Measurements of the ^{226}Ra(*p*,*xn*) excitation functions to improve the supply of the medical radionuclide ^{225}Ac

A. Kellerbauer[1,*], J. Červenák[2], C. de Almeida Carrapiço[1], E. Jajčišinová[1], O. Lebeda[2], R. Malmbeck[1], L. Ondrák[2], K. Ondrák-Fialová[2], J. Ráliš[2], J. Štursa[2]

[1] *European Commission, Joint Research Centre, 76125 Karlsruhe, Germany*

[2] *Nuclear Physics Institute of the CAS, Řež, Czech Republic*

^{225}Ac is recognized as an important alpha-emitting radionuclide for targeted radioligand therapy in nuclear medicine, with significant benefits for patient in clinical trials [1,2]. However, its traditional production from ^{229}Th generators, more recently also from spallation of ^{232}Th, limited its availability and generate problematic long-lived waste, respectively. We aim to improve the production of ^{225}Ac by exploring the proton activation of ^{226}Ra, for which there are few experimental cross-section data. We intend to generate new, precise cross-section data that will facilitate a novel method of producing ^{225}Ac that will increase its availability.

To achieve this, we produced thin, homogenous targets of ^{226}Ra and bombarded them with protons, near the energy corresponding to the maximum in the excitation function, at the Nuclear Physics Institute's U-120M cyclotron. The irradiation was followed by dissolution of the targets and chromatographic separation of Ac isotopes. The activities of these isotopes were then measured using gamma spectrometry, and the cross-sections for the ^{226}Ra(*p*,*xn*)^{224,225,226}Ac reactions were calculated. A comparison with both earlier experimental results and theoretical models offers a more comprehensive understanding of the excitation function, resulting in an optimized cyclotron production of ^{225}Ac. The results have important implications for enhancing the production and purity of this highly relevant medical radionuclide.

References

[1] A. Kellerbauer *et al*., J. Label. Compd. Radiopharm. **62**, 794 (2019), doi: 10.1002/jlcr.3792

[2] M. M. Sathekge *et al*., Lancet Oncology **25**, 175 (2024), doi: 10.1016/S1470-2045(23)00638-1

* Presenting author email: alban.kellerbauer@ec.europa.eu

GAMMA-MRI: A Molecular Imaging modality using anisotropic gamma emission from hyperpolarised nuclei

S. Pallada[1], A. Cooper[1], N. Giandomenico[1], A. Kanellakopoulos[1], B. Musy[1], Q. Rogliardo[1], V. Sanchez Tembleque[1], H. Stoeckli[1], R. De Oliveira Silva[4], P. De Pellegars[6], L. Fraile[3], M. Jerzy Chojnacki[2], R. Jolivet[5], M. Kowalska[2], J. Rivoire[6], D. Sakellariou[4]

stavroula.pallada@hesge.ch

[1]*HESSO, University of Applied Sciences and arts Western Switzerland, Geneva, Switzerland*
[2]*CERN, Meyrin, Switzerland*
[3]*Universidad Complutense de Madrid, Madrid, Spain*
[4]*KU Leuven, Leuven, Belgium*
[5]*Maastricht University, Maastricht, The Netherlands*
[6]*RS2D, Mundolsheim, France*

The GAMMA-MRI project is a Horizon 2020 funded project that aims to bring innovation in clinical molecular imaging. With GAMMA-MRI we promise to overcome the problem of limited tissue signalling, that dictates that a minimum of 10^{24} atoms in an organ are required to record an MRI signal. To mitigate the low signal detection sensitivity of MRI, a radioactive, gamma-emitter isotope with a gamma energy close to the one of ^{99m}Tc (SPECT isotope) is used.

GAMMA-MRI is based on the detection of the asymmetric gamma-emission of long-lived isomers of radioactive noble gas nuclei with spin $I \geq 1/2$. To observe any gamma-ray asymmetry in space the radioactive nuclei need to be polarised. Here we use Spin Exchange Optical Pumping (SEOP), a hyperpolarisation technique being utilised in clinical settings for lung perfusion studies [1]. The long-lived Xenon isomers that were produced via Neutron Activation (in ILL, Grenoble, France and MARIA reactor, Warsaw, Poland) and tested during the current project were ^{129m}Xe ($T_{1/2}$=8.88 d, E_γ=196.6 keV) and ^{131m}Xe ($T_{1/2}$=11.84 d, E_γ=163.9 keV) [2].

Once the radioactive mXe are produced, they are inserted into a SEOP borosilicate glass cell, where natural Rb is present. A mixture of Rb, mXe, N_2 and occasionally He is added in the SEOP cell. The SEOP glass cell is then placed in the centre of a custom made SEOP oven and at the geometrical centre of a 1- 6 mT B_0 magnetic field created by a set of Helmholtz coils of the SEOP Hyperpolarisation (HP) system. Oven heating at T>40 ºC (melting point of Rb) creates Rb vapours and laser irradiation (QCP diode laser, 795 nm) initiates the Optical Pumping process that creates atomic polarization of Rb. Spin Exchange between the Rb atoms and the mXe nuclear spins leads to hyperpolarised (HP) mXe. During the radioactive decay of HP, mXe gamma photons are emitted anisotropically in space following a preferential emission perpendicular to the B_{0Z} axis. Numerous CsI(Tl) Gamma detectors (2-8) surrounding the glass cell can record the gamma count asymmetry between the transversal and the longitudinal planes.

We will present the physical principles of the GAMMA-MRI technique, the systems developed during our project, and the best NMR and MRI results acquired so far. We are currently one step closer to obtaining the first GAMMA-MRI image using the GAMMA-MRI prototype device with radioactive mXe.

References

[1] A. S Khan et al. Angewandte Chemie, **60**, 41 (2021), doi:10.1002/anie.202015200
[2] M. Jerzy Chojnacki et al, Applied Radiation and Isotopes, **205**, (2024),doi:10.2139/ssrn.4575330

Measurement of the 176 Yb(n,γ) cross-section and its application to nuclear medicine

F. García-Infantes[1,2], J. Praena[2], A. Casanovas[3], R. Henkelmann[4], U. Köester[5], and the n_TOF collaboration

[1] *European Organization for Nuclear Research (CERN), Switzerland*
[2] *University of Granada, Spain*
[3] *Instituto de Física Corpuscular, CSIC - Universidad de Valencia, Spain*
[4] *Isotope Technology Munich (ITM), Germany*
[5] *Institut Laue-Langevin (ILL), Grenoble, France*
Presenting author email: francisco.garcia.infantes@cern.ch

Nuclear medicine has proven to be a much needed medical specialty in order to diagnose and treat several diseases, among them, cardiovascular diseases and cancer, the first and the second causes of mortality worldwide, respectively [1]. Several international agencies recommend to study new routes and new facilities for producing radioisotopes with application to nuclear medicine as a complementary option to the conventional ones based on nuclear reactors or dedicated cyclotrons [2,3,4]. This has been especially pushed in the last years with the development and the availability of high-intensity accelerators and new installations because they allow the production of emergent or new radioisotopes. In addition, these new installations can provide quantities of various radioisotopes at regional level. CERN's MEDICIS ISOLDE facility is an excellent example [5].

^{177}Lu is a versatile radioisotope used for therapy and diagnosis (theranostics) of cancer with good success in gastroenteropancreatic neuroendocrine tumours [6]. Currently, the use of ^{177}Lu is under study for several other tumours with good results [7]. ^{177}Lu is produced in a few nuclear reactors mainly by the neutron capture on ^{176}Lu (direct route). However, it could be produced at high-intensity accelerator-based neutron facilities as IFMIF-DONES [8] by means of the route ^{176}Yb(n,γ) (indirect route) [9]. In fact, the produced ^{177}Yb β-decays to ^{177}Lu with a half-life of 1.9 h. Although the cross-section of the direct route is higher, several advantages in the indirect route have been pointed out:

i) The specific activity is four times higher. About 100% of the theoretical specific activity can be achieved [10,11].

ii) The contaminants that remain in the final quantity of the material are much lower.

iii) The undesirable ^{177m}Lu ($t_{1/2}$≈160 d) is produced in the direct route, 0.05%, whereas in the indirect route is less than 10^{-5}% [12].

These properties have a direct impact on the quality of the diagnosis and the therapy. The higher specific activity allows a much better tumour uptake; thus, the dose delivered to the tumour for the same activity is much higher in case of the indirect route, and in addition, the quality of imaging of the tumour is much better [10,11].

The energy of the neutrons in accelerator-based neutron facilities is higher than in thermal reactors. Consequently, experimental data on the ^{176}Yb(n,γ) cross-section in the eV and keV region are mandatory to accurately calculate the production of ^{177}Lu. At present, there is no available experimental ^{176}Yb(n,γ) cross-section data for thermal neutron energies up to 3 keV. In addition, the resonances have not been resolved in the range from 3 to 50 keV.

An experimental campaign at the n_TOF facility provides data from the thermal to the resolved resonance region for the first time, resolving the largest resonances in the ^{176}Yb(n,γ) cross-section. The γ-rays cascade, with a total energy of 5.24 MeV emitted after each capture

reaction in ^{176}Yb, has been detected using a set of four C_6D_6 detectors [13]. The Monte Carlo based Pulse height weighting technique (PWHT) has been used to correct for the detection efficiency [14]. Results of the analysis will be shown with particular attention to the possible confirmation of the 1/v behaviour of of the cross section between thermal and resonance region, where there are not experimental data. Furthermore, this measurement will potentially clarify the existence of resonances which have been observed in transmission experiments but were not measured in previous capture measurements. These data will be ready to be used in future evaluations of the ^{176}Yb(n,γ) cross-section and for the calculation of ^{177}Lu production in accelerator-based neutron sources as IFMIF-DONES.

References:

[1] https://www.euro.who.int/en/health-topics/noncommunicable-diseases/cancer.
[2] Nuclear Physics European Collaboration Committee: nuclear physics for medicine. ISBN: 978-2-36873-008-9. https://www.nupecc.org/pub/npmed2014.pdf.
[3] European Nuclear Society, The Medical Isotope Crisis. http://www.euronuclear.org/1-information/news/medical-isotope-crisis.htm.
[4] NuPEcc. Long Range Plan 2017 Perspectives in Nuclear Physics. https://www.esf.org/fileadmin/user_upload/esf/Nupecc-LRP2017.pdf.
[5] https://medicis.cern/
[6] K. Kim *et al.*, Lu-177-Based Peptide Receptor Radionuclide Therapy for Advanced Neuroendocrine Tumors, Nucl Med Mol Imag., 2018 Jun; **52**(3): 208–215. https://doi.org/10.1007/s13139-017-0505-6.
[7] J. Zhang et al., Clin. Nucl. Med., January 2020, **45**, Issue 1, p e48-e50. https://doi.org/10.1097/RLU.0000000000002655.
[8] D. Bernardi, A. Ibarra, and F. Arbeiter *et al*. The ifmif-dones project: Design status and main achievements within the eurofusion fp8 work programme. Journal of Fusion Energy, **41**(24), 2022.
[9] A. Dash *et al.*, Production of ^{177}Lu for targeted radionuclide therapy: available options. Nuc. Med. and mol. 1Ima., **49**(2):85–107, 2015. https://pubmed.ncbi.nlm.nih.gov/26085854/.
[10] R. Henkelmann, Thursday, 28 February 2013, Lu-177 production with a focus on radiation in the KBA at FRM II, SAAGAS 24, TUM Garching. https://indico.frm2.tum.de/event/0/attachments/4/14/Henkelmann_177Lu_gek.pdf.
[11] E. A. M. Ruigrok et al., Extensive preclinical evaluation of lutetium-177-labeledPSMA-specific tracers for prostate cancer radionuclide therapy, Eur. J. Nucl. Med. Mol. Imaging, 2020 Oct 23. 10.1007/s00259-020-05057-6.
[12] K. M. Ferreira et al., Half-life measurement of the medical radioisotope ^{177}Lu produced from the ^{176}Yb(n,γ) reaction. EPJ Web of Conferences, **146**, pag 08002, EDP Sciences, 2017. https://doi.org/10.1051/epjconf/201714608002.
[13] P. F. Mastinu et al.; New C_6D_6 detectors: reduced neutron sensitivity and improved safety, (The n_TOF Collaboration), CERN-n TOF-PUB-2013-002 (2013).
[14] U. Abbondanno, G. Aerts et al., New experimental validation of the pulse height weighting technique for capture cross-section measurements, https://doi.org/10.1016/j.nima.2003.09.066.

Hospital-Cyclotrons Production of High-Purity ^{155}Tb via ^{155}Gd(p,n)*

Francesca Barbaro[1,2,†], Luciano Canton[2], Nikolay Uzunov[3],
Laura De Nardo[1,2], Laura Meléndez-Alafort[4]

[1] *University of Padova, Department of Physics and Astronomy, Via Marzolo 8, Padova, Italy*
[2] *INFN, Padova unit, Via Marzolo 8, Padova, Italy*
[3] *INFN-Legnaro National Laboratories, Viale dell'Università 2, Legnaro, Italy*
[4] *Istituto Oncologico Veneto IOV IRCCS, Via Gattamelata 64, Padova, Italy*

Terbium radionuclides are of emerging interest for theranostics, a branch of nuclear-precision medicine that conjugates imaging and therapy. The possibility to produce radiopharmaceutical labelled with Tb-pairs, one to image the patient and one for the therapy, makes Terbium attractive and flexible in nuclear-medicine applications [1]. For a precise delivery of therapy, high-quality images are essential. ^{155}Tb is a promising SPECT imaging agent, thanks to its γ emissions (87 keV (32%), 105 keV (25%)) and a long half-life ($T_{1/2}$ = 5.32 d) that allows to trace the biodistribution over several days. However, an efficient and convenient cyclotron production route has still to be identified.

This work focuses on the ^{155}Gd(p,n)^{155}Tb reaction. The challenge is to minimize the co-production of ^{156}Tb ($T_{1/2}$ = 5.35 d) that compromises the image quality and increases the patient absorbed dose due to its high-energy γ emissions [2]. The relevant production cross sections were simulated with the TALYS code [3] and compared with experimental measures [4,5]. Thick-target yields and radionuclidic purity (RNP) were derived. Dosimetric evaluations were accomplished using the OLINDA software [6], considering an injection of ^{xxx}Tb-cm09 [1] and the dose increase (DI) was determined by combining the yield of all Tb radioisotopes produced with the dosimetric outcomes. Since the higher the ^{156}Gd impurity of the enriched ^{155}Gd target, the higher the ^{156}Tb contamination, different isotopic compositions of the target have been compared, namely 91.9%, 98%, 99%, and 100% enrichment. The assessment of the RNP and DI illustrates that a 2% content of ^{156}Gd is the maximum limit that still guarantees a safe clinical application. In addition, ^{155}Tb imaging was simulated and its quality assessed through the Compton-to-peak ratio, expressing the noise due to the Compton scattering of high-energy γ-rays, emitted by the other Tb contaminant isotopes. Following this approach, a comparison between the imaging properties of ^{155}Tb and ^{111}In (currently used in clinics) reveals comparable quality of the SPECT images.

In conclusion, this work proposes a hospital-cyclotron method for high-purity ^{155}Tb production based on an adequate ^{155}Gd-enrichment of the target. The minimum level of enrichment necessary for its use in clinics has been identified. This method serves as an alternative to the post-production mass-spectrometric purification, previously proposed in the literature.

References

[1] C. Müller *et al.*, Nucl Med Biol, 41:e58–65, (2014)
[2] F. Barbaro *et al.*, EJNMMI Phys 11, 26, (2024)
[3] A. J. Koning, S. Hilaire, S. Goriely, EPJ A. 59, (2023)
[4] G. Dellepiane *et al.*, Appl Radiat Isot. 184:110175, (2022)
[5] G. Dellepiane *et al.*, Appl Radiat Isot. 200:110969, (2023)
[6] M. G. Stabin, R. B. Sparks, E. Crowe, J Nucl Med, 46:1023–1027, (2005)

* Funds from projects: REMIX-CSN5, NUCSYS-CSN4, SPES_MED-CSN3, PRIN-APHRODITE-155

† francesca.barbaro@pd.infn.it

An improved radio-epidemiology tool for the analysis of the propagation of radiation following a contamination event

Luca Romano

Department of Industrial Engineering, University of Rome Tor Vergata, Rome (Italy)

Given the current state of global concerns, it is evident that the potential for attacks employing radiological dispersal devices against vulnerable targets, such as population and soft targets, is no longer a distant possibility. Thus, it is crucial for first responders and decision-makers to rapidly understand how radiation can propagate across great distances in limited time frames to effectively handle emergencies. By applying free-license computational codes, deliberate releases of radioactive material and their transmission from person to person might be simulated. In a previous study by Quaranta, Ludovici et al., the HotSpot code was employed to simulate a scenario involving the release of Co-60 subsequent to an RDD explosion in the city center of a major European city. Furthermore, the STEM code is used to simulate the spread of radiation from the individuals initially involved in the incident, comparing them to the vectors of a chimeric viral infection. An attack in which 5,000, 2,500 and 1,000 people are affected, respectively, was assumed for the scenarios. The recovery rates, mortality rates and propagation of the radioactive substance throughout the territory were considered for a timeline of one month. The findings revealed that the scenario yielded relatively minor health repercussions for the affected population. However, the model was not yet tested with data coming from a real case study. In this work, we first improved the model by adding an immunization factor, to better simulate the fact that radionuclides spreading from one person to another yield a lower effective dose for each individual, and then ran a simulation using a different radionuclide (Cs-137) to compare the data with the case study of the Goiania radiological accident (Brazil, 1987). The model yielded encouraging results, with numbers matching the order of magnitude of the case study, and once again minor health repercussions amongst the affected population. However, it is essential to acknowledge that such a scenario poses numerous challenges in emergency management. The incident presents the risk of triggering widespread panic and capturing significant media attention. Decision makers must also consider the potential lack of awareness among those involved in the incident and the general population. These considerations must be taken into account from an emergency management perspective, requiring the involvement of various stakeholders, including law enforcement, firefighters, healthcare professionals, journalists, politicians, and others.

The more recent Radionuclides for Theranostic Applications studied at L.A.S.A Laboratory, Italy*

M. Colucci[1], I. Cardani[1], M. Marrella[1,2], F. Haddad[3,4], F. Groppi[1,†], S. Manenti[1]

[1] *LASA Laboratory, Physics Department of University of Milano & INFN, Segrate (MI), Italy*

[2] *Physics Department, University of Calabria, Arcavacata di Rende, Italy*

[3] *GIP Arronax, Saint-Herblain, France*

[4] *Laboratoire Subatech, IN2P3-CNRS, IMT Atlantique, Nantes Université, Nantes, France*

The use of High Specific Activity Radionuclides HSARNs, obtained by either proton, deuteron or alpha cyclotron irradiation, followed by selective radiochemical separation from the irradiated target in No Carrier Added (NCA) form, is a powerful analytical tool for plenty applications in pure and applied sciences and technologies. The main applications of these RNs are in medical radiodiagnostics and metabolic radiotherapy in addition to toxicological, environmental, and industrial studies. Nowadays the new challenge in Nuclear Medicine is the so called theranostic medicine, a relatively novel paradigm that involves specific individual 'dual-purpose' radionuclides or radionuclide pairs with emissions that are suitable for both imaging, therapy and monitor the response to therapy. The theranostic radionuclides would potentially bring us closer to the age-long dream of personalized medicine [1]. Different radionuclides with the suitable characteristics to be used as theranostic can be produced by bombardment of targets by charged particle beams in NCA form with very high Specific Activity (A_S). The first step in evaluating a production route is the knowledge of the cross-sections of the radionuclide of interest and of its contaminants, especially the isotopic ones that cannot be chemically separated. The presence of contaminants affects the radionuclidic purity (RNP) and the A_S of the final product [2].

Recently there is an increasing interest on the terbium family, due to the four medically relevant radioisotopes ^{149}Tb, ^{152}Tb, ^{155}Tb and ^{161}Tb, that could be employed either in diagnostic or therapy.

To optimize the production routes for theranostic Tb radionuclides, a systematic evaluation of the experimental cross sections of the nuclear reactions induced by light ions (protons, deuterons and alpha particle) on different target materials has been undertaken. The irradiations are carried out at the cyclotron IBA K=70 of ARRONAX Center in Nantes France, that can deliver proton and alpha beams, with variable energy up to 70 MeV and deuteron beams of energy up to 35 MeV. The gamma and X-ray spectra are measured at GIP Arronax Laboratory and Physics Measurements Laboratory in LASA by HPGe detectors.

The results of the different production routs will be presented highlighting and comparing the strengths of each of them and the most efficacious one in term of A_S and RNP, fundamental parameters for use on humans.

References

[1] S.C. Srivastava, Semin. in Nucl. Med. **42(3)** (2012) 151-163, doi: 10.1053/j.semnuclmed.2011.12.004.

[2] F. Groppi *et al*., 6. Groppi, F. *et al*. NATO Science for Peace and Security Series B: Physics and Biophysics, 2009, 113–128.

* This work is made thanks to INFN financial support (Gr V - Interdisciplinary Commission - REMIX experiment), Italy and to the whole staff of the ARRONAX Cyclotron., France.

† flavia.groppi@unimi.it