear Reactor (MNR), a 5 MW open-pool Materials Test Reactor that is as Canada's only major research reactor.

Since 2012, our group has used MNR to produce lutetium-177 via the direct route ( $^{176}\text{Lu}(n,\gamma)^{177}\text{Lu}$ ) in support of local researchers. By utilizing an in-core site with a significant epithermal neutron flux, Lu-177 is generated with a specific activity that is 50% higher than the projected value based solely on the thermal neutron cross-section. The long-lived component (Lu-177m,  $t_{1/2} = 160$  d) is present at low levels ( $\leq 0.01\%$ ) that will decrease further when MNR transitions to a 120 h continuous operating schedule in 2023 from its current intermittent (14 h/d, 5 d/wk) schedule.

In 2019-20, we began developing a process to generate Lu-177 via the indirect route ( $^{176}\text{Yb}(n,\gamma)^{177}\text{Yb} \rightarrow ^{177}\text{Lu}$ ). A method was devised that is capable of processing a 1 g target ( $\geq 20$  GBq Lu-177/g Yb-176) into a stock solution that meets industry standard specifications for no carrier added Lu-177. Scale-up and automation of this technology are currently in progress.





**IAEA-CN-310/324**

### **Direct Radiolabeling of PVP-Nanogel from $^{99m}\text{TcO}_4^-$ Reaction**

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Nanogels are considered promising drug delivery systems for different pathologies, mainly associated with neurological disease, by intranasal administration since drug transport occurs via the olfactory nerve, causing rapid delivery to the brain. The present work aimed to evaluate a protocol for  $^{99m}\text{Tc}$  labeling of poly(N-vinylpyrrolidone) (PVP) nanogel synthesized by an electron beam for future in vivo biodistribution assays. 10 mM PVP K-90 solution saturated with  $\text{N}_2\text{O}$  was irradiated by e-beam using a dose of 7 kGy and a dose rate of 5.35 kGy/s. Nanoparticles characteristic was evaluated by DLS technique to determine the Rh and SLS to determine the Mw and Rg. Rg/Rh and  $\rho_{\text{coil}}$  were calculated. The sample was morphologically characterized using AFM. The same analyzes were performed with a non-irradiated PVP solution. Radiolabeling was performed by mixing 0.55 mg of  $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$  in 50  $\mu\text{L}$  of HCl 0.1 M with (A) 450  $\mu\text{L}$  0.2 M NaOAc buffer, pH 4.1; (B) 200  $\mu\text{L}$  0.2 M NaOAc buffer, pH 4.1 and 0.5 M  $\text{NaHCO}_3$  buffer, pH 7.26; (C) filtered solution B in a 0.22  $\mu\text{m}$  syringe filter. To the solutions (A), (B), and (C) were added 200  $\mu\text{L}$  of nanogel (8.9 mg of PVP K-90), 100  $\mu\text{L}$  of  $^{99m}\text{TcO}_4^-$  (860-980  $\mu\text{Ci}$ ), and the samples were stirred at 500 rpm for 90 minutes at room temperature. The reaction was assessed by W3MM paper/acetone chromatography at the end of the process. All solutions were filtered through a 0.22  $\mu\text{m}$  filter to remove  $^{99m}\text{TcO}_2$ , as a previously validated process, and the radioactivity in the filter and the solution was measured. Finally, the solutions were concentrated in the Amicon® (10 kD), and the radioactivity of the filtered and retained solution were measured too. The solution remaining on the filter was diluted with 300  $\mu\text{L}$  of purified water and the concentration process was repeated twice. Filter content and the sum of filtered solutions 1 and 2 had the radioactivity measured to check labeling efficiency. Nanogel was obtained with an average for Rh of 12.49 nm, Rg of 6.8 nm, Mw of  $1.32 \times 10^6$  g/mol,  $\rho_{\text{coil}}$  of 786.98, and Rg/Rh of 0.620. High relief spherical structures were observed in the AFM images instead of the low roughness film observed in the non-irradiated PVP solution. Chromatographic analysis of the sample prepared only with NaOAc buffer (final pH 3.8) and of the sample with the mixture of buffers without previous filtration (final pH 6.8) indicated, respectively, 99.89 and 99.68% associated with the formation of  $^{99m}\text{Tc}$ -PVP nanogel or  $^{99m}\text{Tc}$ -colloid. In contrast, the sample prepared with the mixture of buffers and previously filtered (final pH 6.8) showed 80.10% of nonreduced  $^{99m}\text{TcO}_4^-$ . Filtration results at 0.22  $\mu\text{m}$  showed that the  $^{99m}\text{Tc}$ -colloid remains 100% retained in the filter, while free  $^{99m}\text{TcO}_4^-$  and  $^{99m}\text{Tc}$ -PVP nanogel are filtered. Amicon® filtration confirmed 95.75% and 92% of  $^{99m}\text{Tc}$ -PVP nanogel formation in the samples with NaOAc buffer and a mixture of buffers without previous filtration, respectively. It was possible to synthesize nanogel by electron beam, obtaining an average Rh of 12.49 nm. The labeling process with  $^{99m}\text{TcO}_4^-$  showed a high radiochemical yield in samples prepared with NaOAc buffer and a mixture of buffers without previous filtration.



IAEA-CN-310/325

### **Uncouple of Glucose Metabolism (18F-FDG) and Regional Cerebral Blood Flow (Measured with 11CPIB-R1) for Dementia Characterization**

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Regional cerebral blood flow (rCBF) is normally coupled to neuronal activity. This process allows the brain to optimize its energy supply in resting conditions and in the face of an increase in neuronal activity. Despite the fact that under physiological conditions in the cerebral cortex these processes are related, in normal aging and in certain pathophysiological situations there may be uncoupling that determines different patterns of affectation.

In this thesis, a quantitative comparison was made between rCBF and glucose metabolism, measured with positron emission tomography (PET), using [11C]-PIB in its early measurement for the quantification of rCBF (PIB-R1) and late for the deposition of  $\beta$ -amyloid ( $A\beta$ -PIB); and FDG for metabolism, in normal controls (NC: 22 subjects; re:  $73 \pm 5.9$  years), in subjects with mild cognitive impairment (MCI: 37 patients; re:  $70 \pm 7.2$  years) and Alzheimer's disease (AD: 36 patients; re:  $69.8 \pm 8$  years). These groups were also studied by dividing them into: MCI in PIB+ and PIB- according to  $A\beta$ -PIB; and AD in LOAD and EOAD (late and early onset) according to the age of onset of the clinical manifestation. In a voxel-level group analysis, the decoupling regions between rCBF and movement were characterized in the categories of the studied cognitive spectrum, being able to identify different patterns and intensities in the regions: anterior and middle cingulum, frontal and superior temporal in NC and MCI<sub>pn</sub>; and posterior cingulum, precuneus, parietal and inferior temporal in MCI<sub>pp</sub>, LOAD and EOAD. Decoupling of paired variables was quantified using normalized difference and principal component analysis (PCA) scores across all cortical and subcortical brain regions (VOIS-wise). The diagnostic value of these variables was evaluated with machine learning (SVM algorithm). Using the decoupling, characterized with PCA, the classification accuracy was improved from 63% to 82%. To compare the diagnostic power in each category, the AUC (area under curve) in the ROC curves was analyzed, obtaining a significant improvement when the decoupling with PCA is calculated (AUC<sub>NC</sub>: 1, AUC<sub>MCI<sub>pn</sub></sub>: 0.941, AUC<sub>MCI<sub>pp</sub></sub>: 0.926, AUC<sub>LOAD</sub>: 0.93 and AUC<sub>EOAD</sub>: 0.949) versus measurements of rCBF and metabolism (AUC<sub>NC</sub>: 0.99, AUC<sub>MCI<sub>pn</sub></sub>: 0.92, AUC<sub>MCI<sub>pp</sub></sub>: 0.83, AUC<sub>LOAD</sub>: 0.68, and AUC<sub>EOAD</sub>: 0.87). This work aims to generate knowledge about the processes that underlie alterations in rCBF and metabolic glucose consumption in normal aging and in neurodegenerative diseases, with a potential projection in clinical applications of molecular imaging studies in this patient population.



**IAEA-CN-310/326**

### **Brain Asymmetries in Normal and Pathological Aging: A Molecular Imaging Perspective**

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Brain asymmetries have been observed in structural, functional and behavioral terms. The aim of this work was to evaluate brain asymmetries of metabolism, regional cerebral blood flow (FSCr) and amyloid deposit in young and elderly controls and in different pathological groups with minimal cognitive impairment and Alzheimer's disease.

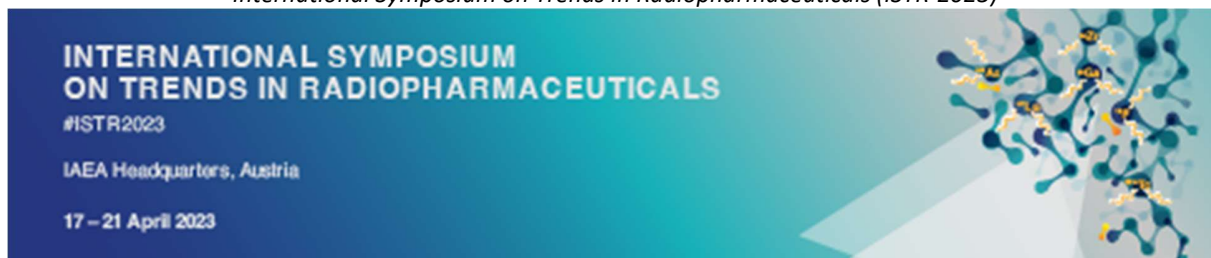
Brain PET images were acquired with [18F]-FDG to measure metabolism and dynamic [11C]-PIB for measurements of FSCr (SRTM2 algorithm) and amyloid deposition in all groups.

Images were spatially normalized using ANS. Based on a generated symmetric template to correct for structural asymmetries, a non-linear warping of all the data, flipped in the midsagittal plane, was generated in order to compare them with the original data.

Parametric ANCOVA multifactorial group statistics and ROI analysis were performed among all the groups.

Regions of asymmetry were evaluated in the different groups; parametric statistical maps were generated for each category and measurement. Statistically significant differences were found ( $p < 0.05$ ) between the studied groups, evaluating gray matter in predefined regions.

The brain mapping approaches for the different measurements can identify asymmetry patterns in the normal population and characterize the alterations that occur in normal and pathological cognitive deterioration.



**IAEA-CN-310/329**

### **99mo/99mtc Gel Generators, Experience and Considerations**

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The Institute of Nuclear Physics in Almaty, Kazakhstan, produces  $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$  gel generators using  $^{99}\text{Mo}$  with a specific activity from 0.8 to 1.8 Ci/g obtained by irradiation of natural molybdenum oxide in WWR-K research reactor with a neutron flux of  $1.7$  to  $2.0 \times 10^{14} \text{ cm}^{-2}\text{s}^{-1}$ .

This paper presents data on more than 20 years of experience in the production of gel generators and the results of study of using the enriched  $^{98}\text{Mo}$  oxide and the feasibility of using molybdenum recovered from used  $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$  gel generators for the production of new generators.

Use of molybdenum enriched to at least 95% of  $^{98}\text{Mo}$  increases the specific activity of  $^{99}\text{Mo}$  up to 3.5 times, depending on target geometry, with a corresponding increase of the generator activity and/or time of precalibration. Purity of  $^{99\text{m}}\text{Tc}$  produced with the recovered molybdenum meets the Pharmacopoeia requirements, so recycling of valuable enriched  $^{98}\text{Mo}$  would improve economic efficiency of the process.



**IAEA-CN-310/330**

**Challenging Development of Astatine-211 Through the European COST NOAR Program.**

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The NOAR Cost Action started in October 2020 in order to demonstrate that  $^{211}\text{At}$  radiopharmaceuticals could become the European standard for treatment of certain cancerous pathologies. The idea was to create in Europe an  $^{211}\text{At}$ -Node network, each node being composed of a production site, a radiopharmaceutical unit and an expert treatment center. 6 to 10  $^{211}\text{At}$ -Nodes will be necessary to cover the European citizen needs.

To this end, efficient exchange of knowledge and networking have been established under the COST Action, bringing together all European stakeholders interested in promotion of  $^{211}\text{At}$  for medical applications.

The first goal of the NOAR Action being to establish a proof of concept (clinical phase I, II), the following scientific, technological, regulatory and societal challenges had to be addressed: production issues, pathology of interest, choice of the vector, labeling processes, automation, dosimetry aspects, regulatory environment, waste management, pharmaco-economics, education and communication aspects.

This presentation will describe what has been achieved so far.

Today, the project has taken a new step by expanding the European network to the American DOE network (US Department Of Energy) and to the Japanese network (Japan Atomic Energy) of cyclotrons.

Our goal is now to define common standards with the description of the first  $^{211}\text{At}$ -Node (Guidance on facility design and production of  $^{211}\text{At}$ -radiopharmaceuticals) and to set it as one of the reference elements in a therapeutic arsenal of TAT.

The World Astatine Community, open to any new members, has been launched at the TAT12 in Cape Town.



## **IAEA-CN-310/331**

### **NNSA Support for Proliferation-Resistant Medical Isotope Production**

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The U.S. Department of Energy's National Nuclear Security Administration (DOE/NNSA) supports nonproliferation efforts to minimize the use and production of special nuclear material and technologies. DOE/NNSA's Office of Conversion supports this by converting research reactors and medical isotope production from the use of highly enriched uranium (HEU) to low enriched uranium (LEU) fuel and targets.

In particular, the Office of Conversion's Molybdenum-99 (Mo-99) Program provided financial and technical assistance for major medical isotope producers in South Africa, the Netherlands, and Belgium to convert to LEU-based Mo-99 production. Domestically, the Mo-99 Program supports non-HEU-based Mo-99 production by providing financial and technical assistance to domestic commercial entities, many of which are using new production technologies.

Looking to the future for research reactors and isotope production facilities, the Office of Conversion launched the Proliferation Resistance Optimization (PRO-X) program. PRO-X leverages over 40 years of experience converting research reactors and medical isotope production facilities from HEU to LEU to explore ways to maximize the performance of nuclear facilities, while minimizing special nuclear material use or production.

This presentation will share information and lessons learned on DOE-NNSA's Office of Conversion efforts on our international and domestic activities and identify future areas in medical isotope production that can benefit from the 40 plus years of experience, technology, and capabilities.





**IAEA-CN-310/332**

### **Targeted Alpha Therapy: Perspectives from Fusion Pharmaceuticals**

Thomas Kostelnik

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Targeted Alpha Therapy (TAT) is a therapeutic strategy in oncology that combines alpha-emitting radionuclides with various targeting molecules to selectively deliver alpha emitting payloads to tumors. Highly promising (pre)clinical results have spurred increasing focus on drug discovery, manufacturing, clinical trials, and commercialization of TAT agents, particularly those harnessing  $^{225}\text{Ac}$ . Fusion Pharmaceuticals is a clinical-stage oncology company with four  $^{225}\text{Ac}$ -radiopharmaceuticals in clinical trials. To support this rapidly growing pipeline of TATs, Fusion has signed strategic actinium supply agreements with TRIUMF, Niowave, Inc. and BWXT Medical. This presentation will focus on the opportunities, challenges, and future trends of  $^{225}\text{Ac}$ -based radiopharmaceuticals.



**IAEA-CN-310/333**

## **Rediscovering the Role of Technetium-99m in the Current Status of Nuclear Medicine Practice**

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Technetium-99m has been the workhorse of diagnostic Nuclear Medicine in supporting diagnostic activities for more than 50 years. During the last two decades the field is undergoing an unprecedented growth, due to the diffusion of more efficient imaging technologies and to the development of new radiopharmaceuticals. Yet, in this context there are some uncertainties as to what will be the role of technetium-99m in the next future, due to the rising of PET technologies in support of radioligand therapy and to the recent difficulties in radioisotope supply.

Luckily, tough times prompt new opportunities for innovation. The future of SPECT is rapidly changing, due to advances in the solid-state detector technology applied to scanners, that combines fast imaging with high spatial resolution and sensitivity. In addition, recent research efforts led to significant achievements for improving the availability of technetium-99m, thus promoting the development of new tracers. An analysis of patent publication activity between 2000-2022 will be illustrated for identifying and measuring the emergent technetium-99m technological innovations, giving a picture of new trends and market orientation. The result is an impulse that fuels the rediscovery of technetium-99m, that remains a unique radionuclide within the scenario of Nuclear Medical imaging for its ideal nuclear properties, availability and the easy preparation of its radiopharmaceuticals.



**IAEA-CN-310/334**

## **Routine Production of Tc-99m Generators**

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Through collaboration with the IAEA, CENTIS has managed to establish a system for the sustainable production of generators and radiopharmaceuticals. Radionuclide generator systems continue to play a key role in providing both diagnostic and therapeutic radionuclides for various applications in nuclear medicine. The generators represent important in-house production systems that can provide daughter radioisotopes generated by parent decay on-demand without the need for local access to an accelerator or nuclear reactor. Cuba has not had accelerators or reactors for many years so its radionuclide and radiopharmaceuticals production is based mainly on importation or local generators production. Our presentation resumes the Cuban experience in the production of radionuclide generators and radiopharmaceuticals.

In CENTIS facilities, the production of  $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$  generator began in 2003 using the column chromatography method as separation technology. More than 4 000 generators has been produced in different presentations (8 GBq, 20 GBq, 37GBq, 55,5 GBq and 74 GBq) during this years. However, long before in the 90s, CENTIS already manufactured cool kits to form radiopharmaceuticals from imported generators. Starting with generator production in 2003 allowed us to guarantee the sustainability of nuclear medicine services in the country.

Among many other requirements one of the main challenge for our radionuclide generators production has been the need to manufacture and operate under the conditions of good manufacturing practices (GMP) guidelines since these products represent final product or active pharmaceutical ingredients (APIs) which will be incorporated into radiopharmaceutical products prepared for human use. In this presentation, we included the necessary modifications performed to our  $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$  generators production and the conditions established to comply with the current GMP guidelines supported by a Technical Cooperation Project with the IAEA (CUB/6/023).



IAEA-CN-310/335

## Setting up a Theranostic Facility: INMOL Experience

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The acronym THERANOSTICS epitomizes the inseparability of diagnosis and therapy, the pillars of medicine and takes into account personalized management of disease for a specific patient. Molecular phenotypes of neoplasms can be determined by molecular imaging with specific probes using PET. The major advantage of PET is that it not only enables in vivo visualization of physiological processes on molecular level in real time, but it also quantifies them by measuring regional concentration of the radiation source. THERANOSTICS of neuroendocrine tumors (NETs) and prostate cancer by using Ga-68 labeled tracers for diagnostics with (PET/CT), and Lu-177 or other metallic radionuclides for radionuclide therapy by applying the same peptide proves that personalized radionuclide therapy today is already a fact and not a fiction. Since its first clinical use at INMOL in November 2017, there has been a tremendous increase in the number of studies with Ga-68 followed by Lu-177 therapy, demonstrating its potential to gradually become a targeted radionuclide therapy in Pakistan in future. Ga-68 is an easily-available generator-derived diagnostic trivalent radio metal with convenient labeling characteristics. Ga-68 is prepared from a TiO<sub>2</sub> based Ge-68/Ga-68 generator system, which has a half-life of 288 days. INMOL has launched a GMP compliant, fully automated click and start cassette-based synthesis system with easy handling (ITG, Germany) for the daily routine production of Ga-68 labeled radiopharmaceuticals. Post-processing of Ge-68/Ga-68 radionuclide generators using cation exchange resin provides chemically and radio-chemically pure Ga-68 within few minutes ready for on-site labeling with high overall product yields. We have established the labeling procedures by using DOTA-NOC (for imaging of NETs) and Prostate-Specific Membrane Antigen (PSMA-11) for imaging of prostate cancer, followed by treatment with <sup>177</sup>Lu/ <sup>90</sup>Y-DOTATATE and <sup>177</sup>Lu/ <sup>225</sup>Ac-PSMA-617. Quality control parameters of these novel radiolabeled-biomolecules were assured according to European pharmacopoeia. The elution efficacy of our Ga-68/Ge-68 generator is approximately  $97 \pm 2.2\%$ , while labeling efficacy of <sup>177</sup>Lu/<sup>90</sup>Y/<sup>225</sup>Ac-biomolecules is usually  $96 \pm 2.8\%$ . Ge-68 Breakthru was checked by well counter. To check Germanium breakthrough the sample is placed for 48 hours then checked again in well counter. The breakthrough should be  $<0.001\%$  which was found in our system well within limits. For quality control and quality assurance of <sup>68</sup>Ga-biomolecules, we follow limits as prescribed in European Pharmacopoeia, e.g., pH of product 4.5 – 7.5, Radiochemical purity  $>95\%$ , Half-life 105 – 115 min, Endotoxins  $<2.5\text{EU/ml}$  and pressure in Filter Integrity Test  $>50$  psi. From above figures and facts, it can be concluded that in Pakistan, there exists a good potential for capacity-building in establishing theranostics facility under GMP environment by using PET/CT imaging in clinical management of various malignancies. Due to rapidly emerging novel biomolecules with theranostic potential, it is anticipated that this modality may play a significant role in the dreadful fight against cancer, thus providing relief to the ailing humanity.



**IAEA-CN-310/336**

## **Production and Development of Tc-99m Radiopharmaceuticals and Cold Kits in China**

Jin Du

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<sup>99m</sup>Tc-radiopharmaceuticals are playing significant roles in the diagnosis of human diseases and efficacy monitoring of therapeutic strategies together with SPECT imaging modality. This presentation provides an overview of current status of <sup>99m</sup>Tc-radiopharmaceuticals and cold kits production in China for clinical use and also describes some important advances on <sup>99m</sup>Tc-radiopharmaceuticals and cold kits development in past ten years. Development of <sup>99m</sup>Tc-labeled radiotracers in China include: (1) Brain perfusion imaging agents and CNS radiotracers for b-amyloid plaques and sigma-1 receptor; (2) Myocardial perfusion imaging agents; (3) Tumor imaging agents including integrin-targeting radiotracer, prostate specific membrane antigen targeting radiotracer, novel sentinel lymph node imaging agent, <sup>99m</sup>Tc-labeled glucose derivatives, <sup>99m</sup>Tc-labeled fibroblast activation protein inhibitor tracer, and hypoxia imaging agents; (4) Potential infection imaging agents and other imaging agents. Moreover, the future trends of <sup>99m</sup>Tc-radiopharmaceuticals in China were discussed.

In conclusion, China has established a complete research and development, production and supply system for <sup>99m</sup>Tc-radiopharmaceuticals and cold kits. The demands for <sup>99m</sup>Tc-radiopharmaceuticals are still strong and it will continue to play an important role in nuclear medicine in China. The development on the novel <sup>99m</sup>Tc-radiopharmaceuticals with high affinity, selectivity and specificity for the tumor imaging together with <sup>99m</sup>Tc labeling methods suitable for clinical use will be the focus of research, it would accelerate the clinical translation of new <sup>99m</sup>Tc-radiopharmaceuticals.



**IAEA-CN-310/337**

## **Critical Evaluation of Quality Control Procedures for Actinium-225 Radiopharmaceuticals**

Kleynhans Janke

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Actinium-225 labelled radiopharmaceuticals are being fast tracked as therapeutic treatments in the Nuclear Medicine clinic. The technicalities associated with accurate quality control (QC) of these radiopharmaceuticals, specifically pertaining to radiochemical purity (RCP), might be underestimated. The European Association of Nuclear Medicine (EANM) guidelines on the validation of analytical methods for radiopharmaceuticals, states that a non-radioactive counterpart is used to identify the radioactive product peak on chromatography. There is no such isotope available for actinium-225. Furthermore, the EANM guidelines suggest that it is appropriate to use two independent chromatographic methods to verify the identity of a radioactive substance. During this presentation, the process of validating QC methods for RCP determination of lutetium-177 containing radiopharmaceuticals is discussed in brief. This is to set the stage of the current norms in the radiopharmaceutical industry. The current methods in literature for the determination of actinium-225 with ITLC is explained and emphasis is given with respect to the matter of secular equilibrium and the practice to calculate RCP of actinium-225 radiopharmaceuticals from the gamma decay of francium-221 and bismuth-213. Currently the standard practice is to wait 2 hours after incubation of the ITLC before quantification of RCP. During this time, it is possible that the RCP of the radiopharmaceutical might have degraded due to radiolysis and instability. As a second chromatography-based method, a radio-HPLC method to analyse actinium-225 radiopharmaceuticals is critically discussed. The biodistribution of free actinium-225 to the bone (9-20% ID/g), liver (>40% ID/g) and salivary glands (2% ID/g) is highlighted to emphasis why validated and effective QC of this radiopharmaceutical is critical. Actinium-225, due to the extremely complicated physical properties not allowing for real-time RCP measurements as well as lack of a stable isotope, does not conform to current GMP guidelines suggested for radiopharmaceuticals.





**IAEA-CN-310/339**

## **Opportunities and Challenges of Using Terbium-161 for Targeted Radionuclide Therapy**

Cristina Müller

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Over the last decade, the production of terbium-161 has been set up at PSI by the Radionuclide Development group. The radionuclide is currently being produced on a routine basis for preclinical research and in view of a clinical translation. Over the years, we have performed a large number of preclinical studies using various tumor targeting agents, cancer cell types and tumor mouse models. The opportunity of using terbium-161 refers to its consistently improved therapeutic efficacy over that of lutetium-177 and the otherwise similar chemical and physical characteristics of these two radiolanthanides. Despite the potential of using terbium-161 for radionuclide therapy, working with this radionuclide also presents several challenges. In this presentation, the opportunities and challenges of translating this radionuclide to clinics will be discussed.



**IAEA-CN-310/340**

## **Non-Clinical Considerations from a Regulatory Perspective**

Clemens Decristoforo

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The development of radiopharmaceuticals requires extensive evaluation before they can be applied in a diagnostic or therapeutic setting in Nuclear Medicine. This includes chemical, radiochemical, and pharmaceutical parameters that must be established and verified to ensure the quality of novel products. Additionally to this, data related to safety and efficacy of these products are required to provide supportive evidence for the expected human in vivo behaviour. Extensive testing, often referred to as "non-clinical" or "preclinical" are required. For radiopharmaceutical these need to take into account effects originating from the emitted radiation, but also of the non-radioactive component of a new compound. They include in vitro testing to elucidate and/or confirm possible mechanisms of action of the radiopharmaceutical and performance of in vivo experiments in animals to establish the pharmacokinetics as well as the pharmacological and toxicological profile. Additionally, the assessment of the radiation dose delivered by the radiopharmaceutical to the various organs needs to be established in preclinical dosimetry studies.

This presentation summarises major considerations for non-clinical studies to accommodate the regulatory requirements for this testing in the clinical translation of radiopharmaceuticals. There is a great degree of uncertainty for an appropriate non-clinical study design due to lack of specific regulations for radiopharmaceuticals and the rapid development in this field. Regulatory bodies often refer to guidance for non-radioactive drugs, not taking into account the specific requirements for radiopharmaceuticals. The IAEA has recently provided support to member states for the technical conduct of non-clinical studies with a dedicated "Guidance for Preclinical Studies with Radiopharmaceuticals" (Radioisotopes and Radiopharmaceuticals Series No. 8, 2023). Additionally, as an outcome of an IAEA technical meeting in Coimbra in 2021, "Practical considerations for navigating the regulatory landscape of non clinical studies for clinical translation of radiopharmaceuticals" were published (EJNMMI RPC 2022) to summarize the expectations from regulatory bodies and provide solutions to meet the specifics of radiopharmaceuticals in the translational process from bench to bedside.

These IAEA documents, together with other international activities, intend to guide radiopharmaceutical scientists, Nuclear Medicine specialists, and regulatory professionals to bring innovative diagnostic and therapeutic radiopharmaceuticals into the clinical evaluation process in a safe and effective way.



IAEA-CN-310/341

## The Importance of In-House Production and European Regulatory Initiatives

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The way radiopharmaceuticals are prepared has changed considerably in parallel to the development of the field of radiopharmaceuticals. The supply of centralized prepared radiopharmaceuticals in combination with the practice of using generators and kits for Tc-99m radiopharmaceutical preparation has been the predominant practice for several decades. The clinical establishment of PET with short lived radionuclides from cyclotrons, but also the development of theranostics with combination of PET-diagnostics such as based on Ga-68 with Lu-177 has made the local preparation of radiopharmaceuticals in-house an important segment to supply patients with novel radiopharmaceuticals not being available by commercial supply. New developments such as in Immuno-PET or in the discovery of many highly promising targets open new possibilities for a more personalized approach in Nuclear Medicine. Technological advances e.g. in automation of radiopharmaceutical preparation has simplified the small scale preparation performed in hospitals or academic research centres often under the responsibility under the responsibility of the nuclear medicine department or a hospital pharmacy. The regulatory environment for medicines and pharmaceuticals in many countries has not been adapted to this development, in particular in Europe. Most EU regulations and other regulatory guidance are tailor-made for the industrial, commercial pharmaceutical production. This is e.g. reflected in an undifferentiated approach to Good manufacturing Practices (GMP) that do not take into account on the one hand the scientific and technological advancements related to novel and complex radiopharmaceutical preparations and on the other hand the specificities of preparations in hospital pharmacies or nuclear medicine departments. The process of authorization of facilities is regulated very heterogeneously even within Europe. Whereas the preparation of radiopharmaceuticals from kits and generators with marketing authorization is reflected in the European regulatory framework, more complex preparations are not considered. Regulatory definitions for starting material for such complex preparations are often misinterpreted due to gaps in regulatory guidance. Additionally training requirements and responsibilities for the involved professionals (radiochemists, radiopharmacists) are not anchored in the legislation. The European Association of Nuclear Medicine (EANM) and other stakeholders have set many initiatives to adapt the current regulatory framework, by specifying definitions in legislation, providing dedicated guidelines for the small scale preparations and defining training requirements and expanding training opportunities for responsible persons in the special field of radiopharmaceutical preparation. The European Pharmacopoeia has developed several monographs and texts to support the quality standards of such preparations. These initiatives in Europe and recent IAEA activities will be presented and discussed.



**IAEA-CN-310/342**

### **Production of Research Candidates for Meitner-Auger Therapy at TRIUMF (Canada)**

Valery Radchenko

Triumf, Vancouver, British Columbia, Canada

Meitner-Auger emitting Radionuclide Ligand Therapy (MAE RLT) has a great potential to be the most selective and precise therapy for cancer and other diseases due to its very low energy (compare with beta and alpha emitters) and high Linear Energy Transfer (LET). This allows the design of the therapeutic agents at the cellular level and minimizes unwanted damage to healthy tissues. One of the advantages of Meitner-Auger emitters (MAE) is that many potent candidates can be produced with the low to medium energy medical cyclotrons (10-20 MeV) which allow wide production and access to those radionuclides. TRIUMF is a Canada particle accelerator center located in Vancouver, Canada operates 5 cyclotrons with energies varied between 13-500 MeV. Life Sciences Division at TRIUMF actively exploring the production of research candidates for AE RLT with its TR-13 (13 MeV) cyclotron.  $^{119}\text{Sb}$  is one the most promising candidate for Auger therapy with  $t_{1/2}$  38.1 hours and 24 low energy electron emission ( $le_3$ ) average per decay with an excellent ratio (0.9) between other emissions and  $le_3$ .  $^{119}\text{Sb}$  radiotracers produced by irradiation of natural tin with proton energy of 12.8 MeV and further liquid-liquid extraction with dibutyl ether are applied for radiochemical purification. Our current work focuses on the chelation of Sb for further incorporation into delivery systems.  $^{197m+g}\text{Hg}$  represents another potent candidate with the theragnostic ability with  $t_{1/2}$  23.8 h for metastable and  $t_{1/2}$  64.1 h for the ground state and with 30 low energy electrons ( $le_2$ ) (for ground state) and ratio 10 between other emissions and  $le_3$ . Mercury- $^{197m+g}$  can be produced from monoisotopic gold-197 via p, n reaction at TRIUMF TR-13 cyclotron. Radiochemical separation was performed by using a previously established separation method (M. Walter et al.) based on LN resin. Currently alternative resins evaluation is performed to improve separation system for Au/Hg. Several potent chelation agents were tested and TCMC showed good potential for preliminary in vitro and in vivo studies. Several novel agents were also synthesized and tested and showed superior performance over existing commercial ligands. We currently have active collaboration with the University of Toronto (Reilly lab) to evaluate Hg-labeled gold nanoparticles and panitumumab in vitro and in vivo.  $^{103}\text{Pd}$  is another candidate for AE RLT with  $t_{1/2}$  17 days and can be produced by proton irradiation of natural monoisotopic Rh-103. The main challenge is the complex dissolution of rhodium. At TRIUMF,  $^{103}\text{Pd}$  was produced with the liquid target from rhodium nitrate salt and further proof-of-principle separation with an anion exchange column was performed. Several other radio Ln's for Auger Therapy are currently produced at TRUMF, including  $^{135}\text{La}$ ,  $^{155}\text{Tb}$  and we are working to establish production of  $^{165}\text{Er}$  in the near future.



**IAEA-CN-310/343**

**Production of Medical Radionuclides Using an Electron Linear Accelerator (Mo-99 and Others)**

Tadokoro Takahiro

Hitachi, Ltd, Tokyo, Japan

An electron linac based Mo-99 production system has many advantages: the size of the system is relatively small, a high beam current is easily achieved and the cross section of the Mo-99 production reaction,  $\text{Mo-100}(\gamma, n)\text{Mo-99}$ , is relatively high. Moreover, the production amounts of impurity nuclides are very small. These advantages can lead to a cost-effective system. With the final goal of implementing such a system, we have been evaluating the Mo-99 production amount in a real-scale system. To provide even more cost-effectiveness, we have been considering production of other medical nuclides using the same system. Cu-67 is recently being studied as a nuclide for new treatment agents. Another such nuclide is Ac-225 which is a descendant nuclide of Ra-225 and has nuclear properties that make it well suited for use in targeted alpha therapy. We also have carried out the evaluation of Cu-67 and Ra-225/Ac-225 production amounts. Our R&D project on radioisotope production using the electron linac will be presented in this conference.



## **IAEA-CN-310/344**

### **Reflection on Global I-131 Supply**

P Louw, Tladi Moloto, A Ntlokwana

NTP Radioisotopes SOC Ltd, South Africa

NTP Radioisotopes SOC Ltd (NTP) manufactures and supplies significant quantities of Mo-99 and I-131 to the global nuclear medicine industry from its production facilities located at Pelindaba. NTP Radioisotopes SOC Ltd is a wholly owned subsidiary of the South African Nuclear Energy Corporation (NECSA). NECSA owns and operates the SAFARI-1 nuclear reactor.

NTP is one of the leading global suppliers of I-131. The production process of I-131 (from Mo-99) is achieved using Low Enriched Uranium targets at the SAFARI reactor. The world has recently experienced global I-131 shortages. The I-131 shortages were due to increased demand and supply disruptions.

During this period NTP continued to be a reliable supplier and partner to ensure that the impact was mitigated as far as possible. NTP's presentation will share NTP's experience in I-131 production and, also reflect on recent challenges and successes.





**IAEA-CN-310/345**

## **Isotope Harvesting at NSCL & FRIB for Nuclear Medicine and Scientific Applications**

Katharina A. Domnanich, Gregory W. Severin

Facility for Rare Isotope Beams & Michigan State University, Dept. of Chemistry, United States of America

In the production of exotic, secondary beams at the Facility for Rare Isotope Beams (FRIB), a majority of the accelerated primary beam will remain unused and will be stopped in a water-traversed, spinning drum of Ti64 alloy.<sup>1</sup> With the dissipation of such large amounts of energy, a plethora of valuable radionuclides will be created. Exploratory research with the heavy ion beams from the National Superconducting Cyclotron Laboratory (NSCL) demonstrated the feasibility of a synergistic collection of radionuclides from the aqueous and gaseous phase, and the process became colloquially known as ‘isotope harvesting’.<sup>2</sup>

In this talk, I will give an overview of the isotope harvesting process, first with a focus on the collection of  $^{62}\text{Zn}$  from a stopped  $^{78}\text{Kr}$  beam. The positron-emitting  $^{62}\text{Zn}$  ( $t_{1/2} = 9.2$  h) decays to the short-lived  $^{62}\text{Cu}$  ( $t_{1/2} = 9.7$  min) and the pair finds application as a radionuclide generator in nuclear medicine. This system allows the repeated isolation of pure samples of  $^{62}\text{Cu}$ , which is a relevant radioisotope for PET-imaging of tissue hypoxia and quantifying the blood flow in organs.<sup>3</sup> The developed purification method facilitated the separation of  $^{62}\text{Zn}$  from accompanying radioactive and stable nuclides.<sup>4</sup> The here presented study shall serve as an example of the numerous opportunities to access medically and scientifically interesting isotopes with the startup of FRIB.

In FRIB’s normal operation mode, a broad variety of multiple isotopes of each element will be created, and often direct harvesting efforts will not yield radioisotopically pure samples. An option to increase the spectrum of pure radioisotopes could be achieved through the implementation of mass separation. At FRIB, a suitable mass analyzer is already part of the existing infrastructure and could be utilized to establish a prototype mass separator.<sup>5</sup> The so-obtained, radioisotopically pure samples will be available for various scientific studies, such as cross-section measurements, and also for applications in nuclear medicine. In the second part of this talk, I will give an outlook on this prospective extension of the current isotope harvesting program.



**IAEA-CN-310/346**

## **Challenges & Opportunities in the Production of Radioisotopes (an Industrial Perspective)**

Cristiana Gameiro

IBA RadioPharma Solutions, Louvain-La-Neuve, Belgium

During this talk, the advances and new trends in the Nuclear Medicine field will be introduced. In this context, the challenges and opportunities in the production of radiopharmaceuticals will be discussed from an industry perspective. Nuclear Medicine per se has intrinsic challenges which has become further complex going from mono- isotope to multi-isotope, multi-product portfolio. But the field has been capable to turn many of these complex challenges into opportunities and taken this discipline to another level.

Despite the evolution of the field, increased professionalization is still required. Early-stage considerations of the regulatory framework and related matters are fundamental towards harmonization/standardization. This is of highest relevance from the industry standpoint.

Lastly, there is a call for action at the European Commission level with the new Pharmaceutical law. This is a unique opportunity to make Nuclear Medicine stands out and to forge the future of this specialty for the next ten to twenty years.



**IAEA-CN-310/347**

## **Production and Quality Control of [18f]Fdg Radiopharmaceuticals: Kfsh&Rc Experience**

Subhani Okarvi

Cyclotron and Radiopharmaceuticals Department, King Faisal Specialist Hospital-Riyadh, Riyadh, Saudi Arabia

Radiopharmaceuticals are essential tools for understanding human physiology and biochemistry, and subsequently, for the diagnosis and therapy of an extensive variety of diseases. Of the various cyclotron-produced radiopharmaceuticals, positron emission tomography (PET) radiopharmaceuticals are being increasingly utilized in nuclear medicine imaging for both research and routine clinical diagnosis. The non-invasive PET imaging modality is unique in its ability to measure functional and metabolic activities of the body's organs or tissues. These images are not available with other imaging technologies, such as CT, MRI, or X-ray. Intending to provide quality clinical service for patients, and acquire the most up-to-date imaging modality, PET has advanced exceptionally in developed countries and with limited prevalence in developing countries. This must be attributed to the cost and complexity of such practice, in addition to the requirement of a cyclotron and a radiochemistry laboratory on-site for radiopharmaceutical production.

The development of [18F]fluorodeoxyglucose ([18F]FDG) in the seventies for studying glucose metabolism together with the establishment of reliable synthesis was a major breakthrough leading to the development of PET. Until now, [18F]FDG is the most widely used radiopharmaceutical in PET imaging which is attributed to its biochemical and physical properties. Consequently, [18F]FDG has allowed earlier detection of disease(s) onset, proper characterization and management of disease at various stages, and earlier and direct assessment of treatment effects, thus enabling effective personalized patient management.

Therefore, as a leading institute in this area of expertise in the region, we demonstrate here the production and quality control of [18F]FDG radiopharmaceuticals.



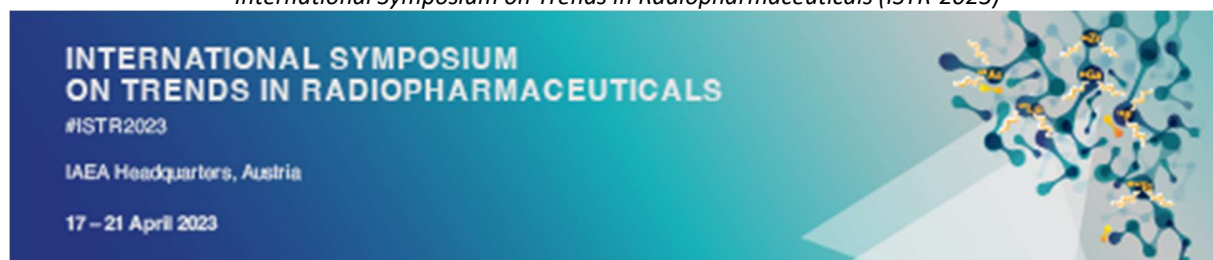
**IAEA-CN-310/348**

## **Production of $^{177}\text{Lu}$ and $^{177}\text{Lu}$ -Based Radiopharmaceuticals**

Tapas Das

Radiopharmaceuticals Division, Bhabha Atomic Research Centre, Mumbai, India

Application of  $^{177}\text{Lu}$ -based radiopharmaceuticals for targeted radionuclide therapy (RNT) has shown tremendous growth world-wide in the last two decades. This has resulted  $^{177}\text{Lu}$  become the second most widely used radionuclide, just after  $^{131}\text{I}$ , for RNT applications. India has made a very significant contribution in the production and growth of  $^{177}\text{Lu}$ -based radiopharmaceuticals. Since early 2000, Radiopharmaceuticals Division (RPhD) of Bhabha Atomic Research Centre (BARC) started exploring the feasibility of producing  $^{177}\text{Lu}$  using Dhruva reactor. The first irradiation of natural  $\text{Lu}_2\text{O}_3$  target was carried out in 2000, which was followed by the production of comparatively higher specific activity  $^{177}\text{Lu}$  using enriched  $\text{Lu}_2\text{O}_3$  (in  $^{176}\text{Lu}$ ) target in mid-2001. Extensive studies were carried out to optimize the production of  $^{177}\text{Lu}$  with maximum achievable specific activity and radionuclidic purity using the highest available flux positions in the reactor and irradiating the target for an optimum period. This enabled production of  $^{177}\text{Lu}$  with sufficiently high specific activity for the preparation of target-specific agents for RNT applications. BARC started producing  $^{177}\text{Lu}$  employing direct route (using enriched  $\text{Lu}_2\text{O}_3$  target) on a regular basis since the end of 2006. Supply of clinical grade  $^{177}\text{LuCl}_3$  to nuclear medicine centres of India was started through BRIT by 2010. Keeping in mind the increasing demand of no-carrier-added (NCA)  $^{177}\text{Lu}$ , BARC and BRIT are presently working on large-scale production of NCA  $^{177}\text{Lu}$  through indirect route (irradiation of enriched  $^{176}\text{Yb}$  target followed by radiochemical separation of  $^{177}\text{Lu}$ ) for clinical deployment. BARC started supply of  $^{177}\text{LuCl}_3$ , as the precursor radiochemical, and along with know-how transfer for the formulation of the finished radiopharmaceutical products, namely  $^{177}\text{Lu}$ -DOTA-TATE (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid coupled Tyr<sup>3</sup>-Octreotate for RNT of neuroendocrine tumours) and  $^{177}\text{Lu}$ -EDTMP (ethylenediamine-tetramethylene phosphonic acid for bone pain palliation) to hospitals since 2008. This pragmatic approach helped the collaborating nuclear medicine centres to formulate the finished product and perform clinical procedures by the end of the first decade of 2000 onwards. The subsequent addition of another important product, namely  $^{177}\text{Lu}$ -PSMA-617 (Prostate Specific Membrane Antigen binder ligand conjugate) by BARC, for treatment of prostate cancer patients, is another significant accomplishment, keeping India at the forefront of targeted RNT. To meet the growing demand of  $^{177}\text{Lu}$ -based PRRT agents, BRIT initiated commercial supply of ready-to-use  $^{177}\text{Lu}$ -DOTA-TATE and  $^{177}\text{Lu}$ -PSMA-617 to nuclear medicine centres of India from 2017 and 2019, respectively. Recently, BRIT has started supplying another  $^{177}\text{Lu}$ -based radiopharmaceutical, namely  $^{177}\text{Lu}$ -HA (Hydroxyapatite particles) for radiation synovectomy of small- and medium-sized joints. Currently, BRIT supplies  $^{177}\text{Lu}$ , both as precursor radiochemical and as ready-to-use  $^{177}\text{Lu}$ -labeled radiopharmaceuticals ( $^{177}\text{Lu}$ -DOTA-TATE,  $^{177}\text{Lu}$ -PSMA-617,  $^{177}\text{Lu}$ -EDTMP,  $^{177}\text{Lu}$ -HA) to more than 75 nuclear medicine centres of India. There are also other  $^{177}\text{Lu}$ -based products, namely  $^{177}\text{Lu}$ -DOTMP (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylene phosphonic acid for bone pain palliation),  $^{177}\text{Lu}$ -RGD (for RNT of cancers),  $^{177}\text{Lu}$ -Rituximab (for RIT of Non-Hodgkin's Lymphoma) and  $^{177}\text{Lu}$ -Trastuzumab (for RIT of breast cancer over-expressing HER2 receptors), whose use have been approved by the regulatory authorities for clinical administration. Clinical studies with these  $^{177}\text{Lu}$ -based agents are presently being carried out in order to establish their potentials in targeted radionuclide therapy.



**IAEA-CN-310/349**

## **Cyclotron Production of Radiometals in Edmonton**

Jan Andersson

Edmonton Radiopharmaceutical Center, Edmonton, Alberta, Canada

Edmonton Radiopharmaceutical Centre (ERC) is a provincial radiopharmaceutical provider, producing 7,000 batches of  $^{99m}\text{Tc}$  radiopharmaceuticals, 1,200 batches of  $^{18}\text{F}$ -FDG and 300 batches of diagnostic and therapeutic radiopharmaceuticals for clinical trials per year. ERC operates one TR19 and one TR24 cyclotron, manufactured by Advanced Cyclotron Systems Inc. Together with University of Alberta, ERC has a collaborative initiative developing radiometal production capabilities, which started with  $^{99m}\text{Tc}$  from  $^{100}\text{Mo}$  target material, where production yields of over 1 TBq were achieved.

University of Alberta and ERC have recently produced numerous radionuclides for diagnostic imaging and industrial applications including  $^{68}\text{Ga}$ ,  $^{133}/^{135}\text{La}$ ,  $^{203}\text{Pb}$ ,  $^{64}\text{Cu}$ ,  $^{67}\text{Ga}$ ,  $^{89}\text{Zr}$ ,  $^{44}\text{Sc}$ , and  $^{48}\text{V}$ . We created and executed an adaptive radionuclide production process to create these radionuclides, which involved a sealed solid target design that allows for the minimal amount of target modification necessary to irradiate a variety of target materials, including those that are sensitive and toxic, a convenient and straightforward target retrieval procedure, and a standardised automated target dissolution purification process on an automated synthesis unit that is compatible with a wide range of separation chemistries. The produced radionuclides are mostly used for preclinical research, however  $^{99m}\text{Tc}$  and  $^{203}\text{Pb}$  have also been used in clinical trials.



## **IAEA-CN-310/350**

### **The Supply of Medical Radionuclides**

Roy W. Brown

Government Affairs and Strategic Alliances at Curium, United States of America

Medical radionuclides are used in nuclear medicine procedures more than 40 millions times each year globally. The reliable supply of these medical radionuclides is necessary in order to provide nuclear medicine physicians with these important products for the diagnosis and treatment of disease. There are several challenges in the supply chain from raw material to production challenges and transport issues which all must be overcome to ensure a reliable supply.

Although Tc-99m derived from Mo-99 is the leading radionuclide used in nuclear medicine, there has been significant growth in other diagnostic and therapeutic products over the last several years. New therapeutic products dominated by beta emitters have had tremendous success with patients globally. New alpha emitters are being developed to further enhance therapeutic nuclear medicine. Production of these radionuclides hold special challenges.





**IAEA-CN-310/351**

## **Prospects for the Use of New Types of Radiopharmaceutical Products**

Maria COJOCARU-TOMA

State Medical and Pharmaceutical University "Nicolae Testemitanu", Bulevardul Ștefan cel Mare și Sfânt 165, Chișinău 2004, Republic of Moldova

The global pharmaceutical industry is unique and spectacular, with impressive developments and advances in chemical and medical-biological sciences, which have led to the use of new types of products, including radiopharmaceuticals. The Republic of Moldova, as a member state of the IAEA, is successfully using nuclear technologies in various areas of the economy, and a large part of them are used in medicine for potential diagnostic or therapeutic applications.

Due to the progress in nuclear medicine, techniques using radiopharmaceutical preparations are being implemented in the Republic of Moldova, such as Fluorodeoxyglucose (FDG-18), which is used as a marker in medical imaging by positron emission tomography (PET) and radiopharmaceutical preparations based on Mo/Th-99 generators. Nuclear medicine techniques based on (I-131) for scintigraphy and (I-125) for in vitro testing, are also used.

At the same time, projects are being developed in the area of expanding the types of radiopharmaceuticals such as the use in nuclear therapy of radionuclides: Yttrium-90 or Samarium-153 and other products that will be implemented in several nuclear medicine centres in the republic.



**IAEA-CN-310/352**

## **Development and Application of Sintered Targets for Radioisotope Production**

Emiliano Cazzola

Sacro Cuore Hospital, Negrar, Italy

Radiometal cyclotron isotope productions, on medical cyclotron, are the more improved process on the last 5 years. The possibility to having traditional generator producing radiometals like Technetium-99m or Gallium-68 combined with a production on demand cyclotron technology, request a cheaper and reliable target production way. Liquid target technology is an option to obtain radiometals from cyclotron, but larger production scale could be reached only through solid target production. Based on this framework, solid target production technologies are fundamental for the application growth. Spark Plasma Sintering technique (SPS) it's a simple cheaper and reliable technique applicable to producing this kind of targets. High quality pellets or foils can be sintered to backing material producing target coin with different proprieties. Multilayer target could be also produced to adapt the solid target proprieties on dissolution request.



**IAEA-CN-310/353**

## **Production and Use of Alpha-Emitting At-211 for Targeted Radionuclide Therapy in Japan**

Kohshin Washiyama

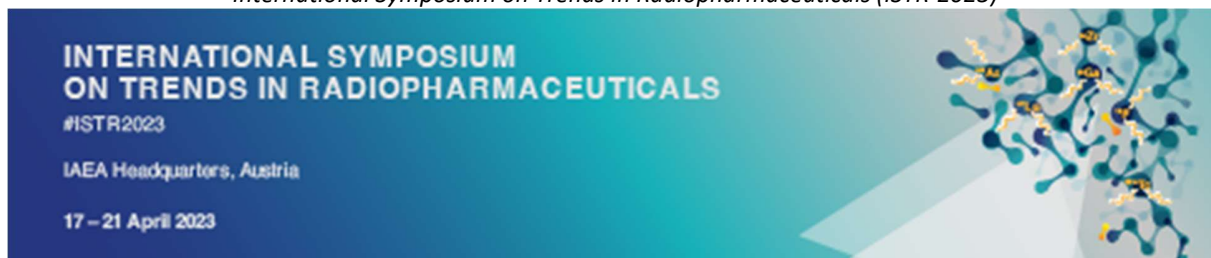
Fukushima Medical University, Fukushima, Japan

Astatine (At) belongs to the halogen series of elements on the periodic table and can be treated like iodine and bromine. No stable isotope exists, with the longest half-life being 8.1 hours for  $^{210}\text{At}$ . Among astatine isotopes,  $^{211}\text{At}$ , with a half-life of 7.2 hours, is expected to be one of the alpha emitters for therapeutic use.

Currently, seven clinical trials are being conducted or planned worldwide. Among them,  $^{211}\text{At}$ -NaAt for thyroid cancer treatment at Osaka University Hospital and  $^{211}\text{At}$ -MABG for the treatment of malignant pheochromocytoma and paraganglioma at Fukushima Medical University are conducted in Japan.

Osaka University has researched Astatine for more than 30 years from a radiochemical perspective. Since 2012, another four facilities have started producing  $^{211}\text{At}$  by the  $^{209}\text{Bi}(\alpha, 2n)^{211}\text{At}$  reaction. In addition, several cyclotron facilities have launched a short-lived RI supply platform to support research activities for short-lived RIs, including  $^{211}\text{At}$  under government financial support. As a result of these efforts, Japanese authors contributed to more than half of the publications of the  $^{211}\text{At}$ -related paper listed in PubMed in the year 2021.

Here, I present our past efforts in  $^{211}\text{At}$  production and development of radiopharmaceuticals and discuss the future vision that  $^{211}\text{At}$  radiopharmaceuticals will bring.



**IAEA-CN-310/354**

### **Cyclotron-Based Tc-99m Production**

Paul Schaffer

TRIUMF, Vancouver, British Columbia, Canada

Many of the ~1400 medical cyclotrons around the world today operate between 16 and 24 MeV, an ideal range for the production of technetium-99m (Tc-99m) via the  $^{100}\text{Mo}(p,2n)$  reaction. In 2010, a consortium of research organizations including TRIUMF, the British Columbia Cancer Agency, Lawson Health Research Institute (LHRI) and the Centre for Probe Development and Commercialization (CPDC) joined forces to develop and demonstrate cyclotron-based production of the world's most-used diagnostic imaging isotope, Tc-99m using local, hospital-based medical cyclotrons. Parameters for producing Tc-99m on various cyclotron models that range in operation from 16.5 MeV through to 24 MeV have been established.

This presentation will provide a status update on the implementation of full clinical scale (GBq to TBq) direct cyclotron-production of Tc-99m. Efforts to date have included a sixty-patient clinical trial, which is now complete, and quality data from three representative radiopharmaceutical kits (anionic, neutral, and cationic), all collected in support of a New Drug Application now approved by Health Canada for human use. Additional efforts are underway for other jurisdictions.

In addition, the cyclotron hardware developed for Tc-99m production, has been adapted to produce large quantities of cyclotron-produced Ga-68, Cu-64 and Zr-89. A summary and status of this technology will be presented.



**IAEA-CN-310/355**

## **Elementally Matched Radiopharmaceuticals for Imaging and Therapy**

Suzanne Lapi

University of Alabama at Birmingham, Birmingham, Alabama, United States of America

The theranostic concept where similar or identical radiopharmaceuticals are used for tandem imaging and therapeutic strategies has been paradigm shifting for the field of nuclear medicine. The theranostic isotope pairing in FDA approved radiopharmaceuticals typically consists of two different radionuclides, for example  $^{68}\text{Ga}$  for imaging and  $^{177}\text{Lu}$  for therapy. A disadvantage of using this pair is that  $^{68}\text{Ga}$  and  $^{177}\text{Lu}$  are chemically different, which may result in different pharmacokinetics of radiopharmaceuticals labelled with these two compounds. The ideal theranostic pair would include radioisotopes of the same element (isotope pairs) but with different emissions (i.e., one suitable for diagnosis and the other for therapy). To this end, our group has focused on the production of  $^{43}\text{Sc}$  and  $^{47}\text{Sc}$  as a true matched theranostic pair for imaging and therapy as well as methods for production of  $^{203}\text{Pb}$  as an imaging analogue for the therapeutic isotope  $^{212}\text{Pb}$ . Additional research has developed chemistry to incorporate these radioisotopes into new imaging radiopharmaceuticals for preclinical and eventually clinical imaging studies.



**IAEA-CN-310/356**

### **Novel Radioisotopes in Preclinical Imaging**

Suzanne Lapi

University of Alabama at Birmingham, Birmingham, Alabama, United States of America

Molecular imaging is a powerful technique that can be applied to basic, translational, and clinical research as well as to routine patient care. In particular, Positron Emission Tomography (PET) allows for spatial localization and quantification of biological processes such as metabolism, enzyme activity, cell proliferation, receptor density and cellular transport that are not readily assessed with conventional anatomic imaging techniques. Using the UAB TR24 cyclotron, our group has focused on the production and purification of radioactive isotopes to expand the toolbox of nuclear imaging agents. These have included transition metals such as  $^{52}\text{Mn}$ ,  $^{64}\text{Cu}$ ,  $^{55}\text{Co}$ ,  $^{89}\text{Zr}$ ,  $^{43,47}\text{Sc}$  and  $^{45}\text{Ti}$ . In particular  $^{45}\text{Ti}$  provides an intermediate half-life isotope suitable for studies with peptides and antibody fragments while  $^{52}\text{Mn}$  is a longer-lived isotope which can be used to study the pharmacokinetics of compounds with long biological half-lives. This work focusses on the production, radiochemistry and imaging characteristics of  $^{45}\text{Ti}$  and  $^{52}\text{Mn}$ .





IAEA-CN-310/357

## Production and Applications of F-18 Radiopharmaceuticals Based on AlF<sub>2</sub><sup>+</sup> Chemistry at the Uruguayan Centre for Molecular Imaging (CUDIM)

Eduardo Savio

Centro Uruguayo de Imagenología Molecular (CUDIM), Av. Dr. Américo Ricaldoni 2010, 11600 Montevideo, Departamento de Montevideo, Uruguay

It is possible to combine the rich chemistry of labeled peptides with a radionuclide that provides excellent decay characteristics such as, [18F]F, using the Al<sup>18</sup>F complex in the peptide labeling. The aluminium-[18F]fluoride ([18F]AlF<sub>2</sub><sup>+</sup>) complex is a “pseudo-radiometal” which combines the favourable decay characteristics and scale of cyclotron produced fluorine-18 with the convenience of metal-based radiochemistry. The radiolabelling technique was first described by McBride et al. (2009). A diverse array of [18F]AlF-based radioconjugates, novel chelators, updated production methods including automated radiosynthesis, GMP compatible and compliant protocols are now available.

This methodology has recently been of great interest, since it would allow direct synthesis of the labelled peptide and small proteins in a few steps. E. Al-Momani et al. (2017) reported that the stability of the radiopharmaceutical was highly dependent of the formulation conditions.

Between the range of [18F]AlF-based radiopharmaceuticals which have been developed for variety of biological targets, those that have transitioned into the clinic for evaluation in patients are mainly for prostate and neuroendocrine cancer diagnosis.

In our center the [18F]AlF method was implemented using the GE Tracer Lab™ FX-FN in a GMP environment. It is being used on routine base, with the following purposes:

- To label the peptidomimetic Glu-NH-CO-NH-Lys(Ahx). enabling specific imaging of tumor cells expressing PSMA.

- To radiolabel a NOTA-conjugated octreotide [18F]AlF-NOTA-octreotide towards SSTR2.

Production and quality control methodologies will be discussed, as well as a comparison with other F-18 and Ga-68 alternatives



**IAEA-CN-310/358**

## **Supply of Mo-99 and Tc-99m Generators**

Bernard PONSARD

SCK.CEN - BR2 REACTOR, Mol, Belgium

Technetium-99m (Tc-99m) is the most widely used radioisotope for medical diagnostic imaging. More than 80% of all nuclear medicine procedures are using Tc-99m ( $T_{1/2}=6$  hours) to perform approximately 35 million examinations worldwide per year. It is obtained from the decay of Mo-99 ( $T_{1/2}=66$  hours). The current global Mo-99 supply chain relies on the irradiation of LEU ('Low Enriched Uranium') solid targets in a few research reactors as BR2 (Belgium), HFR (The Netherlands), MARIA (Poland), LVR-15 (Czech Republic), SAFARI (South Africa) and OPAL (Australia). The irradiated targets are processed by a few facilities as IRE (Belgium), CURIUM (The Netherlands), NTP (South Africa) and ANSTO (Australia). The recovered fission Mo-99 is then sent as bulk to generator manufacturers and supplied as Mo-99/Tc-99m generators to hospitals and radiopharmacies for patient injections. This supply chain is based on proven technology but subject to disruption risks. Therefore, several actions have been taken to improve the reliability and sustainability of Mo-99 supply. Nuclear Medicine Europe (NMEU) is coordinating and monitoring the weekly available irradiation capacity in research reactors to meet the weekly demand of 9000 Ci '6d-calibrated' Mo-99. The EU Observatory is providing high political visibility to ensure a secure supply of medical radioisotopes. The OECD/NEA High-Level Group on the Security of Supply of Medical Radioisotopes (HLG-MR) implemented several principles to ensure sustainability of the supply chain. Replacement projects, alternative production routes of Mo-99 and direct production of Tc-99m are currently under development to diversify the supply chain. All these considerable efforts should improve the security of supply and mitigate the impact of shortages in future.



**IAEA-CN-310/359**

## **Dosimetric Evaluation of Intensity Modulated Radiotherapy and Three-Dimensional Conformal Radiotherapy Treatment Planning of Prostate Cancer at an Oncology Center in Ghana**

Kofi Adesi KYEI

National Centre for Radiotherapy and Nuclear Medic, Harley St, Accra, Ghana

Prostate cancer is the second most prevalent malignancy after lung cancer in men and the sixth cause of death in men globally, with a mortality rate of 6.7 per 100,000. Ghana has an incidence of more than 200 cases per 100,000 population per year. Treatment modalities for prostate cancer mostly include surgery, radiotherapy, chemotherapy, cryotherapy, hormone therapy, and immunotherapy. Radiotherapy uses high-energy ionizing radiation to destroy cancer by employing techniques such as three-dimensional conformal radiotherapy (3DCRT), intensity modulated radiotherapy (IMRT), intensity modulated arc therapy, and volumetric modulated arc therapy (VMAT). In prostate cancer, the most commonly used techniques are 3DCRT and IMRT, which are also used in Ghana.

The aim of this study is to evaluate the dosimetric properties of IMRT and 3DCRT treatment plans in prostate cancer irradiation at the National Radiotherapy Oncology and Nuclear Medicine Centre.

One hundred and sixty treatment plans for eighty patients were created using 3DCRT and IMRT on the Eclipse Treatment Planning System (version 13.6). The target volume, volume at 95% of prescribed dose, and dose at 2%, 5%, 95%, and 98% of PTV and prescribed dose were collected from the dose volume histogram of each plan. The conformity index and homogeneity index were then calculated and evaluated. The doses of the organs at risk were also collected and evaluated.

The mean HIs for the IMRT and 3DCRT treatment techniques were  $0.04 \pm 0.02$  (range: 0.01 - 0.011) and  $0.09 \pm 0.02$  (range: 0.04 - 0.016) respectively. The lower HI value for IMRT is indicative of better homogeneity. The mean CI for IMRT and 3DCRT techniques were  $1.257 \pm 0.112$  (range: 0.99–1.58) and  $1.302 \pm 0.196$  (range: 1.10–2.26). The lower CI value for IMRT is indicative of better conformity. IMRT had a better significant mean homogeneity index and conformity index compared to 3DCRT. Generally, for this study, IMRT had better organ sparing compared to 3DCRT. The mean doses for the OARs ranged from 4.3 - 74.6 Gy of IMRT and 3.1 - 75.9 Gy for 3DCRT technique. The findings from this study suggest that IMRT is better compared to 3DCRT.



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## **Ga-68 Generators, Challenges, Considerations**

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The  $^{68}\text{Ge}/^{68}\text{Ga}$  generator concept providing cationic  $^{68}\text{Ga}$  ready for labelling entered the nuclear medicine community at the beginning of the third millennium. After more than 20 years of radiochemical development and improvement, there is no doubt that the  $^{68}\text{Ge}/^{68}\text{Ga}$  generator is a central component of nuclear medicine PET/CT diagnosis. The generator has matured. In this regard, its availability and performance may be compared with its "big brother", the #1 generator in nuclear medicine, the  $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$  generator. Parameters to discuss are production pathways of the parent isotope, design of the generator, labelling strategies, alternative access of the generator daughter, and availability of established and R&D for new pharmaceuticals. Concerning the last aspect, radiopharmaceutical sciences are contributing a wide range of extremely important  $^{68}\text{Ga}$ -tracers for tumor diagnosis. Moreover,  $^{68}\text{Ga}$ -labelled peptides and inhibitors are essential for tumor therapy with  $^{90}\text{Y}$ ,  $^{177}\text{Lu}$  and  $^{225}\text{Ac}$  labelled analogs and represent key components of the theranostic principle. However, challenges still exist. Is the availability of  $^{68}\text{Ge}/^{68}\text{Ga}$  generators sufficient for the increasing clinical applications of new and especially registered  $^{68}\text{Ga}$  tracers? What about cost considerations? Is the direct production of  $^{68}\text{Ga}$  an option? Wouldn't it be great to achieve instant kit-type labeling strategies for  $^{68}\text{Ga}$  tracers at room temperature? This would be in line with the standard set and appreciated for the "big brother" of generator-based radiometal-labeled diagnostics, i.e.,  $^{99\text{m}}\text{Tc}$ .



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### **Update on the U.S. DOE Production Effort to Provide Alpha Emitters Radiotherapy.**

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The US Department of Energy Isotope Program (DOE-IP) has had a long history in the development of radioisotopes and has been a leader in the field of producing and supplying alpha emitters. A major focus has been increasing the supply of alpha emitters to support their evaluation in targeted alpha therapy (TAT) applications. For over 25 years it has been supplying  $^{225}\text{Ac}$  from a  $^{229}\text{Th}$  generator located and developed at Oak Ridge National Laboratory (ORNL). This material is available in 1.2 – 1.7 Ci quantities worldwide per year and is not sufficient to support clinical evaluations. Interest has increased in the use of  $^{225}\text{Ac}$  (as demonstrated by the tremendous growth in pre-clinical/clinical trials and related publications). Astatine-211 is another alpha emitter that has been growing in interest. Although DOE does not have its own production capability it has been supporting and growing the University network to support regional production of  $^{211}\text{At}$  across the US. The development of alpha emitters such as  $^{225}\text{Ac}$  and other alpha emitters for TAT will require additional sources and increased levels of production to support the numerous applications being developed for selective targeting of cancer that has spread to multiple sites and is nonresponsive to traditional treatments. This talk will present an update on DOE efforts to increase the availability of alpha emitters.